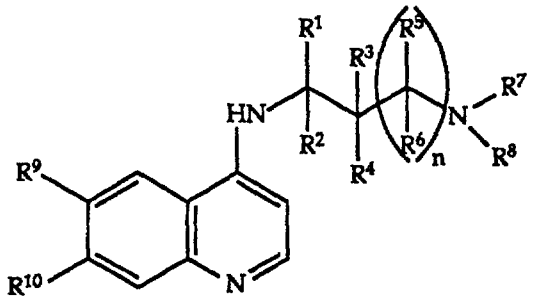
9405663-5 IPO2

PCT/ACRD SHEETS
✓ Description : pages 1 to 45
✓ Claim(s) : pages 46 to 51
Drawing(s) : pages ... to ...
✓ ... : pages 52 to 53
IA/... SHEET

RAN 4465/16

The invention is concerned with aminoquinoline derivatives of the general formula



I

wherein the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, octahydroindole or 3-azabicyclo[3,2,2]nonane and n = 0 or 1 or

wherein the symbols R^1 and R^3 signify tri- or tetramethylene, all remaining symbols to R^6 signify hydrogen, n = 0 and R^7 and R^8 have the above significances or

wherein the symbols R^1 and R^7 signify methylene or dimethylene and n = 1,
R^1 and R^7 signify di- or trimethylene and n = 0,
R^3 and R^7 signify di- or trimethylene and n = 1
R^3 and R^7 signify tri- or tetramethylene and n = 0
R^5 and R^7 signify tri- or tetramethylene and n = 1
R^1 and R^5 signify di- or tri-methylene and n = 1, all remaining substituents signify hydrogen, except R^8 which signifies alkyl, alkenyl or alkynyl or

wherein the symbols R^3 and R^5 signify tri- or tetramethylene and n = 1, all remaining substituents to R^6 signify hydrogen and R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl,

This Sheet Has Been Replaced



R^9 signifies hydrogen or halogen and R^{10} signifies halogen or trifluoromethyl,

as well as pharmaceutically acceptable salts of basic compounds of general formula I.

These compounds are novel with the exception of

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propan-1,3-diamine,

(7-chloro-quinolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine,

(7-chloro-quinolin-4-yl)-[(1-ethyl-pyrrolidin-2-yl)-methyl]-amine,

(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine,

(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-2-yl-methyl)-amine and

(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-3-yl)-amine,

and they have the surprising property that they have an equally good effect not only against chloroquine-sensitive malaria pathogens, but also against chloroquine-resistant malaria pathogens, that is to say, they exhibit no cross-resistance with chloroquine.

This Sheet Has Been Replaced



Not only the absence of cross-resistance, but also the good activity, which is to some extent better compared with chloroquine, were surprising. Hitherto it had been assumed that cross-resistance exists between chloroquine-like compounds. Only certain bis-quinolines, which contain two quinoline rings and which bear little structural relationship to chloroquine, have a definite activity against chloroquine-resistant malaria pathogens, especially the compounds which have been described by J.L.Vennerstrom (J. L. Vennerstrom et al, J.Med.Chem., ***35***, 2129-2134 (1992). Further, it had hitherto been assumed that chloroquine analogues having shortened or lengthened side-chains were less active against malaria pathogens compared with chloroquine (R.L.O'Brien and F.E.Hahn, Chloroquin Structural Requirements for Binding to Deoxyribonucleic Acid and Antimalarial Activity, Antimicrob. Agents Chemother, **1965**, 315 - 320).

Simple analogues of chloroquine have therefore hitherto been considered to be uninteresting and not suitable for the treatment for malaria. In contrast to this assumption, it has now been found that the compounds of formula I are outstandingly suitable for the prophylaxis of malaria and for its treatment, especially in cases where the pathogens are resistant to chloroquine.

Objects of the present invention are the use of compounds of formula I and of pharmaceutically usable salts thereof in the control or prevention of diseases, especially in the control of chloroquine-resistant and of chloroquine-sensitive malaria pathogens, the novel compounds and salts of formula I per se and for use as therapeutically active substances, the manufacture of the novel compounds and salts as well as medicaments containing a novel compound or a salt and the manufacture of such medicaments.

The term "alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl,

This Sheet Has Been Replaced



t-butyl and the like. Halogen signifies chlorine, bromine, fluorine or iodine.

Compounds in which the symbols R^1 to R^6 signify hydrogen and one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, and n = 0 or 1 are especially preferred.

Particularly preferred compounds of general formula I are:

(S)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

(R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

N_1-(7-chloro-quinolin-4-yl)-2,N_2,N_2-trimethyl-propane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine,

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-3-yl)-amine and

(RS)-(7-choro-quinolin-4-yl)-(1-methyl-pyrrolidin-3-yl)-amine.

Also preferred are:

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

(RS)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

This Sheet Has Been Replaced



(S)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(RS)-7-chloro-quinolin-4-yl)-(1-methyl-2-pyrrolidin-1-yl-ethyl)-amine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

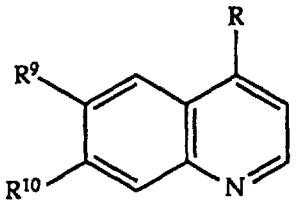
(R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine,

(S)-N_1-(7-chloro-quinoline-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine and

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine.

The novel compounds of formula I can be manufactured in accordance with the invention by

a) reacting quinoline derivatives of the general formula

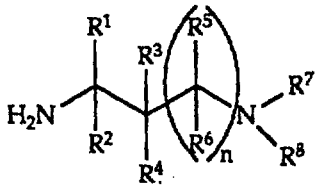


II

This Sheet Has Been Replaced

wherein R^9 and R^{10} have the above significances and R signifies a leaving group,

with amino compounds of the general formula

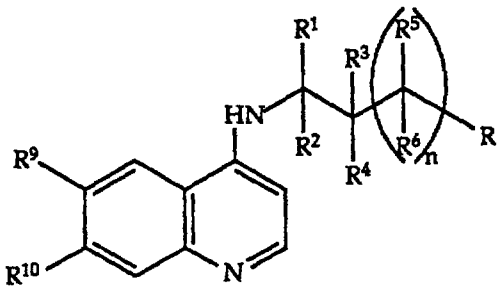


III

wherein the substituents R^1 to R^8 have the above significances,

or

b) reacting alkylamino-quinoline derivatives of the general formula



IV

wherein R^1 to R^6 and R^9 and R^{10} have the above significances and R signifies a leaving group,

with amines of the formula

$$HNR^7R^8 \qquad V$$

wherein R^7 and R^8 have the above significances,

or

c) reacting compounds of formula I in which R^1 to R^6 as well as R^9 and R^{10} have the above significance and R^7 and R^8 signify hydrogen or one of them signifies hydrogen and the other signifies an alkyl group with alkylating agents which are suitable for the alkylation of amino groups,

and

This Sheet Has Been Replaced

d) if desired, converting a basic compound of formula I into a pharmaceutically usable salt by means of an acid.

According to variant a) of the process in accordance with the invention correspondingly substituted quinoline derivatives which contain a leaving group in the 4-position are reacted with amino compounds of general formula III, the substituents having the significances given above and R signifying a leaving group.

Leaving groups are conveniently halogen, O-methylsulphonyl or O-toluenesulphonyl groups. The reaction is conveniently effected in a temperature range between 120 and 180°C and in a solvent, with phenol, ethoxyethanol, dimethylacetamide or N-methylpyrrolidine being especially preferred. The reaction time can vary between 2 and 28 hours.

A further possibility for the manufacture of the compounds of general formula I comprises using process variant b).

Conveniently, the compounds of formula IV in which R signifies a leaving group and all other substituents correspond to the significances given above is reacted in the form of the hydrochloride of the correspondingly substituted alkylamino-quinoline derivative with an aliphatic or cyclic amine of formula V in a sealed tube, whereby the amine can simultaneously serve as the solvent. The reaction can take up to 24 h. The preferred temperature range embraces temperatures between 90 and 110°C. This reaction can also be effected in solvents in which both reaction partners are soluble, for example in DMF, DMA, N-methylpyrrolidone or acetonitrile. The conversion into a pharmaceutically usable salt is effected by adding an acid. HCl is especially preferred because of the physiological compatibility of the hydrochloride. Convenient solvents which are especially suitable are: isopropanol, diethyl ether or dioxan.

Alkylating agents which are suitable for process variant c) are, for example, formaldehyde in combination with formic acid, in which case the reaction is preferably carried out in excess

This Sheet Has Been Replaced



formic acid. Other alkylating agents which come into consideration are combinations of aliphatic or aromatic aldehydes with complex hydrides such as sodium borohydride or sodium cyanoborohydride. Such reactions can be conveniently carried out in alcoholic or aqueous solutions.

The quinoline derivatives of general formula II required for synthesis variant a) are commercial products or can be prepared according to methods known per se, for example 7-chloro-4-hydroxyquinoline can be converted with phosphorus oxybromide into 7-chloro-4-bromo-quinoline.

The aliphatic or cyclic amines of general formula III are also to some extent commercial products or can be prepared according to methods known per se. Conveniently, the starting point can be a cyclic amine, for example pyrrolidine or piperidine, or an aliphatic amine, e.g. dimethylamine or diethylamine, which can be reacted with nitroethane or 2-nitropropane. The resulting nitro compound can subsequently be reduced according to methods known per se, e.g. by hydrogenation with Raney-nickel, to the compounds of general formula III.

A further possibility for the preparation of the compounds of general formula III comprises converting cycloalkane oxides with diethylamine and perchlorates into 2-(diethylamio)-cyclo-alkanols. These are conveniently dissolved, without further purification, in THF and treated with phthalimide and triphenyl-phosphine and subsequently stirred at room temperature for several hours. After purification the resulting N,N-diethyl-2-phthalimido-cycloalkylamine is saponified with concentrated hydrochloric acid.

In analogy thereto, in place of diethylamine and other aliphatic amines there can also be used, for example, cyclic amines such as pyrrolidine. When cyclic amines, for example piperidine, are reacted with acrylonitrile there is obtained the corresponding propionitrile which can be hydrogenated to the

This Sheet Has Been Replaced



corresponding propylamine in the presence of platinum dioxide at RT under 10 bar.

The corresponding alkylamino-quinoline derivative of general formula IV in which the leaving group signifies a halogen group, preferably chlorine, required as the starting material for synthesis variant b) can conveniently be prepared as follows:

A suspension of the corresponding quinolinamino-ethanol, which can be prepared according to a synthesis of R.C. Elderfield, J. Am. Chem. Soc. 68, 1250 (1946), is treated with thionyl chloride, whereby the reaction temperature should not exceed 30°C. Subsequently, the mixture is stirred at RT for 1 h., evaporated to dryness and purified.

As mentioned earlier, the aminoquinoline derivatives of general formula I and their pharmaceutically usable salts have extremely valuable pharmacological properties.

Their activity against not only chloroquine-resistant, but also chloroquine-sensitive malaria pathogens will be evident from the following Tables:

Test method for the determination of the activity against P. falciparum in vitro

The preparations are tested on intraerythrocytary stages of P. falciparum from asynchronous cultures according to the method of Desjardin et al. (Desjardins, R.E. et al: Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique. Antimicrob. Agents Chemother. 16, 710-718, (1979)).

The culture medium consists of RPMI 1640 with the addition of 25 mM HEPES, 25 mM $NaHCO_3$, 100 µg/ml neomycin and 10% human serum (A^+). Human-A^+ erythrocytes are used as the P. falciparum host cells. The parasites are maintained at

This Sheet Has Been Replaced



37°C in an atmosphere of 3% O_2, 4% CO_2, 93% N_2 and at 95% relative humidity.

In order to determine the activity, the preparations are dissolved in DMSO, pre-diluted in the culture medium to a suitable starting concentration and subsequently titrated-out into microtitre plates in the 2nd stage over 6-7 steps. After the addition of the parasite culture (0.7% parasitemia in 2.5% erythrocyte suspension) the test plates are incubated under the conditions given above for 48 h - 72 h. The parasite growth in the different preparation concentrations is determined using [G-^{3}H]-hypoxanthin incorporation compared to untreated control cultures on the same test plates. The 50% growth inhibition (IC50) is calculated according to logit regression analysis from the resulting dosage-activity curve.

The preparations are tested on at least one chloroquine-resistant and one chloroquine-sensitive P. falciparum strain. Additional sensitive and resistant strains are included for futher characterization.

Test method for the determination of the activity against Plasmodium berghei in vivo

The preparations are tested on mice infected with malaria pathogens (Plasmodium berghei). Male albino mice (IBM:MORO(SPF), FUELLINSDORF) weighing about 25 g are used as the test animals. They are kept in climatized rooms at 21-22°C in groups of 5 animals per cage. They receive ad libitum a diet feed with a low PABA content (NAFAG FUTTER © No. 9009 PAB-45, PABA content 45 mg/kg) and drinking water. On the first day of the test (D0) the test animals are infected with Plasmodium berghei (strain ANKA). For this there is used heparinized blood of a donor mouse with about 30% parasitemia, which is diluted with physiological saline such that it contains 10^8 parasitized erythrocytes per ml. 0.2 ml of this suspension is injected intravenously (i.v.) into the mice to be treated and into the control mice. In untreated control animals the parasitemia

This Sheet Has Been Replaced



normally reaches 30-40% on the third day after the infection (D+3) and the test animals die between days +5 and +7.

The substances to be tested are dissolved or suspended in distilled water or in a mixture of 7% Tween 80, 3% alcohol (96%) and water. Usually, 0.25 ml of this solution or suspension is administered once subcutaneously and perorally to groups of 5 test animals. Treatment is effected 24 hours after the infection. 10 control animals are treated in the same manner with solvent or suspension medium per test.

All substances are tested in a first test in a single dosage of 10 mg/kg. Only those substances which in this test (10 mg/kg) have shown a parasitaemia reduction of 90% are used for the titration.

48 hours after the treatment (D+3) blood smears are prepared from all animals using blood from tail veins and are stained with Giemsa. The average erythrocyte infection rate (parasitemia in %) in the control groups as well as in the groups which have been treated with the test compounds is determined by counting under a microscope. The difference in the average values of the infection rates of control group (100%) and treated groups is calculated and expressed as a percentage reduction (GI%). The ED50 or ED90 is determined mathematically by means of the JMP programme (nonlinear fit). The ED50 (ED90) in mg/kg is that dose which after single administration reduces the average erythrocyte infection rate by 50% (90%) in comparison to the control group.

Table 1 contains the IC50 values measured in vitro for the growth inhibition of chloroquine-sensitive and chloroquine-resistant strains of the human pathogenic Plasmodium falciparum.

Table 2 contains data with respect to the activity measured against Plasmodium berghei in mice: GI% is the percentage reduction in the parasitemia after a single dose of 10 mg/kg of

This Sheet Has Been Replaced



the test substance administered perorally (po) or subcutaneously (sc); ED50 and ED90 are the effective doses of the test substance administered perorally or subcutaneously.

This Sheet Has Been Replaced



Table 1

Example No.	Chloroquine-sensitive strain, IC50 (ng/ml)					Chloroquine-resistant strain, IC50 (ng/ml)						
	NF54	FCH5C2	HB3	RFMEF3	Ro7 3	RFCR3	ItG2 F6	Indo	K1	W2	7G8	W2 Mef
1	4	8	7	7	5	15	4	8	9	9	9	7
2	7	7	7	7	6	8	5	6	14	8	8	9
3	7	7	5	7	4	8	5	6	12	7	7	11
4	7	8	8	7	4	9	5	8	15	15	7	14
5	4	9	6			6	4	4	7	7	7	9
6	5	8	8			8	5	4	9	8	9	8
7	4	7	6			7	5	4	8	7	8	8
8	5	9	7	9	4	10	4	5	11	11	7	9
9	11	15	14	12	11	17	17	18	32	31	30	25
10	7	5	8	6	7	18	7	16	17	13	15	15
11	5	7	6	6	5	13	6	10	18	15	9	9
11a	7	7	6	7	4	18	8	15	15	17	14	15
12	6	9	7	8	7	15	8	12	10	15	15	9
12a	7	8	10	8	7	11	5	11	9	9	8	6
13	30	28	38	27	30	58	25	40	47	34	39	41
14	9	8	9	6	4	8	6	10	21	20	7	14
15	2	5	3			5	3	3	6	7	7	12
16	3	6	5			8	5	4	9	9	9	9
17	3	4	6	8	6	11	7	7	15	14	14	14
18	4	4	8	8	7	8	7	7	14	11	12	12
19	7	5	4	5	3	10	6	7	9	10	7	11
19a	6	7	6	7	5	11	5	8	9	10	8	6
20	3	7	4	4	7	14	7	8	10	11	15	14
21	21	35	33	35	28	54	28	31	34	57	49	
22	14	17	20	18	11	20	14	16	22	11	29	23
23	6	6	7	7	4	10	6	8	15	15	8	13
24	7	7	7	7	4	9	6	8	15	15	7	9
25	8	8	10	8	5	14	8	15	22	26	11	16
26	7	8	8	9	5	8	6	9	15	15	8	13
27	8	10	9	7	3	15	7	9	18	19	7	14
28	7	14	11	9	5	16	6	9	16	18	9	15
29	6	6	7	5	3	11	6	7	16	15	5	11
30	7	9	10	8	11	16	7	7	14	15	15	8
31	5	5	5	6	5	14	7	7	11	14	9	7
32	7	9	9	8	7	16	10	15	16	15	15	13
33	8	15	15	16	10	18	9	14	14	21	18	15
33a	7	8	7	7	5	9	5	9	8	9	9	7
33b	8	11	12	8	4	10	17	9	17	9	18	18
33c	8								24			
33d	8								23			
33e	12								53			
33f	12								41			
33g	5								17			
33h	7								18			
Chloroquine diphosphate	8	12	11	14	8	130	68	52	114	123	81	79

This Sheet Has Been Replaced

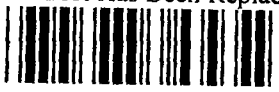
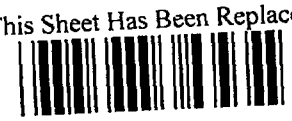


Table 2

Activity in vivo			
Example No.	GI % at 10 mg/kg po	GI % at 10 mg/kg sc	ED50 mg/kg po
1	99.9	99.9	2.3
2	99.8	99.9	3.2
5	99.5	99.0	3.3
6	99.0	99.0	3.5
9	99.0	99.6	4.4
10	99.0	99.0	6.4
11	99.9	99.9	2.2
11a	99.0	99.6	4.5
12a	91.0	91.0	4.8
15	99.8	99.9	2.0
16	99.9	99.9	2.0
17	95.0	99.0	4.6
18	83.0	96.0	6.9
19	99.0	99.6	5.3
19a	99.9	99.9	2.4
20	99.9	99.9	4.4
33	97.0	97.0	5.9
33a	99.7	99.9	3.3
33b	99.9	99.9	
33c	99.9	99.9	1.9
33d	99.9	99.9	2.2
33e	99.8	99.9	3.1
33f	99.8	99.9	2.8
Chloroquine diphosphate	99.9	99.9	2.4

This Sheet Has Been Replaced



In the following Examples, which illustrate the present invention, but which are not intended to limit its scope in any manner, all temperatures are given in degrees Celsius. The 250 Mz-1H-NMR spectra were taken at room temperature; chemical compounds δ (ppm) relative to δ (TMS) = 0.0 ppm.

Example 1

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine

5 g of 4,7-dichloroquinoline, 6.5 ml 1-N,N-dimethylamino-2-propylamine and 0.8 g of phenol are reacted at 140°C for 6 hours. After cooling 40 ml of water are added, the mixture is adjusted to pH 12 using concentrated sodium hydroxide solution and extracted three times with 150 ml of ethyl acetate each time. The residue remaining after evaporation of the solvent is recrystallized 1x from isopropanol and 1x from acetonitrile. 3.48 g of colourless crystals are obtained, m.p.: 168-170°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.29 (d, J = 7 Hz, 3H), 2.24 (s, 6H), 2.36 (dd, J = 6Hz and 12.5 Hz, 1H), 2.59 (dd, J = 9 Hz and 12.5 Hz, 1H), 3.62 (m, 1H), 5.90 (broad, 1H), 6.44 (d, J = 6 Hz, 1H), 7.34 (dd, J = 3 Hz and 9 Hz, 1H), 7.74 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The following compounds can be prepared in an analogous manner:

Example 2

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine

3.91 g of base from 5 g of 4,7-dichloroquinoline and 6.56 g of 1-N,N-diethylamino-2-propylamine; colourless crystals from acetonitrile, m.p.: 90-92°C.

This Sheet Has Been Replaced



^{1}H-NMR in $CDCl_3$, δ (ppm): 1.01 (t, J = 7 Hz, 6H), 1.30 (d, J = 6.5 Hz, 3H), 2.4 - 2.7 (m, 6H), 3.57 (m, 1H), 6.13 (br., 1H), 6.44 (d, J = 6 Hz, 1H), 7.36 (dd, J = 3 Hz and 9 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained by adding HCl to a solution in isopropanol; colourless crystals, m.p.: 268-270°C.

Example 3

(RS)-(7-Chloro-quinolin-4-yl)-(1-methyl-2-pyrrolidin-1-yl-ethyl)-amine

3.36 g of base from 3.18 g of 4,7-dichloroquinoline and 4.12 g of 2-(pyrrolidin-1-yl-propyl)-amine; colourless crystals from acetonitrile, m.p.: 160-163°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.32 (t, J = 7 Hz, 3H), 1.75 (m, 4H), 2.55 (m, 5H), 2.83 (dd, J = 9 Hz and J = 12 Hz, 1H), 3.67 (m, 1H), 5.92 (br., 1H), 6.44 (d, J = 6 Hz, 1H), 7.35 (dd, J = 3 Hz and 9 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained in the form of colourless crystals which decompose at 143° by the dropwise addition of a solution of the base in isopropanolic hydrochloric acid (0.35N) to a 4-fold volume of diethyl ether.

Example 4

(RS)-(7-Chloro-quinolin-4-yl)-(1-methyl-2-piperidin-1-yl-ethyl)-amine

3.62 g from 5.22 g of 4,7-dichloroquinoline and 7.5 g of 2-(piperidin-1-yl-propyl)-amine; colourless crystals from ethanol, m.p.: 168-171°C.

This Sheet Has Been Replaced



^{1}H-NMR in $CDCl_3$, δ (ppm): 1.30 (d, J = 6.5 Hz, 3H), 1.3-1.6 (m, 6H). 2.3-2.6 (m, 6H), 3.62 (m, 1H), 6.20 (broad, 1H), 6.44 (d, J = 6 Hz, 1H), 7.39 (dd, J = 3 Hz and 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 5

N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine

1.09 g from 5.9 g of 4,7-dichloroquinoline and 5.3 g of 2-dimethylamino-ethylamine; colourless crystals from ethyl acetate, m.p.: 122-124°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 2.30 (s, 6H), 2.68 (m, 2H), 3.28 (m, 2H), 5.91 (br.t, 1H), 6.37 (d, J = 5.5 Hz, 1H), 7.36 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.95 (d, J = 2.5 Hz, 1H), 8.53 (d, J = 5.5 Hz, 1H).

Example 6

N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine

From 4,7-dichloroquinoline and 2-(N,N-dimethylamino)-ethylamine; colourless crystals from isopropanol, m.p.: above 250°C.

^{1}H-NMR in DMSO-d_6/D_2O, δ (ppm): 1.28 (t, J = 7.5 Hz, 6H), 3.28 (q, J = 7.5 Hz, 4H), 3.49 (t, J = Hz, 2H), 4.00 (t, J = Hz, 2H), 7.06 (d, J = 7 Hz, 1H), 7.75 (dd, J = 2 Hz and 9 Hz, 1H), 8.02 (d, J = 2 Hz, 1H), 8.59 (d, J = 7 Hz, 1 H), 8.65 (d, J = 9 Hz, 1H).

This Sheet Has Been Replaced



Example 7

(7-Chloro-quinolin-4-yl)-(2-pyrrolidin-1-yl-ethyl)-amine

3.37 g of base from 3.96 g of 4,7-dichloroquinoline and 5 ml of 1-(2-aminoethyl)-pyrrolidine; prior to recrystallization the crude product is purified by filtration with ethyl acetate over 300 g of aluminium oxide (activity grade II). From 400 ml of eluate there are obtained yellowish crystals which, recrystallized from 95 ml of acetonitrile, give 3.37 g of colourless crystalline product, m.p.: 134-136°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.83 (m, 4H), 2.59 (m, 4H), 2.87 (dd, J = 6 Hz and 7 Hz, 2H), 3.33 (m, 2H), 5.92 (broad 1H), 6.38 (d, J = 6 Hz, 1H), 7.36 (dd, J = 3 Hz and 9 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained in the form of colourless crystals, m.p.: 212-213°C, by adding HCl to a solution of the base in isopropanol.

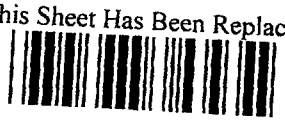
Example 8

(7-Chloro-quinolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine

3.57 g of base from 3.96 g of 4,7-dichloroquinoline and 4.8 g of 1-(2-aminoethyl)-piperidine (reaction duration, 5 hours at 140°C); yellowish crystals from acetonitrile, m.p.: 148-151°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.45-1.7 (m, 6H), 2.46 (m, 4H), 2.72 (t, J = 6 Hz, 2H), 3.29 (m, 2H), 6.12 (br., 1H), 6.36 (d, J = 6 Hz, 1H), 7.38 (dd, J = 2.5 Hz and 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.95 (d J = 2.5 Hz, 1H), 8.53 (d, J = 6 Hz).

This Sheet Has Been Replaced



Example 9

(1RS,2RS)-N_1-(7-Chloro-quinolin-4-yl)-N_2,N_2-diethyl-cyclohexane-1,2-diamine

11.3 g of base from 15.2 g of 4,7-dichloroquinoline and 13.4 g of 2-(diethylamino)-cyclohexylamine (reaction duration, 16 hours at 140°C); colourless crystals from acetonitrile, m.p.: 110-114°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 0.98 (t, J = 7 Hz, 6H), 1.1- 145 (m, 5H), 1.75-2.0 (m, 3H), 2.38 (m, 2H), 2.54 (m, 2H), 2.70 (m, 1H), 3.10 (m, 1H), 6.43 (d, J = 6 Hz, 1H), 6.55(br.s, 1H), 7.36 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained from isopropanolic hydrochloric acid; colourless crystals from acetonitrile, dec. at 198°C.

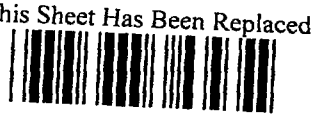
Example 10

(1RS,2RS)-(7-Chloro-quinolin-4-yl)-(2-pyrrolidin-1-yl-cyclohexyl)-amine

3.87 g from 3.6 g of 4,7-dichloroquinoline and 3.06 g of (2-pyrrolidin-1-yl-cyclohexyl)-amine (reaction duration 24 hours at 120°C); colourless crystals from acetonitrile/ethanol, m.p.: 228 - 231°C.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.25-2.0 (m, 12H), 2.22 (m,1H), 3.11 (m, 1H), 3.40 (m, 1H), 3.98 (m, 1H), 4.47 (m, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.75 (dd, J = 2.5 Hz and 9.5 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.64 (d, J = 7.5 Hz, 1 H), 8.98 (d, J = 9.5 Hz, 1H), 9.65 (d, J = 9.5 Hz, 1H), 10.15 (br.s, 1H). 14.63 (br.s, 1H).

This Sheet Has Been Replaced



Example 11

(1RS,2RS)-N_1-(7-Chloro-quinolin-4-yl)-N_2,N_2-diethyl-cyclopentane-1,2-diamine

8.16 g of base from 16 g of 4,7-dichloroquinoline and 12.7 g of 2-(diethylamino)cyclopentylamine (16 hours reaction duration at 140°C). With isopropanolic hydrochloric acid there are obtained therefrom 7.84 g of dihydrochloride; colourless crystals from acetonitrile/ethanol, m.p.: 186-190°C.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.45 (d, J = 6 Hz, 6H), 1.8-2.4 (m, 6H), 2.56 (m, 1H), 3.1-3.5 (m, 4H), 5.20 (m, 2H), 6.90 (d, J = 7.5 Hz, 1H), 7.45 (dd, J = 2.5 Hz and 9.5 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H), 8.24 (d, J = 7.5 Hz, 1 H), 9.41 (d, J = 9.5 Hz, 1H), 11.55 (br.s, 1H). 14.55 (br.s, 1H).

Example 11a

(1RS,2RS)-N1-(7-Chloro-quinolin-4-yl)-(2-pyrrolidin-1-yl-cyclopentyl)-amine

1.78 g of base from 3.56 g of 4,7-dichloroquinoline and 2.79 g of 2-(pyrrolidin-1-yl)-cyclopentylamine.

$C_{18}H_{22}ClN_3$ (315.85):

Calc.: C 68.45%, H 7.02%, Cl 11.22%, N 13.30%

Found: C 68.32%, H 7.00%, Cl 11.36%, N 13.11%

With isopropanolic hydrochloric acid there are obtained therefrom 1.64 g of dihydrochloride; colourless crystals from acetonitrile/ethanol, m.p.: 173°C (dec.).

1H-NMR in DMSO-d6, δ (ppm): 1.7-2.0 (m, 8H), 2.3-2.4 (m, 2H), 3.09 (m, 2H), 3.53 (m, 2H), 4.40 (m, 1H), 4.79 (m, 1H), 7.01 (d, 1 H, J = 7 Hz), 7.79 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.11 (d, J = 2.5 Hz,

This Sheet Has Been Replaced

This Sheet Has Been Replaced



1H), 8.66 (d, J = 7 Hz, 1 H), 9.04 (d, J = 9Hz, 1H), 9.86 (d, J = 7.5 Hz, 1H), 11.75 (br.s, 1H). 14.55 (br.s, 1H).

Example 12

(7-Chloro-quinolin-4-yl)-(1-ethyl-pyrrolidin-2-yl-methyl)-amine

9.64 g of base from 8.5 g of 4,7-dichloroquinoline and 11 g of 2-(aminomethyl)-1-ethyl-pyrrolidine. Prior to recrystallization the crude reaction product is purified by chromatography on 400 g of aluminium oxide (activity grade II); a 1:1 mixture of ethyl acetate and hexane is used as the eluent. After a fore-run of 400 ml the product is eluted with 1.5 l of eluent and gives, after recrystallization from 120 ml of hexane, 9.64 g of colourless crystals; m.p.: 85-86°C.

12 g of colourless crystalline dihydrochloride, m.p. 239-240°C, are obtained by dissolution in 15 ml of isopropanol, addition of 20 ml of 3.6N isopropanolic hydrochloric acid and dropwise addition to 100 ml of diethyl ether.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.28 (t, J = 7.5 Hz, 3H), 1.95 (m, 3H), 2.27 (m,1H), 3.16 (m, 2H), 3.48 (m, 2H), 3.88 (m, 1H), 4.14 (m, 2H), 7.09 (d, J = 8 Hz, 1H), 7.78 (dd, J = 3 Hz and 9 Hz, 1H), 8.24 (d, J = 3 Hz, 1H), 8.69 (d, J = 8 Hz, 1 H), 8.94 (d, J = 9 Hz, 1H), 10.08 (t, J = 6 Hz, 1H), 11.20 (br.s, 1H). 14.80 (br.s, 1H).

Example 12a

(7-Chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine

Analogously to Example 12 there are obtained 60 mg of base from 2.91 g of 4,7-dichloroquinoline and 1.68 g of 2-(amino-methyl)-1-methyl-pyrrolidine; colourless crystals from hexane, m.p.: 114-116°C.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.5 1.7 (m, 3H), 1.80-2.0 (m, 1H), 2.17 (m,1H), 2.35 (s, 3H), 2.55-2.60 (m, 1H), 2.98 (m, 1H),

3.14 (m, 1H), 3.40 (m, 1H), 6.50 (d, J = 5 Hz, 1H), 7.21 (t, J= 6 Hz, 1H), 7.45 (dd, J = 2.5 Hz und 9.5 Hz, 1H), 7.79 (d, J = 2.5 Hz, 1H), 8.24 (d, J = 5 Hz, 1 H), 8.40 (d, J = 9.5 Hz, 1H).

Example 13

(7-Chloro-quinolin-4-yl)-(1,1-dimethyl-2-pyrrolidin-1-yl-ethyl)-amine

4.95 g of 4,7-dichloroquinoline, 7.1 g of 2-methyl-2-(pyrrolidin-1-yl)-propylamine and 5 g of phenol are reacted at 140°C for 16 hours. After cooling the melt 25 ml of water are added, the mixture is adjusted to pH 1 with a small amount of concentrated hydrochloric acid and extracted three times with 50 ml of ethyl acetate each time. Thereafter, concentrated sodium hydroxide solution is added to pH 12 and the product is extracted three times with 100 ml of ethyl acetate each time. The crude product obtained after evaporation of the solvent is purified by chromatography on 400 g of aluminium oxide (activity grade II) with a mixture of ethyl acetate and hexane (1:4). 2.37 g of colourless crystals, m.p.: 89-91°C, are obtained after recrystallization from hexane.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.48 (s, 6H), 1.86 (m, 4H), 2.71(s, 2H), 2.75 (m, 4H), 6.60 (d, J = 6 Hz, 1H), 6.84 (br., 1H), 7.33 (dd, J = 3 Hz and 9 Hz, 1H), 7.62 (d, J = 9 Hz, 1H), 7.91 (d, J = 3 Hz, 1 H), 8.45 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained by adding 3.3N HCl in dioxan to a solution of the base in anhydrous dioxan; colourless crystals, m.p.: 249-252°C.

This Sheet Has Been Replaced



Example 14

(7-Chloro-quinolin-4-yl)-(1,1-dimethyl-2-piperidin-1-yl-ethyl)-amine

4.57 g of 4,7-dichloroquinoline, 7.5 g of 2-methyl-2-(piperidin-1-yl)-propylamine and 0.75 g of phenol are reacted at 180°C for 16 hours. The crude reaction product, isolated as in the foregoing Example, is purified on 200 g of aluminium oxide (activity grade II) prior to recrystallization; a 1:1 mixture of toluene and acetone is used as the eluent. After a fore-run, which contains unreacted 4,7-dichloroquinoline, the product is eluted and, after recrystallization from 5 ml of acetonitrile, gives 0.8 g of colourless crystals, m.p.: 143-147°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.46 (s, 6H), 1.50 (m, 2H), 1.65 (m, 4H), 2.51 (s, 2H), 2.65 (m, 4H), 6.62 (d, J = 6 Hz, 1H), 6.83 (br.s, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.93 (d, J = 3 Hz, 1 H), 8.46 (d, J = 6 Hz, 1H).

Example 15

N_3-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine

From 4,7-dichloroquinoline and 3-(N,N-dimethylamino)-propylamine; colourless crystals from ethyl acetate-hexane, m.p.: 111-113°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.86 (quintet, J = 6 Hz, 2H), 2.37 (s, 6H), 2.58 (m, 2H), 3.39 (m, 2H), 6.31 (d, J = 5.5 Hz, 1H), 7.32 (dd, J = 2 Hz and 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.92 (d, J = 2 Hz, 1H), 7.94 (br. s, 1H). 8.48 (d, J = 5.5 Hz).

This Sheet Has Been Replaced



Example 16

N_3-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine

2.99 g of base from 3.96 g of 4,7-dichloroquinoline and 5.2 g of 3-(N,N-diethylamino)-propylamine (reaction duration 4 hours at 140°C); colourless crystals from acetonitrile, m.p.: 77-78°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.10 (t, J = 7 Hz, 6H), 1.92 (quintet, J = 6 Hz, 2H), 2.65 (m, 6H), 3.38 (m, 2H), 6.29 (d, J = 5.5 Hz, 1H), 7.32 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.92 (d J = 2.5 Hz, 1H), 8.18 (br. s, 1H). 8.50 (d, J = 5.5 Hz).

The dihydrochloride is obtained with isopropanolic hydrochloric acid; colourless crystals from isopropanol, dec. from 118°C,

Example 17

(7-Chloro-quinolin-4-yl)-(3-pyrrolidin-1-yl-propyl)-amine

3.08 g from 7.72 g of 4,7-dichloroquinoline and 5 g of 3-(pyrrolidin-1-yl)-propylamine (reaction duration 16 hours at 140°C); the base is converted with isopropanolic hydrochloric acid into the dihydrochloride which, recrystallized from acetonitrile/ethanol, gives colourless crystals, m.p.: 204-206°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.96 (m, 4H), 2.14 (m, 2H), 3.00 (m, 2H), 3.26 (m, 2H), 3.51 (m, 2H), 3.67 (m, 2H), 6.96 (d, J = 7 Hz, 1H), 7.78 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.13 (d, J = 2.5 Hz, 1H), 8.59 (d, J = 7 Hz, 1 H), 8.81 (d, J = 9 Hz, 1H), 9.86 (d, J = 6 Hz, 1H), 11.13 (br.s, 1H). 14.55 (br.s, 1H).

This Sheet Has Been Replaced



Example 18

(7-Chloro-quinolin-4-yl)-(3-piperidin-1-yl-propyl)-amine

2.73 g from 2.83 g of 3-(piperidin-1-yl)-propylamine and 3.94 g of 4,7-dichloroquinoline (reaction duration, 16 hours at 140°C); the base (yellowish crystals from acetonitrile, m.p.: 113-116°C) is converted with isopropanolic hydrochloric acid into the dihydrochloride which, recrystallized from acetonitrile/ethanol, gives colourless crystals, m.p.: 137-141°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.28 (m, 1H), 1.54-1.76 (m, 5H), 2.08 (m, 2H), 2.78 (m, 2H), 3.07 (m, 2H), 3.27 - 3.38 (m, 2H), 3.53 (m, 2H), 6.21 (d, J = 7 Hz, 1H), 7.55 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 8.43 (d, J = 7 Hz, 1 H), 8.73 (d, J = 9 Hz, 1H), 9.88 (d, J = 6 Hz, 1H), 10.67 (br.s, 1H). 14.63 (br.s, 1H).

Example 19

(1-Benzyl-piperidin-4-yl)-(7-chloro-quinolin-4-yl)-amine

5.65 g from 10 g of 4,7-dichloroquinoline and 10.26 ml of 4-amino-1-benzylpiperidine; colourless crystals from acetonitrile, m.p.: 166-168°C. The dihydrochloride, colourless crystals from acetonitrile/ethanol, m.p. above 25°C, is obtained therefrom using isopropanolic hydrochloric acid.

^{1}H-NMR in DMSO-d_6; δ (ppm): 2.1-2.4 (m, 4H), 3.04 (m, 2H), 3.44 (m, 2H), 4.08 (br.s, 1H), 4.30 (s, 2H), 7.04 (d, J = 7.5 Hz, 1H), 7.48 (m, 3H), 7.67 (m, 2H), 7.78 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.61 (d, J = 7.5 Hz, 1 H), 8.81 (d, J = 9.5 Hz, 1H), 9.30 (d, J = 7.5 Hz, 1H), 11.50 (br.s, 1H). 14.55 (br.s, 1H).

This Sheet Has Been Replaced



Example 19a

(RS)-(7-Chloro-quinolin-4-yl)-(1-methyl-piperidin-3-yl)-amine

4 g from 11.29 g of 4,7-dichloroquinoline and 6.5 g of 3-amino-1-methyl-piperidine; colourless crystals from acetonitrile, m.p.: 149-150°C.

$C_{15}H_{18}ClN_3$ (275.78):

Calc.: C 65.33%, H 6.58%, Cl 12.86%, N 15.24%

Found: C 65.25%, H 6.64%, Cl 12.87%, N 15.11%

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.3-1.95 (multiple m, 6H), 2.02 (s, 3H), 2.67 (m, 1H), 2.92 (m, 1H), 3.67 (m, 1H), 6.54 (d, J = 6 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 7.44 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 9 Hz, 1 H), 8.39 (d, J = 6 Hz, 1H).

Example 20

(5-Amino-2,2,4-trimethyl-cyclopentylmethyl)-(7-chloro-quinolin-4-yl)-amine

480 mg as a mixture of isomers from 3.1 g of 4-bromo-7-chloroquinoline and 11 ml of 2-(aminomethyl)-3,3,5-trimethyl-cyclopentylamine; colourless crystals from isopropanolic hydrochloric acid, m.p. above 250°C. The ^{1}H-NMR (250 Mz) shows the presence of a mixture of two main components and two secondary components.

$C_{18}H_{24}N_3Cl \cdot 2HCl \cdot 0{\cdot}5\ H_2O$:

Calculated: C: 54.08%, H: 6.81%, N: 10.51%, Cl: 26.60%

Found: C: 54.24%, H: 6.82%, N: 10.76%, Cl: 26.71%

This Sheet Has Been Replaced



Example 21

N_1,N_1-Diethyl-N_2-(7-trifluoromethyl-quinolin-4-yl)-ethane-1,2-diamine

5 g of 4-chloro-7-(trifluoromethyl)-quinoline and 10 g of 2-N,N-diethylamino-ethylamine in 150 ml of dimethylacetamide are stirred at 120°C for 16 hours. After cooling the mixture is concentrated in a water-jet vacuum and the residue is taken up with 150 ml of water and a small amount of hydrochloric acid such that the pH amounts to 4.8. After three-fold extraction with 100 ml of ethyl acetate each time the mixture is adjusted to pH 10.2 by means of 1N sodium hydroxide solution and the basic product is extracted with 3 x 100 ml of ethyl acetate. After evaporation of the solvent the product is recrystallized from acetonitrile and there are obtained 1.96 g of colourless crystals, m.p.: 122-124°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.08 (t, J = 7 Hz, 6H), 2.61 (q, J = 7 Hz, 4 H), 2.83 (t, J = 6 Hz, 2H), 3.27 (m, 2H), 6.23 (m, 1H), 6.45 (d, J = 6 Hz, 1H), 7.60 (dd, J = 3 Hz and 9 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 8.26 (m, 1H), 8.61 (d, J = 6 Hz, 1H).

In an analogous manner there was prepared:

Example 22

N_1,N_1-Dimethyl-N_2-(7-trifluoromethyl-quinolin-4-yl)-ethane-1,2-diamine

From 4-chloro-7-(trifluoromethyl)-quinoline and 2-N,N-dimethylamino-ethylamine; colourless crystals from hexane, m.p.: 110-113°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 2.31 (s, 6H), 2.69 (m, 2H), 3.29 (m, 2H), 6.05 (m, 1H), 6.44 (d, J = 6 Hz, 1H), 7.51 (dd, J = 3 Hz and 9 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 8.26 (m, 1H), 8.61 (d, J = 6 Hz, 1H).

This Sheet Has Been Replaced



Example 23

(RS)-(7-Chloro-quinolin-4-yl)-[2-(3-methyl-piperidin-1-yl)-ethyl]-amine

2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride in 25 ml of 3-methylpiperidine are held at 100°C in a sealed tube for 24 hours. Thereafter, 100 ml of water are added, the mixture is adjusted to pH 12 by means of concentrated sodium hydroxide solution and extracted three times with 50 ml of ethyl acetate each time. The combined extracts are washed with a small amount of water and concentrated. The residue is recrystallized from 80 ml of acetone. 0.88 g of colourless crystals, m.p.: 148-151°C, is obtained.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.90 (d, J = 6 Hz, 3H), 0.98 (m, 1H), 1.6-1.75 (m, 5H), 2.04 (dt, J = 3.5 Hz and 7 Hz, 1H), 2.75 (m, 2H), 2.84 (m,2H), 3.31 (m, 2H), 6.20 (broad, 1H), 6.37 (d, J = 6 Hz, 1H), 7.38 (dd, J = 3 Hz and 9 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.96 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The following compounds can be prepared in an analogous manner using suitable amines:

Example 24

(7-Chloro-quinolin-4-yl)-[2-(4-methyl-piperidin-1-yl)-ethyl]-amine

2.72 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 154-156°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.96 (d, J = 6 Hz, 3H), 1.28 (m, 2H), 1.43 (m, 1H), 1.68 (m, 1H), 2.06 (m, 2H), 2.73 (m, 2H), 2.90 (m,2H), 3.29 (m, 2H), 6.10 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.36

This Sheet Has Been Replaced

(dd, J = 3 Hz and 9 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

Example 25

(7-Chloro-quinolin-4-yl)-[2-(3,3-dimethyl-piperidin-1-yl)-ethyl]-amine

2.1 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolin-amine hydrochloride; colourless crystals from acetonitrile, m.p.: 151-153°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.98 (s, 6H), 1.29 (m, 2H), 1.66 (m, 1H), 2.12 (m, 2H), 2.45 (m, 2H), 2.69 (t, J = 6 Hz, 2H), 3.28 (m, 2H), 6.20 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.96 (d, J = 3 Hz, 1H), 8.52 (d, J = 6 Hz, 1H).

Example 26

(RS)-(7-Chloro-quinolin-4-yl)-[2-(2-methyl-piperidin-1-yl)-ethyl]-amine

1.4 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolin-amine hydrochloride; colourless crystals from acetonitrile, m.p.: 133-134°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.12 (d, J = 6.5 Hz,6H), 1.30-1.75 (m, 6H), 2.17 (dt, J = 4 Hz and 10 Hz, 2H), 2.45-2.55 (m, 2H), 2.86 (tm, 1H), 3.1-3.3 (m, 3H), 6.13 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.38 (dd, J = 3 Hz and 9 Hz, 1H), 7.67 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

This Sheet Has Been Replaced



Example 27

(RS)-(7-Chloro-quinolin-4-yl)-[2-(2-ethyl-piperidin-1-yl)-ethyl]-amine

1.52 g from N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 115-117°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.93 (t, J = 7.5Hz, 3H), 1.3-1.75 (m, 8H), 2.21 (m, 2H), 2.39 (m, 2H), 2.57 (m, 1H), 2.85 (m, 1H), 3.16 (m, 1H), 3.26 (m, 2H), 5.17 (broad 1H), 6.36 (d, J = 6 Hz, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.65 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

Example 28

(2R,6S)-(7-Chloro-quinolin-4-yl)-[2-(2,6-dimethyl-piperidin-1-yl)-ethyl]-amine

0.4 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 138-139°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.14 (d, J = 6.5 Hz, 6H), 1.2-1.7 (m, 6H), 2.57 (m, 2H), 2.94 (t, J = 7 Hz, 2H), 3.31 (m, 2H), 5.85 (broad, 1H), 6.38 (d, J = 6 Hz, 1H), 7.37 (dd, J = 2.5 Hz and 9.5 Hz, 1H), 7.70 (d, J = 9.5 Hz, 1H), 7.95 (d, J = 2.5 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 29

(7-Chloro-quinolin-4-yl)-[2-(3,5-dimethyl-piperidin-1-yl)-ethyl]-amine

0.67 g (isomer mixture cis:trans = 3:1) from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 142-143°C.

This Sheet Has Been Replaced



^{1}H-NMR in $CDCl_3$; δ (ppm): 0.88 and 1.00(d, J = 6.5 Hz, 6H; ratio 3:1), 1.3-2.0 (several m, 4H), 2.2-2.84 (several m, 6H), 3.29 (m, 2H), 6.12 and 6.20 (broad, 1H; ratio 3:1), 6.37 (d, J = 6 Hz, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.66 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 30

(7-Chloro-quinolin-4-yl)-[2-(2,5-dimethyl-pyrrolidin-1-yl)-ethyl]-amine

0.35 g (isomer mixture cis:trans = 15:1) from 1.3 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; yellowish crystals from acetone, m.p.: 127-130°C.

^{1}H-NMR in DMSO-D_6; δ (ppm): 0.94 and 1.06(d, J = 6.5 Hz, 6H; ratio 15:1), 1.29 (m, 2H), 1.80 (m, 2H), 2.67 (m, 2H), 2.79 (m, 2H), 3.34 (m, 2H),), 6.47 (d, J = 6 Hz, 1H), 7.05 (br.t, 1H), 7.46 (dd, J = 3 Hz and 9 Hz, 1H), 7.78 (d, J = 3 Hz, 1H), 8.19 (d, J = 9 Hz, 1 H), 8.40 (d, J = 6 Hz, 1H).

Example 31

(7-Chloro-quinolin-4-yl)-[2-octahydro-indol-1-yl)-ethyl]-amine

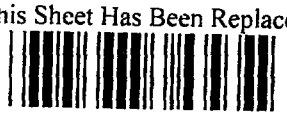
0.3 g from 2.2 g of N-(2-chloroethyl)-7-chloro-4-quinolin-amine hydrochloride; colourless crystals from ethyl acetate, m.p.: 115-117°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.1 - 2.0 (m, 11H), 2.15 - 2.45 (m, 2H), 2.95 (m, 1H), 3.18 (m, 1H), 3.36 (m, 4H), 6.48 (d, J = 6 Hz, 1H), 7.22 (t, J = 6 Hz, 1H), 7.45 (dd, J = 3 Hz and 9 Hz, 1H), 7.91 (d, J = 3 Hz, 1H), 8.19 (d, J = 9 Hz, 1 H), 8.40 (d, J = 6 Hz, 1H).

This Sheet Has Been Replaced



This Sheet Has Been Replaced



Example 32

2-(3-Azabicyclo[3.2.2]nonan-3-yl)-ethyl]-(7-chloro-quinolin-4-yl)-amine

0.45 g from 1.48 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; yellowish crystals from ethanol, m.p.: 205 - 207°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.60-1.82 (m, 8H), 1.95 (br.s, 2H), 2.66 (d, J = 4.5 Hz, 4H), 2.81 (m, 2H), 3.27 (m, 2H), 6.30 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.39 (dd, J = 3 Hz and 9 Hz, 1H), 7.69 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 33

N_1-Allyl-N_2-(7-chloro-quinolin-4-yl)-N_1-methyl-ethane-1,2-diamine

0.56 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 91-93°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 2.24 (s,3H),), 2.62 (t, J = 7 Hz, 2H), 3.04 (d, J = 7 Hz, 2H), 3.37 (m, 2H), 5.1-5.2 (m, 2H), 5.84 (m, 1H), 6.49 (d, J = 6 Hz, 1H), 7.21 (t, J = 6 Hz, 1H), 7.45 (dd, J = 3 Hz and 9 Hz, 1H), 7.78 (d, J = 3 Hz, 1H), 8.22 (d, J = 9 Hz, 1 H), 8.40 (d, J = 6 Hz, 1H).

Example 33a

(R,S)-(7-Chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-3-yl)-amine

0.42 g of (R,S)-(7-chloro-quinolin-4-yl)-(pyrrolidin-3-yl)-amine dihydrobromide is boiled under reflux overnight in 2 ml of formic acid and 2 ml of 37% formalin solution. Thereafter, 10 ml of water are added, the mixture is adjusted to pH 2 with conc. hydrochloric acid and extracted three times with 20 ml of

ethyl acetate each time. Thereafter, the aqueous phase is adjusted to pH 12 by the addition of conc. sodium hydroxide solution and extracted three times with 20 ml of ethyl acetate each time. After evaporation of the solvent the residue is recrystallized from tert.-butyl methyl ether and acetone and there are obtained 20 mg of colourless crystals, m.p.: 150-152°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.75-2 (m, 1H), 2.29 (s,3H), 2.3-2.8 (multiple m, 5H), 4.13 (m, 1H), 6.47 (d, J = 6 Hz, 1H), 7.29 (d, J = 6.5 Hz, 1H), 7.45 (dd, J = 3 Hz and 9 Hz, 1H), 7.78 (d, J = 3 Hz, 1H), 8.39 (d, J = 6 Hz, 1 H), 8.40 (d, J = 9 Hz, 1H).

Example 33b

N_1-(7-Chloro-quinolin-4-yl)-2,N_2,N_2-trimethyl-propane-1,2-diamine

30 g of N_1-(7-chloro-quinolin-4-yl)-2-methyl-propane-1,2-diamine are boiled under reflux for 3 hours in 21.6 ml of aqueous formaldehyde solution (37%) and 45.3 ml of formic acid. Thereafter, the mixture is evaporated to dryness in a vacuum and the residue is taken up in 100 ml of water and adjusted to pH 12 using conc. potassium hydroxide solution. The precipitated product is recrystallized from 250 ml of acetonitrile and gives 25.1 g, m.p.: 114-116°C.

$C_{11}H_{20}ClN_3$ (277.80):

Calc.: C 64.85%, H 7.26%, Cl 12.76%, N 15.13%

Found: C 64.64%, H 7.18%, Cl 12.79%, N 15.07%

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.09 (s, 6H), 2.22 (s, 6H), 3.18 (d, J = 5.5 Hz, 2H), 6.46 (t, J = 5.5 Hz, 1H), 6.51 (d, J = 6 Hz, 1H), 7.48 (dd, J = 2 Hz and 9.5 Hz, 1H), 7.82 (d, J = 2.5 Hz, 1H), 8.07 (d, J = 9.5 Hz, 1 H), 8.42 (d, J = 6 Hz, 1H).

This Sheet Has Been Replaced



Example 33c

(S)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine

19 g of (S)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride are dissolved in 190 ml of dimethylamine solution (33% in ethanol) and held at 110°C in an autoclave for 15 hrs. After cooling and evaporation the residue is dissolved in 200 ml of dichloromethane and extracted with 200 ml of 1N NaOH. The basic aqueous phase is back-extracted with 200 ml of dichloromethane. The dichloromethane phases are dried and evaporated. The crude product is chromatographed on neutral aluminium oxide (act. II) in hexane/ethyl acetate 2:1, then in ethyl acetate alone. The resulting oil is triturated with 100 ml of diethyl ether and, after crystallization has taken place, diluted with 50 ml of hexane. There are obtained 13.5 g (79%) of white crystals; m.p. 110°C, $[\alpha]_D = +115°$ (c = 1.0, MeOH).

For the preparation of the dihydrochloride, 19.8 g of free base are dissolved in 200 ml of acetone, cooled in ice and then treated with 75 ml of 2N HCl and stirred for 10 min. After evaporation the residue is treated with 200 ml of toluene and again evaporated. The resulting oil is dissolved in 200 ml of ethanol while warming, filtered and, after crystallization has taken place, diluted with 50 ml of diethyl ether. There are obtained 23.7 g (94%) of white crystals; m.p.: >260°C, $[\alpha]_D = +136.5°$ (c = 1.0, MeOH).

^{1}H-NMR (250 MHz) in d_6-DMSO, signals at δ (ppm): 1.31 (d, J = 6.3, 3H), 2.81 (s, 6H), 3.39 (dd, 1H), 4.00 (dd, 1H), 4.73 (m, 1H), 7.08 (d, J = 7, 1H), 7.75 (dd, J_1 = 9, J_2 = 2, 1H), 8.15 (d, J = 2, 1H), 8.65 (d, J = 7, 1H), 9.06 (d, J = 9, 1H), 9.67 (d, J = 9, 1H), 10.5 (br, 1H), 15.0 (br, 1H)

This Sheet Has Been Replaced



Example 33d

(R)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine

Analogously to Example 33c, starting from (R)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride there is prepared (R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine hydrochloride; white crystals; m.p.: >260°C, $[\alpha]_D$ = -132° (c = 1.0, MeOH).

Example 33e

(S)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine

15 g of (S)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride are dissolved in 100 ml of methanol and 50 ml of diethylamine and held at 125°C in an autoclave for 15 hrs. After cooling and evaporation the residue is dissolved in 200 ml of dichloromethane and extracted with 200 ml of 1N NaOH. The basic aqueous phase is back-extracted with 200 ml of dichloromethane. The dichloromethane phases are dried and evaporated. The crude product is chromatographed on neutral aluminium oxide (act. II) in hexane/ethyl acetate 2:1. The resulting oil is dissolved in 40 ml of diethyl ether and diluted slowly with 200 ml of hexane. There are obtained 10.3 g (69%) of white crystals; m.p.: 89°C, $[\alpha]_D$ = +122.6° (c = 1.0, MeOH).

For the preparation of the dihydrochloride, 18.1 g of free base are dissolved in 190 ml of acetone, cooled in ice and then treated with 62.5 ml of 2N HCl and stirred for 10 min. After evaporation the residue is treated with 200 ml of toluene and again evaporated. The resulting oil is dissolved in 200 ml of ethanol while warming, filtered, concentrated to 100 ml and, for crystallization, diluted with 2 x 50 ml of diethyl ether. There are obtained 21.8 g (96%) of white crystals; m.p.: 165-170°C, $[\alpha]_D$ = +150.6° (c = 1.0, MeOH).

This Sheet Has Been Replaced



^{1}H-NMR (250 MHz) in d$_6$-DMSO, signals at δ (ppm): 1.26 (t, J = 7, 6H), 1.36 (d, J = 6.3, 3H), 3.17 (q, J = 7, 4H), 3.35 (dd, 1H), 4.01 (dd, 1H), 4.72 (m, 1H), 7.10 (d, J = 7, 1H), 7.75 (dd, J_1 = 9, J_2 = 2, 1H), 8.17 (d, J = 2, 1H), 8.65 (d, J = 7, 1H), 9.08 (d, J = 9, 1H), 9.81 (d, J = 9, 1H), 10.5 (br, 1H), 15.0 (br, 1H)

Example 33f

(R)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine

Analogously to Example 33e, starting from (R)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride there is prepared (R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine hydrochloride; white crystals, mp.: 165-170°C, $[\alpha]_D$ = -140.3° (c = 1.0, MeOH).

Example 33g

2.2 g of (S)-N_2,N_2-dimethyl-1,2-propanediamine and 2 g of 4,7-dichloroquinoline in 4 ml of 1-methyl-2-pyrrolidone are held at 150°C in an autoclave for 6.5 hrs. After cooling the reaction mixture is poured into 20 ml of 3N HCl and extracted with 4 x 20 ml of dichloromethane. The acidic-aqueous phase is made basic with 28% NaOH and then extracted with 3 x 20 ml of dichloromethane. The crude product is chromatographed on neutral aluminium oxide (act. II) in hexane/ethyl acetate 10:3. 1.25 g of yellow oil are obtained. This is dissolved in 10 ml of ethanol and converted into the dihydrochloride with ethanolic HCl solution. There are obtained 450 mg of white crystals; m.p.: 165°C, $[\alpha]_D$ = +15.1° (c = 1.0, MeOH).

^{1}H-NMR (250 MHz) in d$_6$-DMSO, signals at δ (ppm): 1.34 (d ,J = 6.1, 3H), 2.79 (s, 6H), 3.80 (m, 2H), 4.01 (m, 1H), 7.16 (d, J = 7, 1H), 7.78 (dd, J_1 = 9, J_2 = 2, 1H), 8.17 (d, J = 2, 1H), 8.65 (d, J = 7, 1H), 8.93 (d, J = 9, 1H), 9.92 (br, 1H), 11.1 (br, 1H), 15.0 (br, 1H)

This Sheet Has Been Replaced



This Sheet Has Been Replaced



Example 33h

(R)-N_1-(7-Chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine

Analogously to Example 33g, starting from (R)-N_2,N_2-dimethyl-1,2-propanediamine hydrochloride there is prepared (R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine hydrochloride; white crystals, m.p.: 250°C, $[\alpha]_D$ = -9.4° (c = 1.0, MeOH).

$C_{14}H_{19}Cl_3N_3$ (336.69):

Calc.: C 49.94%, H 5.99%, Cl 31.59%, N 12.48%

Found: C 49.69%, H 6.18%, Cl 31.85%, N 12.28%

Preparation of intermediates

Example 34

(7-Chloro-quinolin-4-yl)-(2-chloro-ethyl)-amine

20 ml of thionyl chloride are slowly added dropwise while stirring to a suspension of 12.3 g of 2-(7-chloro-quinolin-4-amino)-ethanol [prepared according to R.C.Elderfield et al., J.Am.Chem.Soc. 68, 1250 (1946)] in such a manner that the temperature can be held at about 30°C without external cooling. The mixture is stirred at RT for one hour and thereafter evaporated to dryness. The residue is crystallized from 120 ml of glacial acetic acid. There are obtained colourless crystals which, after suspension in 250 ml of toluene, are dried at 50°C under a water-jet vacuum. 9.75 g of colourless crystalline product, m.p. 239-240°C, are obtained.

^{1}H-NMR in $CDCl_3$; δ (ppm): 3.97 (s, 4H), 7.02 (d, J = 8 Hz, 1H), 7.80 (dd, J = 3 Hz and 9 Hz, 1H), 8.14 (d, J = 3 Hz, 1H), 8.60 (d, J = 8 Hz, 1 H), 8.75 (d, J = 9 Hz, 1H), 9.85 (br.s, 1H), 14.63 (br.s, 1H).

Example 35

4-Bromo-7-chloro-quinoline

83.9 g of 7-chloro-4-hydroxyquinoline are added portion-wise at 60° to 150 g of phosphorus oxybromide and the mixture is thereafter heated to 140°C for 6 hours. After cooling the mixture is treated with 3 l of ice-water and extracted with 2 x 1.5 l of dichloromethane. After evaporation of the solvent and crystallization from 1.3 l of hexane 34 g of product are obtained as colourless crystals, m.p.: 102-103°C.

Example 36

1-Methyl-2-pyrrolidin-1-yl-ethylamine

15 ml of aqueous formaldehyde solution (37%) are added dropwise at 5°C within one hour to 16.5 ml of pyrrolidine. Thereafter, 57.2 ml of nitroethane are added and the mixture is stirred at RT overnight. 150 ml of ethyl acetate and 400 ml of saturated sodium chloride solution are added, the organic phase is separated and is distilled in a water-jet vacuum. The product, 1-(2-nitropropyl)-pyrrolidine (18.5 g), passes over at 85-87°C.

13.1 g of this intermediate are then hydrogenated in 100 ml of methanol under 100 bar and at 80°C after the addition of 0.65 g of Raney-nickel. The product, 1-methyl-2-pyrrolidin-1-yl-ethylamine, is obtained by distillation at 49-52°C in a water-jet vacuum (4.7 g; colourless liquid).

The following diamines can be prepared in an analogous manner using the corresponding amines:

1-Methyl-2-piperidin-1-yl-ethylamine;
N,N-diethyl-propane-1,2-diamine;
N,N-dimethyl-propane-1,2-diamine.

This Sheet Has Been Replaced



Example 37

N,N-Diethyl-cyclohexane-1,2-diamine

30 g of cyclohexene oxide are reacted with 44.8 g of diethylamine and 32.6 g of lithium perchlorate in 300 ml of acetonitrile overnight while stirring and under reflux. Thereafter, 200 ml of water are added and the product is extracted with 3 x 150 ml of ethyl acetate. After evaporation of the solvent 30.4 g of 2-(diethylamino)-cyclohexanol remain behind. This is dissolved in 150 ml of tetrahydrofuran without further purification. After the addition of 38.6 g of phthalimide and 68.7 g of triphenylphosphine 45.9 g of diethyl azodicarboxylate are added dropwise at a temperature of 10-15°C and the mixture is stirred at RT overnight. Thereafter, the mixture is evaporated, the residue is suspended in dilute hydrochloric acid (200 ml, pH 1) and washed with 3 x 150 ml of ethyl acetate. The pH is then adjusted to 12-13 by adding concentrated sodium hydroxide solution and the intermediate is extracted using 3 x 200 ml of ethyl acetate. After evaporation of the solvent N,N-diethyl-2-phthalimido-cyclohexylamine (36.8 g) remains behind in the form of yellow crystals.

These are saponified overnight in 250 ml of concentrated hydrochloric acid under reflux. After three-fold washing using 200 ml of dichloromethane each time the pH is adjusted to 13-14 by adding concentrated sodium hydroxide solution and the product is extracted using 3 x 200 ml of ethyl acetate and, after evaporation of the solvent, is obtained as a yellowish oil (13.4 g) which is processed without further purification.

2-Pyrrolidin-1-yl-cyclohexylamine is prepared in an analogous manner using pyrrolidine in place of diethylamine.

In an analogous manner, from cyclopentene oxide and diethylamine there is obtained N,N-diethyl-cyclopentane-1,2-diamine and from cyclopentene oxide and pyrrolidine there is obtained 2-pyrrolidin-1-yl-cyclopentylamine.

This Sheet Has Been Replaced



This Sheet Has Been Replaced



Example 38

1,1-Dimethyl-2-pyrrolidin-1-yl-ethylamine

18 ml of 2-nitropropane and 16.5 ml of pyrrolidine are dissolved in 60 ml of dioxan. 15 ml of aqueous formaldehyde solution (37%) and 8 ml of 2% sodium hydroxide solution are added at 5°C. The mixture is heated to 90°C while stirring for 1 hour, cooled and thereafter extracted with 3 x 150 ml of ethyl acetate. Upon distillation in a water-jet vacuum there are obtained 19 g of 1-(2-nitro-2-methylpropyl)-pyrrolidine.

This intermediate is then hydrogenated in 100 ml of methanol under 100 bar and at 80°C after the addition of 1.5 g of Raney-nickel. The product, 1,1-dimethyl-2-pyrrolidin-1-yl-ethylamine, is obtained by distillation in a water-jet vacuum at 52-57°C (13.1 g; colourless liquid).

1,1-Dimethyl-2-piperidin-1-yl-ethylamine can be prepared in an analogous manner using piperidine in place of pyrrolidine.

Example 39

3-Piperidin-1-yl-propylamine

3.7 g of piperidine and 2.3 g of acrylonitrile are pooled and heated to 100°C for 3 hours. After cooling the mixture is taken up in 40 ml of isopropanol and the 3-(1-piperidino)-propionitrile is precipitated using 12.8 ml of 3.6N isopropanolic hydrochloric acid (colourless crystals, m.p. 186-190°C, 6.68 g).

This intermediate is hydrogenated in 31 ml of 25% HCl and 31 ml of glacial acetic acid in the presence of 0.13 g of platinum dioxide at RT under 10 bar. After evaporation of the hydrogenation solution the residue is taken up in 50 ml of water, adjusted to pH 13 using concentrated sodium hydroxide solution and extracted with 3 x 150 ml of ethyl acetate. 3-Piperidin-1-

This Sheet Has Been Replaced

yl-propylamine is obtained as a colourless oil, b.p. 45-50°C/0.1 mm Hg, by distillation.

Example 40

(R,S)-(7-Chloro-quinolin-4-yl)-(pyrrolidin-3-yl)-amine

9.85 g of 3-aminopyrrolidine are benzoylated with 16 g of benzoyl chloride at 0°C in 90 ml of dichloromethane, 17.7 ml of N,N-dimethylformamide and 25.5 ml of triethylamine. After warming to room temperature the mixture is filtered and the filtrate is evaporated to dryness. The residue is taken up in 100 ml of water (pH 8), filtered and again evaporated to dryness. The residue is digested in succession with in each case 90 ml of toluene, ethyl acetate and dichloromethane, the solution being decanted off each time from initially oily, but later crystalline, residue. The organic solutions are combined and evaporated. The dark coloured oil obtained (2.7 g) is then reacted at 140°C overnight with 2.1 g of 4,7-dichloroquinoline and 2.1 g of phenol. The reaction mixture is taken up with 50 ml of water, adjusted to pH 2 by the addition of conc. hydrochloric acid and extracted three times with 50 ml of ethyl acetate each time. Thereafter, the aqueous phase is adjusted to pH 12 using conc. sodium hydroxide solution and extracted three times with 50 ml of ethyl acetate each time. After evaporation of the solvent the residue is crystallized from 10 ml of ethyl acetate/toluene. The resulting product (0.6 g) is then saponified to (R,S)-(7-chloro-quinolin-4-yl)-(pyrrolidin-3-yl)-amine dihydrobromide by boiling in 10 ml of 48% HBr for 12 hours.

Example 41

N_1-(7-Chloro-quinolin-4-yl)-2-methyl-propane-1,2-diamine

52.8 g of 4,7-dichloroquinoline and 30.85 g of 1,2-diamino-2-methylpropane are stirred in 530 ml of N-methyl-2-pyrrolidone under argon at 150°C for 5 hours. Thereafter, the

solvent is evaporated in a vacuum and the residue is taken up in 1250 ml of water. After adjustment to pH 1 using conc. hydrochloric acid the mixture is extracted once with 200 ml of ethyl acetate and twice with 100 ml of ethyl acetate each time and subsequently treated with about 170 ml of 30% potassium hydroxide solution until the pH has reached 12. Thereby, 88 g of N_1-(7-chloro-quinolin-4-yl)-2-methyl-propane-1,2-diamine separate in crystalline form; m.p.: 169-171°C.

Example 42

(S)-2-Amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane

23 g of L-alaninol and 57.4 g of 4,7-dichloroquinoline in 100 ml of 1-methyl-2-pyrrolidone are held at 150°C for 6 hrs. After cooling the reaction mixture is poured into 500 ml of cold 2N HCl and extracted with 3 x 200 ml of dichloromethane. The acidic-aqueous phase is made basic with 28% NaOH, whereby the crude product precipitates. After stirring in an ice bath for 30 min. it is filtered off and then recrystallized from 300 ml of 2-propanol/150 ml of ethanol. There are obtained 51.2 g (74%) of (S)-2-amino-N-(7-chloro-quinolin-4-yl)-1-propanol; white crystals, m.p.: 225°C, $[\alpha]_D = +35^o$ (c = 1.0, MeOH).

^{1}H-NMR (250 MHz) in d6-DMSO, signals at δ (ppm): 1.24 (d, J = 6.4, 3H), 3.45 (m, 1H), 3.58 (m, 1H), 3.73 (m, 1H), 4.87 (t, J = 5.6, 1H), 6.53 (d, J = 7, 1H), 6.84 (d, J = 7.7, 1H), 7.44 (dd, J_1 = 9, J_2 = 2, 1H), 7.78 (d, J = 2, 1H), 8.35 (d, J = 7, 1H), 8.39 (d, J = 9, 1H)

27.3 g of (S)-2-amino-N-(7-chloro-quinolin-4-yl)-1-propanol are suspended in 270 ml of chloroform. Then, a solution of 72 ml of thionyl chloride in 70 ml of chloroform are added dropwise over 30 min. while cooling with ice, whereby the temperature should not exceed 25°C. Subsequently, the mixture is stirred at room temperature for a further 30 min. and at 70°C for 90 min. The reaction mixture is cooled and evaporated, then treated with toluene and again evaporated. The resulting foam is dissolved in 500 ml of ethanol while warming, filtered and

This Sheet Has Been Replaced



concentrated to about 300 ml, whereupon crystallization occurs. There are obtained 31.6 g (94%) of (S)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride as white crystals; m.p.: 210°C, $[\alpha]_D$ = +90° (c = 1.0, MeOH).

The R enantiomer, (R)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane, can be obtained as the hydrochloride starting from D-alaninol; white crystals, m.p.: 210°C, $[\alpha]_D$ = -88° (c = 1.0, MeOH).

1H-NMR (250 MHz) in d6-DMSO, signals at d (ppm): 1.41 (d, J = 6.5, 3H), 3.88-4.06 (m, 2H); 4.48 (m, 1H), 7.03 (d, J = 7.3, 1H), 7.79 (dd, J_1 = 9, J_2 = 2, 1H), 8.15 (d, J = 2, 1H) 8.59 (d, J = 7.3, 1H), 8.89 (d, J = 9, 1H), 9.44 (d, J = 8.4, 1H), 14.66 (s, 1H)

Example 43

(S)-N_2,N_2-Dimethyl-1,2-propanediamine

7.6 g of L-alaninol are stirred at 90°C for 14 hrs. in 20 ml of formic acid and 20 ml of 37% formaldehyde solution. After cooling the reaction mixture is poured on to 100 g of ice and 60 ml of 28% NaOH and extracted with 3 x 100 ml of dichloro-methane. After drying and evaporating the dichloromethane phases the crude produce is distilled at normal pressure. There are obtained 7.8 g of (S)-2-dimethylamino-1-propanol as a colourless oil; b.p. 147°C, $[\alpha]_D$ = +2.7° (c = 1.0, MeOH).

7.3 g of (S)-2-dimethylamino-1-propanol, 37 g of triphenylphospine and 20.8 g of phthalimide are suspended in 70 ml of tetrahydrofuran under argon and cooled in an ice bath. Then, 24 ml of diethyl azodicarboxylate are added dropwise over 30 min. and the mixture is stirred at room temperature for a further 5 hrs. Then, the mixture is poured into 200 ml of ice-cold 1N HCl and extracted with 3 x 200 ml of ethyl acetate. The acidic-aqueous phase is made basic with 28% NaOH and then extracted with 3 x 200 ml of dichloromethane. After drying and evaporating the dichloromethane phases the 12 g of crude

This Sheet Has Been Replaced



product (GC 78% + 16% regioisomer) are chromatographed on silica gel in ethyl acetate. There are obtained 6 g of yellow oil which solidifies (regioisomer not separated). This 6 g of product are boiled at reflux in 50 ml of conc. HCl for 20 hrs. After cooling the precipitated phthalic acid is filtered off. The filtrate is washed with 2 x 50 ml of dichloromethane and then made basic cautiously with solid KOH while cooling in an ice bath and finally extracted with 3 x 80 ml of dichloromethane. After drying and evaporating the dichloromethane phases the crude product is distilled at normal pressure. There are obtained 1.2 g of (S)-N_2,N_2-dimethyl-1,2-propanediamine as a colourless oil; b.p.: 127°C.

^{1}H-NMR (250MHz) in $CDCl_3$, signals at d (ppm): 0.89 (d, J = 6.4, 3H), 1.37 (s, 2H), 2.22 (s, 6H), 2.48 - 2.67 (m, 3H)

The R enantiomer, (R)-N_2,N_2-dimethyl-1,2-propanediamine, can be prepared in an analogous manner starting from D-alaninol.

Example A

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine can be formulated as the active ingredient according to methods known per se to give pharmaceutical preparations of the following composition:

1. 500 mg tablets	
Active ingredient	500 mg
Powd. lactose.	149 mg
Polyvinylpyrrolidone	15 mg
Dioctyl sodium sulphosuccinate	1 mg
Na carboxymethylstarch	30 mg
Magnesium stearate	5 mg
	700 mg

This Sheet Has Been Replaced



2. 50 mg tablets	
Active ingredient	50 mg
Powd. lactose	50 mg
Microcrystalline cellulose	82 mg
Na carboxymethylstarch	15 mg
	200 mg
3. 100 mg capsules	
Active ingredient	100.0 mg
Powd lactose	104.7 mg
Corn starch	70.0 mg
Hydroxypropylmethylcellulose	10.0 mg
Dioctyl sodium sulphosuccinate	0.3 mg
Talc	12.0 mg
Magnesium stearate	3.0 mg
	300.0 mg
4. 500 mg suppositories	
Active ingredient	500 mg
Suppository mass	ad 2000 mg
5. 100 mg soft gelatine capsules	
Active ingredient	100 mg
Medium chain triglyceride	300 mg
	400 mg

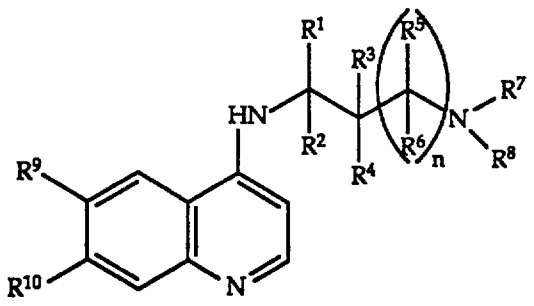
This Sheet Has Been Replaced



This Sheet Has Been Replaced

Claims

1. The use of aminoquinoline derivatives of the general formula



I

wherein the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, octahydroindole or 3-azabicyclo[3,2,2]nonane and n = 0 or 1 or

wherein the symbols R^1 and R^3 signify tri- or tetramethylene, all remaining symbols to R^6 signify hydrogen, n = 0 and R^7 and R^8 have the above significances or

wherein the symbols R^1 and R^7 signify methylene or dimethylene and n = 1,
R^1 and R^7 signify di- or trimethylene and n = 0,
R^3 and R^7 signify di- or trimethylene and n = 1
R^3 and R^7 signify tri- or tetramethylene and n = 0
R^5 and R^7 signify tri- or tetramethylene and n = 1
R^1 and R^5 signify di- or tri-methylene and n = 1, all remaining substituents signify hydrogen, except R^8 which signifies alkyl, alkenyl or alkynyl or

wherein the symbols R^3 and R^5 signify tri- or tetramethylene and n = 1, all remaining substituents to R^6 signify hydrogen and R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl,

* C L M S *

This Sheet Has Been Replaced

R^9 signifies hydrogen or halogen and R^{10} signifies halogen or trifluoromethyl,

as well as pharmaceutically acceptable salts of basic compounds of general formula I for the manufacture of medicaments for the control of not only chloroquine-resistant malaria pathogens, but also chloroquine-sensitive malaria pathogens.

2. The use of compounds of formula I according to claim 1 in which the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, and n = 0 or 1.

3. The use of (S)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine according to claim 2.

4. The use of (R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine according to claim 2.

5. The use of N_1-(7-chloro-quinolin-4-yl)-2,N_2,N_2-trimethyl-propane-1,2-diamine according to claim 2.

6. The use of N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine according to claim 2.

7. The use of (RS)-(7-chloro-quinoline-4-yl)-(1-methyl-piperidine-3-yl)amine according to claim 2.

8. The use of (RS)-(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-3-yl)-amine according to claim 2.

9. The use of (RS)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

(RS)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

This Sheet Has Been Replaced

(S)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-2-pyrrolidin-1-yl-ethyl)-amine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

(R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine,

(S)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine and

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine

according to claim 2.

10. Compounds of general formula I defined in claim 1, except

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine,

(7-chloro-quinolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine,

(7-chloro-quinolin-4-yl)-[(1-ethyl-pyrrolidin-2-yl)-methyl]-amine,

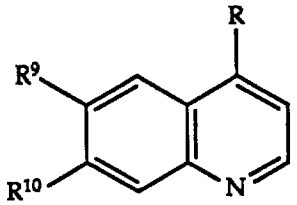
(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine,

(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-2-yl-methyl)-amine and

(7-chloro-quinolin-4-yl)-(1-ethyl-piperidin-3-yl)-amine.

11. A process for the manufacture of compounds according to claim 10, which process comprises

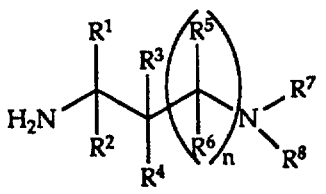
a) reacting quinoline derivatives of the general formula



II

wherein R^9 and R^{10} have the significances given in claim 1 and R signifies a leaving group,

with amino compounds of the general formula



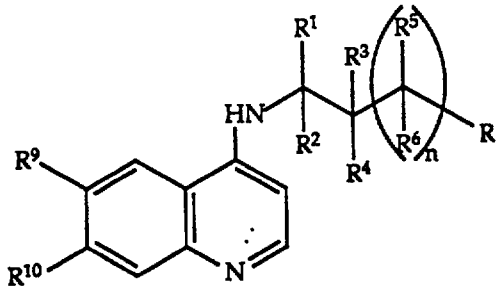
III

This Sheet Has Been Replaced

wherein the substituents R^1 to R^8 have the significances given in claim 1,

or

b) reacting alkylamino-quinoline derivatives of the general formula



IV

wherein R^1 to R^6 and R^9 and R^{10} have the significances given in claim 1 and R signifies a leaving group,

with amines of the formula

$$HNR^7R^8 \qquad V$$

wherein R^7 and R^8 have the significances given in claim 1,

or

c) reacting compounds of formula I in which R^1 to R^6 as well as R^9 and R^{10} have the significances given in claim 1 and R^7 and R^8 signify hydrogen or one of them signifies hydrogen and the other signifies an alkyl group with alkylating agents which are suitable for the alkylation of amino groups,

and

d) if desired, converting a basic compound of formula I into a pharmaceutically usable salt by means of an acid.

12. Compounds according to claim 10 for use as therapeutically active substances.

13. Compounds according to claim 10 for use as active substances against not only chloroquine-resistant malaria pathogens, but also chloroquine-sensitive malaria pathogens.

* C L M S *

This Sheet Has Been Replaced

14. The use of compounds according to claim 10 in the control of diseases or in the improvement of health.

15. A medicament containing one or more compounds according to claim 10 and a therapeutically inert excipient.

16. A medicament according to claim 15 for the treatment or prevention of malaria.

17. Compounds in accordance with claim 10 whenever prepared according to the process as claimed in claim 11 or by an obvious chemical equivalent thereof.

18. The invention as hereinbefore described.

19. A method of treating or preventing malaria, caused not only by chloroquine-sensitive but also by chloroquine-resistant malaria pathogens, which comprises administering to a patient requiring such treatment or prevention an effective amount of a compound in accordance with formula I of claim 1.

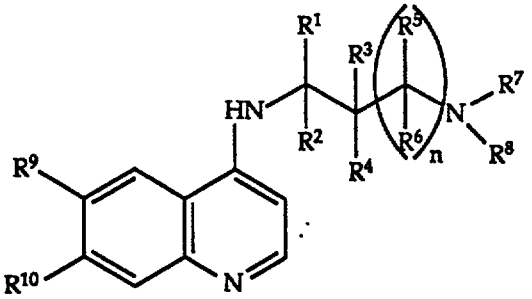
***

* C L M S *

This Sheet Has Been Replaced

Abstract

The invention is concerned with aminoquinoline derivatives of the general formula



I

wherein the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, octahydroindole or 3-azabicyclo[3,2,2]nonane and n = 0 or 1 or

wherein the symbols R^1 and R^3 signify tri- or tetramethylene, all remaining symbols to R^6 signify hydrogen, n = 0 and R^7 and R^8 have the above significances or

wherein the symbols R^1 and R^7 signify methylene or dimethylene and n = 1,
R^1 and R^7 signify di- or trimethylene and n = 0,
R^3 and R^7 signify di- or trimethylene and n = 1
R^3 and R^7 signify tri- or tetramethylene and n = 0
R^5 and R^7 signify tri- or tetramethylene and n = 1
R^1 and R^5 signify di- or tri-methylene and n = 1, all remaining substituents signify hydrogen, except R^8 which signifies alkyl, alkenyl or alkynyl or

wherein the symbols R^3 and R^5 signify tri- or tetramethylene and n = 1, all remaining substituents to R^6 signify hydrogen and R^7 and R^8 signify alkyl, alkenyl or

aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl,
R^9 signifies hydrogen or halogen and R^{10} signifies halogen or trifluoromethyl,

as well as pharmaceutically acceptable salts of basic compounds of general formula I for the manufacture of medicaments for the control of not only chloroquine-resistant malaria pathogens, but also of chloroquine-sensitive malaria pathogens.

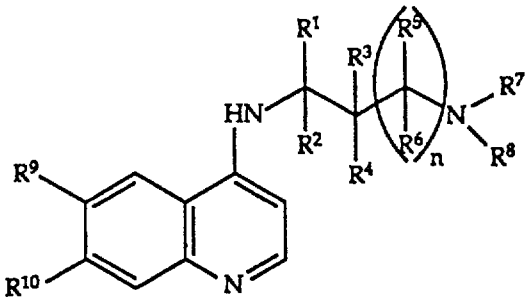
This Sheet Has Been Replaced



960563-5 SB03

AMINOQUINOLINE DERIVATIVES FOR USE AGAINST CHLOROQUINE-RESISTANT AND CHLOROQUINE-SENSITIVE MALARIA PATHOGENS

The invention is concerned with aminoquinoline derivatives of the general formula



I

wherein the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, octahydroindole or 3-azabicyclo[3,2,2]nonane and n = 0 or 1 or

wherein the symbols R^1 and R^3 signify tri- or tetramethylene, all remaining symbols to R^6 signify hydrogen, n = 0 and R^7 and R^8 have the above significances or

wherein the symbols R^1 and R^7 signify methylene or dimethylene and n = 1,
R^1 and R^7 signify di- or trimethylene and n = 0,
R^3 and R^7 signify di- or trimethylene and n = 1
R^3 and R^7 signify tri- or tetramethylene and n = 0
R^5 and R^7 signify tri- or tetramethylene and n = 1
R^1 and R^5 signify di- or tri-methylene and n = 1, all remaining substituents signify hydrogen, except R^8 which signifies alkyl, alkenyl or alkynyl or

wherein the symbols R^3 and R^5 signify tri- or tetramethylene and n = 1, all remaining substituents to R^6 signify hydrogen and R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl,

This is the replacement sheet

Date: 31 OCT 1996

R^9 signifies hydrogen or halogen and R^{10} signifies halogen or trifluoromethyl,

as well as pharmaceutically acceptable salts of basic compounds of general formula I.

These compounds are novel with the exception of

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propan-1,3-diamine,

(7-chloro-quinolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine,

(7-chloro-quinolin-4-yl)-[(1-ethyl-pyrrolidin-2-yl)-methyl]-amine,

(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine,

(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-2-yl-methyl)-amine and

(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-3-yl)-amine,

and they have the surprising property that they have an equally good effect not only against chloroquine-sensitive malaria pathogens, but also against chloroquine-resistant malaria pathogens, that is to say, they exhibit no cross-resistance with chloroquine.

This is the replacement sheet
Date: 31 OCT 1996

Not only the absence of cross-resistance, but also the good activity, which is to some extent better compared with chloroquine, were surprising. Hitherto it had been assumed that cross-resistance exists between chloroquine-like compounds. Only certain bis-quinolines, which contain two quinoline rings and which bear little structural relationship to chloroquine, have a definite activity against chloroquine-resistant malaria pathogens, especially the compounds which have been described by J.L.Vennerstrom (J. L. Vennerstrom et al, J.Med.Chem., ***35***, 2129-2134 (1992). Further, it had hitherto been assumed that chloroquine analogues having shortened or lengthened side-chains were less active against malaria pathogens compared with chloroquine (R.L.O'Brien and F.E.Hahn, Chloroquin Structural Requirements for Binding to Deoxyribonucleic Acid and Antimalarial Activity, Antimicrob. Agents Chemother, **1965**, 315 - 320).

Simple analogues of chloroquine have therefore hitherto been considered to be uninteresting and not suitable for the treatment for malaria. In contrast to this assumption, it has now been found that the compounds of formula I are outstandingly suitable for the prophylaxis of malaria and for its treatment, especially in cases where the pathogens are resistant to chloroquine.

Objects of the present invention are the use of compounds of formula I and of pharmaceutically usable salts thereof in the control or prevention of diseases, especially in the control of chloroquine-resistant and of chloroquine-sensitive malaria pathogens, the novel compounds and salts of formula I per se and for use as therapeutically active substances, the manufacture of the novel compounds and salts as well as medicaments containing a novel compound or a salt and the manufacture of such medicaments.

The term "alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl,

t-butyl and the like. Halogen signifies chlorine, bromine, fluorine or iodine.

Compounds in which the symbols R^1 to R^6 signify hydrogen and one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, and n = 0 or 1 are especially preferred.

Particularly preferred compounds of general formula I are:

(S)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

(R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

N_1-(7-chloro-quinolin-4-yl)-2,N_2,N_2-trimethyl-propane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine,

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-3-yl)-amine and

(RS)-(7-choro-quinolin-4-yl)-(1-methyl-pyrrolidin-3-yl)-amine.

Also preferred are:

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

(RS)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

This is the replacement sheet

Date: 31 OCT 1996

(S)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(RS)-7-chloro-quinolin-4-yl)-(1-methyl-2-pyrrolidin-1-yl-ethyl)-amine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

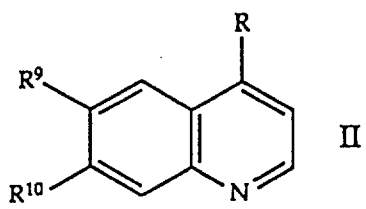
(R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine,

(S)-N_1-(7-chloro-quinoline-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine and

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine.

The novel compounds of formula I can be manufactured in accordance with the invention by

a) reacting quinoline derivatives of the general formula

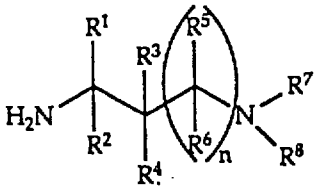


II

This is the replacement sheet
Date: 31 OCT 1996

wherein R^9 and R^{10} have the above significances and R signifies a leaving group,

with amino compounds of the general formula

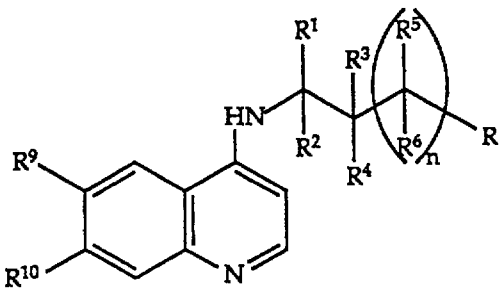


III

wherein the substituents R^1 to R^8 have the above significances,

or

b) reacting alkylamino-quinoline derivatives of the general formula



IV

wherein R^1 to R^6 and R^9 and R^{10} have the above significances and R signifies a leaving group,

with amines of the formula

$$HNR^7R^8 \qquad V$$

wherein R^7 and R^8 have the above significances,

or

c) reacting compounds of formula I in which R^1 to R^6 as well as R^9 and R^{10} have the above significance and R^7 and R^8 signify hydrogen or one of them signifies hydrogen and the other signifies an alkyl group with alkylating agents which are suitable for the alkylation of amino groups,

and

d) if desired, converting a basic compound of formula I into a pharmaceutically usable salt by means of an acid.

According to variant a) of the process in accordance with the invention correspondingly substituted quinoline derivatives which contain a leaving group in the 4-position are reacted with amino compounds of general formula III, the substituents having the significances given above and R signifying a leaving group.

Leaving groups are conveniently halogen, O-methylsulphonyl or O-toluenesulphonyl groups. The reaction is conveniently effected in a temperature range between 120 and 180°C and in a solvent, with phenol, ethoxyethanol, dimethylacetamide or N-methylpyrrolidine being especially preferred. The reaction time can vary between 2 and 28 hours.

A further possibility for the manufacture of the compounds of general formula I comprises using process variant b).

Conveniently, the compounds of formula IV in which R signifies a leaving group and all other substituents correspond to the significances given above is reacted in the form of the hydrochloride of the correspondingly substituted alkylamino-quinoline derivative with an aliphatic or cyclic amine of formula V in a sealed tube, whereby the amine can simultaneously serve as the solvent. The reaction can take up to 24 h. The preferred temperature range embraces temperatures between 90 and 110°C. This reaction can also be effected in solvents in which both reaction partners are soluble, for example in DMF, DMA, N-methylpyrrolidone or acetonitrile. The conversion into a pharmaceutically usable salt is effected by adding an acid. HCl is especially preferred because of the physiological compatibility of the hydrochloride. Convenient solvents which are especially suitable are: isopropanol, diethyl ether or dioxan.

Alkylating agents which are suitable for process variant c) are, for example, formaldehyde in combination with formic acid, in which case the reaction is preferably carried out in excess

This is the replacement sheet

Date:

formic acid. Other alkylating agents which come into consideration are combinations of aliphatic or aromatic aldehydes with complex hydrides such as sodium borohydride or sodium cyanoborohydride. Such reactions can be conveniently carried out in alcoholic or aqueous solutions.

The quinoline derivatives of general formula II required for synthesis variant a) are commercial products or can be prepared according to methods known per se, for example 7-chloro-4-hydroxyquinoline can be converted with phosphorus oxybromide into 7-chloro-4-bromo-quinoline.

The aliphatic or cyclic amines of general formula III are also to some extent commercial products or can be prepared according to methods known per se. Conveniently, the starting point can be a cyclic amine, for example pyrrolidine or piperidine, or an aliphatic amine, e.g. dimethylamine or diethylamine, which can be reacted with nitroethane or 2-nitropropane. The resulting nitro compound can subsequently be reduced according to methods known per se, e.g. by hydrogenation with Raney-nickel, to the compounds of general formula III.

A further possibility for the preparation of the compounds of general formula III comprises converting cycloalkane oxides with diethylamine and perchlorates into 2-(diethylamio)-cyclo-alkanols. These are conveniently dissolved, without further purification, in THF and treated with phthalimide and triphenyl-phosphine and subsequently stirred at room temperature for several hours. After purification the resulting N,N-diethyl-2-phthalimido-cycloalkylamine is saponified with concentrated hydrochloric acid.

In analogy thereto, in place of diethylamine and other aliphatic amines there can also be used, for example, cyclic amines such as pyrrolidine. When cyclic amines, for example piperidine, are reacted with acrylonitrile there is obtained the corresponding propionitrile which can be hydrogenated to the

This is the replacement sheet
31 OCT 1996
Date:

corresponding propylamine in the presence of platinum dioxide at RT under 10 bar.

The corresponding alkylamino-quinoline derivative of general formula IV in which the leaving group signifies a halogen group, preferably chlorine, required as the starting material for synthesis variant b) can conveniently be prepared as follows:

A suspension of the corresponding quinolinamino-ethanol, which can be prepared according to a synthesis of R.C. Elderfield, J. Am. Chem. Soc. 68, 1250 (1946), is treated with thionyl chloride, whereby the reaction temperature should not exceed 30°C. Subsequently, the mixture is stirred at RT for 1 h., evaporated to dryness and purified.

As mentioned earlier, the aminoquinoline derivatives of general formula I and their pharmaceutically usable salts have extremely valuable pharmacological properties.

Their activity against not only chloroquine-resistant, but also chloroquine-sensitive malaria pathogens will be evident from the following Tables:

Test method for the determination of the activity against P. falciparum in vitro

The preparations are tested on intraerythrocytary stages of P. falciparum from asynchronous cultures according to the method of Desjardin et al. (Desjardins, R.E. et al: Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique. Antimicrob. Agents Chemother. 16, 710-718, (1979)).

The culture medium consists of RPMI 1640 with the addition of 25 mM HEPES, 25 mM $NaHCO_3$, 100 µg/ml neomycin and 10% human serum (A^+). Human-A^+ erythrocytes are used as the P. falciparum host cells. The parasites are maintained at

31 OCT 1996

37°C in an atmosphere of 3% O_2, 4% CO_2, 93% N_2 and at 95% relative humidity.

In order to determine the activity, the preparations are dissolved in DMSO, pre-diluted in the culture medium to a suitable starting concentration and subsequently titrated-out into microtitre plates in the 2nd stage over 6-7 steps. After the addition of the parasite culture (0.7% parasitemia in 2.5% erythrocyte suspension) the test plates are incubated under the conditions given above for 48 h - 72 h. The parasite growth in the different preparation concentrations is determined using [G-^{3}H]-hypoxanthin incorporation compared to untreated control cultures on the same test plates. The 50% growth inhibition (IC50) is calculated according to logit regression analysis from the resulting dosage-activity curve.

The preparations are tested on at least one chloroquine-resistant and one chloroquine-sensitive P. falciparum strain. Additional sensitive and resistant strains are included for futher characterization.

Test method for the determination of the activity against Plasmodium berghei in vivo

The preparations are tested on mice infected with malaria pathogens (Plasmodium berghei). Male albino mice (IBM:MORO(SPF), FUELLINSDORF) weighing about 25 g are used as the test animals. They are kept in climatized rooms at 21-22°C in groups of 5 animals per cage. They receive ad libitum a diet feed with a low PABA content (NAFAG FUTTER © No. 9009 PAB-45, PABA content 45 mg/kg) and drinking water. On the first day of the test (D0) the test animals are infected with Plasmodium berghei (strain ANKA). For this there is used heparinized blood of a donor mouse with about 30% parasitemia, which is diluted with physiological saline such that it contains 10^8 parasitized erythrocytes per ml. 0.2 ml of this suspension is injected intravenously (i.v.) into the mice to be treated and into the control mice. In untreated control animals the parasitemia

This is the replacement sheet

Date:

normally reaches 30-40% on the third day after the infection (D+3) and the test animals die between days +5 and +7.

The substances to be tested are dissolved or suspended in distilled water or in a mixture of 7% Tween 80, 3% alcohol (96%) and water. Usually, 0.25 ml of this solution or suspension is administered once subcutaneously and perorally to groups of 5 test animals. Treatment is effected 24 hours after the infection. 10 control animals are treated in the same manner with solvent or suspension medium per test.

All substances are tested in a first test in a single dosage of 10 mg/kg. Only those substances which in this test (10 mg/kg) have shown a parasitaemia reduction of 90% are used for the titration.

48 hours after the treatment (D+3) blood smears are prepared from all animals using blood from tail veins and are stained with Giemsa. The average erythrocyte infection rate (parasitemia in %) in the control groups as well as in the groups which have been treated with the test compounds is determined by counting under a microscope. The difference in the average values of the infection rates of control group (100%) and treated groups is calculated and expressed as a percentage reduction (GI%). The ED50 or ED90 is determined mathematically by means of the JMP programme (nonlinear fit). The ED50 (ED90) in mg/kg is that dose which after single administration reduces the average erythrocyte infection rate by 50% (90%) in comparison to the control group.

Table 1 contains the IC50 values measured in vitro for the growth inhibition of chloroquine-sensitive and chloroquine-resistant strains of the human pathogenic Plasmodium falciparum.

Table 2 contains data with respect to the activity measured against Plasmodium berghei in mice: GI% is the percentage reduction in the parasitemia after a single dose of 10 mg/kg of

This is the replacement sheet
31 OCT 1996
Date:

the test substance administered perorally (po) or subcutaneously (sc); ED50 and ED90 are the effective doses of the test substance administered perorally or subcutaneously.

31 OCT 1995

Table 1

Example No.	Chloroquine-sensitive strain, IC50 (ng/ml)					Chloroquine-resistant strain, IC50 (ng/ml)						
	NF54	FCHSC2	HB3	RFMEF3	Ro7 3	RFCR3	ItG2 F6	Indo	K1	W2	7G8	W2 Mef
1	4	8	7	7	5	15	4	8	9	9	9	7
2	7	7	7	7	6	8	5	6	14	8	8	9
3	7	7	5	7	4	8	5	6	12	7	7	11
4	7	8	8	7	4	9	5	8	15	15	7	14
5	4	9	6			6	4	4	7	7	7	9
6	5	8	8			8	5	4	9	8	9	8
7	4	7	6			7	5	4	8	7	8	8
8	5	9	7	9	4	10	4	5	11	11	7	9
9	11	15	14	12	11	17	17	18	32	31	30	25
10	7	5	8	6	7	18	7	16	17	13	15	15
11	5	7	6	6	5	13	6	10	18	15	9	9
11a	7	7	6	7	4	18	8	15	15	17	14	15
12	6	9	7	8	7	15	8	12	10	15	15	9
12a	7	8	10	8	7	11	5	11	9	9	8	6
13	30	28	38	27	30	58	25	40	47	34	39	41
14	9	8	9	6	4	8	6	10	21	20	7	14
15	2	5	3			5	3	3	6	7	7	12
16	3	6	5			8	5	4	9	9	9	9
17	3	4	6	8	6	11	7	7	15	14	14	14
18	4	4	8	8	7	8	7	7	14	11	12	12
19	7	5	4	5	3	10	6	7	9	10	7	11
19a	6	7	6	7	5	11	5	8	9	10	8	6
20	3	7	4	4	7	14	7	8	10	11	15	14
21	21	35	33	35	28	54	28	31	34	57	49	
22	14	17	20	18	11	20	14	16	22	11	29	23
23	6	6	7	7	4	10	6	8	15	15	8	13
24	7	7	7	7	4	9	6	8	15	15	7	9
25	8	8	10	8	5	14	8	15	22	26	11	16
26	7	8	8	9	5	8	6	9	15	15	8	13
27	8	10	9	7	3	15	7	9	18	19	7	14
28	7	14	11	9	5	16	6	9	16	18	9	15
29	6	6	7	5	3	11	6	7	16	15	5	11
30	7	9	10	8	11	16	7	7	14	15	15	8
31	5	5	5	6	5	14	7	7	11	14	9	7
32	7	9	9	8	7	16	10	15	16	15	15	13
33	8	15	15	16	10	18	9	14	14	21	18	15
33a	7	8	7	7	5	9	5	9	8	9	9	7
33b	8	11	12	8	4	10	17	9	17	9	18	18
33c	8								24			
33d	8								23			
33e	12								53			
33f	12								41			
33g	5								17			
33h	7								18			
Chloroquine diphosphate	8	12	11	14	8	130	68	52	114	123	81	79

This is the replacement sheet

Date:

Table 2

Activity in vivo			
Example No.	GI % at 10 mg/kg po	GI % at 10 mg/kg sc	ED50 mg/kg po
1	99.9	99.9	2.3
2	99.8	99.9	3.2
5	99.5	99.0	3.3
6	99.0	99.0	3.5
9	99.0	99.6	4.4
10	99.0	99.0	6.4
11	99.9	99.9	2.2
11a	99.0	99.6	4.5
12a	91.0	91.0	4.8
15	99.8	99.9	2.0
16	99.9	99.9	2.0
17	95.0	99.0	4.6
18	83.0	96.0	6.9
19	99.0	99.6	5.3
19a	99.9	99.9	2.4
20	99.9	99.9	4.4
33	97.0	97.0	5.9
33a	99.7	99.9	3.3
33b	99.9	99.9	
33c	99.9	99.9	1.9
33d	99.9	99.9	2.2
33e	99.8	99.9	3.1
33f	99.8	99.9	2.8
Chloroquine diphosphate	99.9	99.9	2.4

This is the replacement sheet

Date: 31 OCT 1996

In the following Examples, which illustrate the present invention, but which are not intended to limit its scope in any manner, all temperatures are given in degrees Celsius. The 250 Mz-1H-NMR spectra were taken at room temperature; chemical compounds δ (ppm) relative to δ (TMS) = 0.0 ppm.

Example 1

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine

5 g of 4,7-dichloroquinoline, 6.5 ml 1-N,N-dimethylamino-2-propylamine and 0.8 g of phenol are reacted at 140°C for 6 hours. After cooling 40 ml of water are added, the mixture is adjusted to pH 12 using concentrated sodium hydroxide solution and extracted three times with 150 ml of ethyl acetate each time. The residue remaining after evaporation of the solvent is recrystallized 1x from isopropanol and 1x from acetonitrile. 3.48 g of colourless crystals are obtained, m.p.: 168-170°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.29 (d, J = 7 Hz, 3H), 2.24 (s, 6H), 2.36 (dd, J = 6Hz and 12.5 Hz, 1H), 2.59 (dd, J = 9 Hz and 12.5 Hz, 1H), 3.62 (m, 1H), 5.90 (broad, 1H), 6.44 (d, J = 6 Hz, 1H), 7.34 (dd, J = 3 Hz and 9 Hz, 1H), 7.74 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The following compounds can be prepared in an analogous manner:

Example 2

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine

3.91 g of base from 5 g of 4,7-dichloroquinoline and 6.56 g of 1-N,N-diethylamino-2-propylamine; colourless crystals from acetonitrile, m.p.: 90-92°C.

31 OCT 1996

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.01 (t, J = 7 Hz, 6H), 1.30 (d, J = 6.5 Hz, 3H), 2.4 - 2.7 (m, 6H), 3.57 (m, 1H), 6.13 (br., 1H), 6.44 (d, J = 6 Hz, 1H), 7.36 (dd, J = 3 Hz and 9 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained by adding HCl to a solution in isopropanol; colourless crystals, m.p.: 268-270°C.

Example 3

(RS)-(7-Chloro-quinolin-4-yl)-(1-methyl-2-pyrrolidin-1-yl-ethyl)-amine

3.36 g of base from 3.18 g of 4,7-dichloroquinoline and 4.12 g of 2-(pyrrolidin-1-yl-propyl)-amine; colourless crystals from acetonitrile, m.p.: 160-163°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.32 (t, J = 7 Hz, 3H), 1.75 (m, 4H), 2.55 (m, 5H), 2.83 (dd, J = 9 Hz and J = 12 Hz, 1H), 3.67 (m, 1H), 5.92 (br., 1H), 6.44 (d, J = 6 Hz, 1H), 7.35 (dd, J = 3 Hz and 9 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained in the form of colourless crystals which decompose at 143° by the dropwise addition of a solution of the base in isopropanolic hydrochloric acid (0.35N) to a 4-fold volume of diethyl ether.

Example 4

(RS)-(7-Chloro-quinolin-4-yl)-(1-methyl-2-piperidin-1-yl-ethyl)-amine

3.62 g from 5.22 g of 4,7-dichloroquinoline and 7.5 g of 2-(piperidin-1-yl-propyl)-amine; colourless crystals from ethanol, m.p.: 168-171°C.

This is the replacement sheet

Date:

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.30 (d, J = 6.5 Hz, 3H), 1.3-1.6 (m, 6H). 2.3-2.6 (m, 6H), 3.62 (m, 1H), 6.20 (broad, 1H), 6.44 (d, J = 6 Hz, 1H), 7.39 (dd, J = 3 Hz and 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 5

N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine

1.09 g from 5.9 g of 4,7-dichloroquinoline and 5.3 g of 2-dimethylamino-ethylamine; colourless crystals from ethyl acetate, m.p.: 122-124°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 2.30 (s, 6H), 2.68 (m, 2H), 3.28 (m, 2H), 5.91 (br.t, 1H), 6.37 (d, J = 5.5 Hz, 1H), 7.36 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.95 (d, J = 2.5 Hz, 1H), 8.53 (d, J = 5.5 Hz, 1H).

Example 6

N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine

From 4,7-dichloroquinoline and 2-(N,N-dimethylamino)-ethylamine; colourless crystals from isopropanol, m.p.: above 250°C.

^{1}H-NMR in DMSO-d_6/D_2O, δ (ppm): 1.28 (t, J = 7.5 Hz, 6H), 3.28 (q, J = 7.5 Hz, 4H), 3.49 (t, J = Hz, 2H), 4.00 (t, J = Hz, 2H), 7.06 (d, J = 7 Hz, 1H), 7.75 (dd, J = 2 Hz and 9 Hz, 1H), 8.02 (d, J = 2 Hz, 1H), 8.59 (d, J = 7 Hz, 1 H), 8.65 (d, J = 9 Hz, 1H).

This is the replacement sheet

Date:

Example 7

(7-Chloro-quinolin-4-yl)-(2-pyrrolidin-1-yl-ethyl)-amine

3.37 g of base from 3.96 g of 4,7-dichloroquinoline and 5 ml of 1-(2-aminoethyl)-pyrrolidine; prior to recrystallization the crude product is purified by filtration with ethyl acetate over 300 g of aluminium oxide (activity grade II). From 400 ml of eluate there are obtained yellowish crystals which, recrystallized from 95 ml of acetonitrile, give 3.37 g of colourless crystalline product, m.p.: 134-136°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.83 (m, 4H), 2.59 (m, 4H), 2.87 (dd, J = 6 Hz and 7 Hz, 2H), 3.33 (m, 2H), 5.92 (broad 1H), 6.38 (d, J = 6 Hz, 1H), 7.36 (dd, J = 3 Hz and 9 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained in the form of colourless crystals, m.p.: 212-213°C, by adding HCl to a solution of the base in isopropanol.

Example 8

(7-Chloro-quinolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine

3.57 g of base from 3.96 g of 4,7-dichloroquinoline and 4.8 g of 1-(2-aminoethyl)-piperidine (reaction duration, 5 hours at 140°C); yellowish crystals from acetonitrile, m.p.: 148-151°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.45-1.7 (m, 6H), 2.46 (m, 4H), 2.72 (t, J = 6 Hz, 2H), 3.29 (m, 2H), 6.12 (br., 1H), 6.36 (d, J = 6 Hz, 1H), 7.38 (dd, J = 2.5 Hz and 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.95 (d J = 2.5 Hz, 1H), 8.53 (d, J = 6 Hz).

31 OCT 1996

Example 9

(1RS,2RS)-N_1-(7-Chloro-quinolin-4-yl)-N_2,N_2-diethyl-cyclohexane-1,2-diamine

11.3 g of base from 15.2 g of 4,7-dichloroquinoline and 13.4 g of 2-(diethylamino)-cyclohexylamine (reaction duration, 16 hours at 140°C); colourless crystals from acetonitrile, m.p.: 110-114°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 0.98 (t, J = 7 Hz, 6H), 1.1- 145 (m, 5H), 1.75-2.0 (m, 3H), 2.38 (m, 2H), 2.54 (m, 2H), 2.70 (m, 1H), 3.10 (m, 1H), 6.43 (d, J = 6 Hz, 1H), 6.55(br.s, 1H), 7.36 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained from isopropanolic hydrochloric acid; colourless crystals from acetonitrile, dec. at 198°C.

Example 10

(1RS,2RS)-(7-Chloro-quinolin-4-yl)-(2-pyrrolidin-1-yl-cyclohexyl)-amine

3.87 g from 3.6 g of 4,7-dichloroquinoline and 3.06 g of (2-pyrrolidin-1-yl-cyclohexyl)-amine (reaction duration 24 hours at 120°C); colourless crystals from acetonitrile/ethanol, m.p.: 228 - 231°C.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.25-2.0 (m, 12H), 2.22 (m,1H), 3.11 (m, 1H), 3.40 (m, 1H), 3.98 (m, 1H), 4.47 (m, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.75 (dd, J = 2.5 Hz and 9.5 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.64 (d, J = 7.5 Hz, 1 H), 8.98 (d, J = 9.5 Hz, 1H), 9.65 (d, J = 9.5 Hz, 1H), 10.15 (br.s, 1H). 14.63 (br.s, 1H).

This is the replacement sheet

Date: 31 OCT 1996

Example 11

(1RS,2RS)-N_1-(7-Chloro-quinolin-4-yl)-N_2,N_2-diethyl-cyclopentane-1,2-diamine

8.16 g of base from 16 g of 4,7-dichloroquinoline and 12.7 g of 2-(diethylamino)cyclopentylamine (16 hours reaction duration at 140°C). With isopropanolic hydrochloric acid there are obtained therefrom 7.84 g of dihydrochloride; colourless crystals from acetonitrile/ethanol, m.p.: 186-190°C.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.45 (d, J = 6 Hz, 6H), 1.8-2.4 (m, 6H), 2.56 (m, 1H), 3.1-3.5 (m, 4H), 5.20 (m, 2H), 6.90 (d, J = 7.5 Hz, 1H), 7.45 (dd, J = 2.5 Hz and 9.5 Hz, 1H), 8.15 (d, J = 2.5 Hz, 1H), 8.24 (d, J = 7.5 Hz, 1 H), 9.41 (d, J = 9.5 Hz, 1H), 11.55 (br.s, 1H). 14.55 (br.s, 1H).

Example 11a

(1RS,2RS)-N1-(7-Chloro-quinolin-4-yl)-(2-pyrrolidin-1-yl-cyclopentyl)-amine

1.78 g of base from 3.56 g of 4,7-dichloroquinoline and 2.79 g of 2-(pyrrolidin-1-yl)-cyclopentylamine.

$C_{18}H_{22}ClN_3$ (315.85):

Calc.: C 68.45%, H 7.02%, Cl 11.22%, N 13.30%

Found: C 68.32%, H 7.00%, Cl 11.36%, N 13.11%

With isopropanolic hydrochloric acid there are obtained therefrom 1.64 g of dihydrochloride; colourless crystals from acetonitrile/ethanol, m.p.: 173°C (dec.).

1H-NMR in DMSO-d6, δ (ppm): 1.7-2.0 (m, 8H), 2.3-2.4 (m, 2H), 3.09 (m, 2H), 3.53 (m, 2H), 4.40 (m, 1H), 4.79 (m, 1H), 7.01 (d, 1 H, J = 7 Hz), 7.79 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.11 (d, J = 2.5 Hz,

This is the replacement sheet

Date: 3.1.01

1H), 8.66 (d, J = 7 Hz, 1 H), 9.04 (d, J = 9Hz, 1H), 9.86 (d, J = 7.5 Hz, 1H), 11.75 (br.s, 1H). 14.55 (br.s, 1H).

Example 12

(7-Chloro-quinolin-4-yl)-(1-ethyl-pyrrolidin-2-yl-methyl)-amine

9.64 g of base from 8.5 g of 4,7-dichloroquinoline and 11 g of 2-(aminomethyl)-1-ethyl-pyrrolidine. Prior to recrystallization the crude reaction product is purified by chromatography on 400 g of aluminium oxide (activity grade II); a 1:1 mixture of ethyl acetate and hexane is used as the eluent. After a fore-run of 400 ml the product is eluted with 1.5 l of eluent and gives, after recrystallization from 120 ml of hexane, 9.64 g of colourless crystals; m.p.: 85-86°C.

12 g of colourless crystalline dihydrochloride, m.p. 239-240°C, are obtained by dissolution in 15 ml of isopropanol, addition of 20 ml of 3.6N isopropanolic hydrochloric acid and dropwise addition to 100 ml of diethyl ether.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.28 (t, J = 7.5 Hz, 3H), 1.95 (m, 3H), 2.27 (m,1H), 3.16 (m, 2H), 3.48 (m, 2H), 3.88 (m, 1H), 4.14 (m, 2H), 7.09 (d, J = 8 Hz, 1H), 7.78 (dd, J = 3 Hz and 9 Hz, 1H), 8.24 (d, J = 3 Hz, 1H), 8.69 (d, J = 8 Hz, 1 H), 8.94 (d, J = 9 Hz, 1H), 10.08 (t, J = 6 Hz, 1H), 11.20 (br.s, 1H). 14.80 (br.s, 1H).

Example 12a

(7-Chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine

Analogously to Example 12 there are obtained 60 mg of base from 2.91 g of 4,7-dichloroquinoline and 1.68 g of 2-(amino-methyl)-1-methyl-pyrrolidine; colourless crystals from hexane, m.p.: 114-116°C.

^{1}H-NMR in DMSO-d_6, δ (ppm): 1.5 1.7 (m, 3H), 1.80-2.0 (m, 1H), 2.17 (m,1H), 2.35 (s, 3H), 2.55-2.60 (m, 1H), 2.98 (m, 1H),

3.14 (m, 1H), 3.40 (m, 1H), 6.50 (d, J = 5 Hz, 1H), 7.21 (t, J= 6 Hz, 1H), 7.45 (dd, J = 2.5 Hz und 9.5 Hz, 1H), 7.79 (d, J = 2.5 Hz, 1H), 8.24 (d, J = 5 Hz, 1 H), 8.40 (d, J = 9.5 Hz, 1H).

Example 13

(7-Chloro-quinolin-4-yl)-(1,1-dimethyl-2-pyrrolidin-1-yl-ethyl)-amine

4.95 g of 4,7-dichloroquinoline, 7.1 g of 2-methyl-2-(pyrrolidin-1-yl)-propylamine and 5 g of phenol are reacted at 140°C for 16 hours. After cooling the melt 25 ml of water are added, the mixture is adjusted to pH 1 with a small amount of concentrated hydrochloric acid and extracted three times with 50 ml of ethyl acetate each time. Thereafter, concentrated sodium hydroxide solution is added to pH 12 and the product is extracted three times with 100 ml of ethyl acetate each time. The crude product obtained after evaporation of the solvent is purified by chromatography on 400 g of aluminium oxide (activity grade II) with a mixture of ethyl acetate and hexane (1:4). 2.37 g of colourless crystals, m.p.: 89-91°C, are obtained after recrystallization from hexane.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.48 (s, 6H), 1.86 (m, 4H), 2.71(s, 2H), 2.75 (m, 4H), 6.60 (d, J = 6 Hz, 1H), 6.84 (br., 1H), 7.33 (dd, J = 3 Hz and 9 Hz, 1H), 7.62 (d, J = 9 Hz, 1H), 7.91 (d, J = 3 Hz, 1 H), 8.45 (d, J = 6 Hz, 1H).

The dihydrochloride is obtained by adding 3.3N HCl in dioxan to a solution of the base in anhydrous dioxan; colourless crystals, m.p.: 249-252°C.

This is the replacement sheet

Date: 31 OCT 1996

Example 14

(7-Chloro-quinolin-4-yl)-(1,1-dimethyl-2-piperidin-1-yl-ethyl)-amine

4.57 g of 4,7-dichloroquinoline, 7.5 g of 2-methyl-2-(piperidin-1-yl)-propylamine and 0.75 g of phenol are reacted at 180°C for 16 hours. The crude reaction product, isolated as in the foregoing Example, is purified on 200 g of aluminium oxide (activity grade II) prior to recrystallization; a 1:1 mixture of toluene and acetone is used as the eluent. After a fore-run, which contains unreacted 4,7-dichloroquinoline, the product is eluted and, after recrystallization from 5 ml of acetonitrile, gives 0.8 g of colourless crystals, m.p.: 143-147°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.46 (s, 6H), 1.50 (m, 2H), 1.65 (m, 4H), 2.51 (s, 2H), 2.65 (m, 4H), 6.62 (d, J = 6 Hz, 1H), 6.83 (br.s, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.71 (d, J = 9 Hz, 1H), 7.93 (d, J = 3 Hz, 1 H), 8.46 (d, J = 6 Hz, 1H).

Example 15

N_3-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine

From 4,7-dichloroquinoline and 3-(N,N-dimethylamino)-propylamine; colourless crystals from ethyl acetate-hexane, m.p.: 111-113°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.86 (quintet, J = 6 Hz, 2H), 2.37 (s, 6H), 2.58 (m, 2H), 3.39 (m, 2H), 6.31 (d, J = 5.5 Hz, 1H), 7.32 (dd, J = 2 Hz and 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.92 (d, J = 2 Hz, 1H), 7.94 (br. s, 1H). 8.48 (d, J = 5.5 Hz).

This is the replacement sheet

Date: 31 OCT 1996

Example 16

N_3-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine

2.99 g of base from 3.96 g of 4,7-dichloroquinoline and 5.2 g of 3-(N,N-diethylamino)-propylamine (reaction duration 4 hours at 140°C); colourless crystals from acetonitrile, m.p.: 77-78°C.

^{1}H-NMR in $CDCl_3$, δ (ppm): 1.10 (t, J = 7 Hz, 6H), 1.92 (quintet, J = 6 Hz, 2H), 2.65 (m, 6H), 3.38 (m, 2H), 6.29 (d, J = 5.5 Hz, 1H), 7.32 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.92 (d J = 2.5 Hz, 1H), 8.18 (br. s, 1H). 8.50 (d, J = 5.5 Hz).

The dihydrochloride is obtained with isopropanolic hydrochloric acid; colourless crystals from isopropanol, dec. from 118°C,

Example 17

(7-Chloro-quinolin-4-yl)-(3-pyrrolidin-1-yl-propyl)-amine

3.08 g from 7.72 g of 4,7-dichloroquinoline and 5 g of 3-(pyrrolidin-1-yl)-propylamine (reaction duration 16 hours at 140°C); the base is converted with isopropanolic hydrochloric acid into the dihydrochloride which, recrystallized from acetonitrile/ethanol, gives colourless crystals, m.p.: 204-206°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.96 (m, 4H), 2.14 (m, 2H), 3.00 (m, 2H), 3.26 (m, 2H), 3.51 (m, 2H), 3.67 (m, 2H), 6.96 (d, J = 7 Hz, 1H), 7.78 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.13 (d, J = 2.5 Hz, 1H), 8.59 (d, J = 7 Hz, 1 H), 8.81 (d, J = 9 Hz, 1H), 9.86 (d, J = 6 Hz, 1H), 11.13 (br.s, 1H). 14.55 (br.s, 1H).

Example 18

(7-Chloro-quinolin-4-yl)-(3-piperidin-1-yl-propyl)-amine

2.73 g from 2.83 g of 3-(piperidin-1-yl)-propylamine and 3.94 g of 4,7-dichloroquinoline (reaction duration, 16 hours at 140°C); the base (yellowish crystals from acetonitrile, m.p.: 113-116°C) is converted with isopropanolic hydrochloric acid into the dihydrochloride which, recrystallized from acetonitrile/ethanol, gives colourless crystals, m.p.: 137-141°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.28 (m, 1H), 1.54-1.76 (m, 5H), 2.08 (m, 2H), 2.78 (m, 2H), 3.07 (m, 2H), 3.27 - 3.38 (m, 2H), 3.53 (m, 2H), 6.21 (d, J = 7 Hz, 1H), 7.55 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 8.43 (d, J = 7 Hz, 1 H), 8.73 (d, J = 9 Hz, 1H), 9.88 (d, J = 6 Hz, 1H), 10.67 (br.s, 1H). 14.63 (br.s, 1H).

Example 19

(1-Benzyl-piperidin-4-yl)-(7-chloro-quinolin-4-yl)-amine

5.65 g from 10 g of 4,7-dichloroquinoline and 10.26 ml of 4-amino-1-benzylpiperidine; colourless crystals from acetonitrile, m.p.: 166-168°C. The dihydrochloride, colourless crystals from acetonitrile/ethanol, m.p. above 25°C, is obtained therefrom using isopropanolic hydrochloric acid.

^{1}H-NMR in DMSO-d_6; δ (ppm): 2.1-2.4 (m, 4H), 3.04 (m, 2H), 3.44 (m, 2H), 4.08 (br.s, 1H), 4.30 (s, 2H), 7.04 (d, J = 7.5 Hz, 1H), 7.48 (m, 3H), 7.67 (m, 2H), 7.78 (dd, J = 2.5 Hz and 9 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.61 (d, J = 7.5 Hz, 1 H), 8.81 (d, J = 9.5 Hz, 1H), 9.30 (d, J = 7.5 Hz, 1H), 11.50 (br.s, 1H). 14.55 (br.s, 1H).

This is the replacement sheet

Date:

Example 19a

(RS)-(7-Chloro-quinolin-4-yl)-(1-methyl-piperidin-3-yl)-amine

4 g from 11.29 g of 4,7-dichloroquinoline and 6.5 g of 3-amino-1-methyl-piperidine; colourless crystals from acetonitrile, m.p.: 149-150°C.

$C_{15}H_{18}ClN_3$ (275.78):

Calc.: C 65.33%, H 6.58%, Cl 12.86%, N 15.24%

Found: C 65.25%, H 6.64%, Cl 12.87%, N 15.11%

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.3-1.95 (multiple m, 6H), 2.02 (s, 3H), 2.67 (m, 1H), 2.92 (m, 1H), 3.67 (m, 1H), 6.54 (d, J = 6 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 7.44 (dd, J = 2.5 Hz and 9 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 9 Hz, 1 H), 8.39 (d, J = 6 Hz, 1H).

Example 20

(5-Amino-2,2,4-trimethyl-cyclopentylmethyl)-(7-chloro-quinolin-4-yl)-amine

480 mg as a mixture of isomers from 3.1 g of 4-bromo-7-chloroquinoline and 11 ml of 2-(aminomethyl)-3,3,5-trimethyl-cyclopentylamine; colourless crystals from isopropanolic hydrochloric acid, m.p. above 250°C. The ^{1}H-NMR (250 Mz) shows the presence of a mixture of two main components and two secondary components.

$C_{18}H_{24}N_3Cl \cdot 2HCl \cdot 0{\cdot}5\ H_2O$:

Calculated: C: 54.08%, H: 6.81%, N: 10.51%, Cl: 26.60%

Found: C: 54.24%, H: 6.82%, N: 10.76%, Cl: 26.71%

This is the replacement sheet

Date: 31 OCT 1995

Example 21

N_1,N_1-Diethyl-N_2-(7-trifluoromethyl-quinolin-4-yl)-ethane-1,2-diamine

5 g of 4-chloro-7-(trifluoromethyl)-quinoline and 10 g of 2-N,N-diethylamino-ethylamine in 150 ml of dimethylacetamide are stirred at 120°C for 16 hours. After cooling the mixture is concentrated in a water-jet vacuum and the residue is taken up with 150 ml of water and a small amount of hydrochloric acid such that the pH amounts to 4.8. After three-fold extraction with 100 ml of ethyl acetate each time the mixture is adjusted to pH 10.2 by means of 1N sodium hydroxide solution and the basic product is extracted with 3 x 100 ml of ethyl acetate. After evaporation of the solvent the product is recrystallized from acetonitrile and there are obtained 1.96 g of colourless crystals, m.p.: 122-124°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.08 (t, J = 7 Hz, 6H), 2.61 (q, J = 7 Hz, 4 H), 2.83 (t, J = 6 Hz, 2H), 3.27 (m, 2H), 6.23 (m, 1H), 6.45 (d, J = 6 Hz, 1H), 7.60 (dd, J = 3 Hz and 9 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 8.26 (m, 1H), 8.61 (d, J = 6 Hz, 1H).

In an analogous manner there was prepared:

Example 22

N_1,N_1-Dimethyl-N_2-(7-trifluoromethyl-quinolin-4-yl)-ethane-1,2-diamine

From 4-chloro-7-(trifluoromethyl)-quinoline and 2-N,N-dimethylamino-ethylamine; colourless crystals from hexane, m.p.: 110-113°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 2.31 (s, 6H), 2.69 (m, 2H), 3.29 (m, 2H), 6.05 (m, 1H), 6.44 (d, J = 6 Hz, 1H), 7.51 (dd, J = 3 Hz and 9 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 8.26 (m, 1H), 8.61 (d, J = 6 Hz, 1H).

31 OCT 1995

Example 23

(RS)-(7-Chloro-quinolin-4-yl)-[2-(3-methyl-piperidin-1-yl)-ethyl]-amine

2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride in 25 ml of 3-methylpiperidine are held at 100°C in a sealed tube for 24 hours. Thereafter, 100 ml of water are added, the mixture is adjusted to pH 12 by means of concentrated sodium hydroxide solution and extracted three times with 50 ml of ethyl acetate each time. The combined extracts are washed with a small amount of water and concentrated. The residue is recrystallized from 80 ml of acetone. 0.88 g of colourless crystals, m.p.: 148-151°C, is obtained.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.90 (d, J = 6 Hz, 3H), 0.98 (m, 1H), 1.6-1.75 (m, 5H), 2.04 (dt, J = 3.5 Hz and 7 Hz, 1H), 2.75 (m, 2H), 2.84 (m,2H), 3.31 (m, 2H), 6.20 (broad, 1H), 6.37 (d, J = 6 Hz, 1H), 7.38 (dd, J = 3 Hz and 9 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.96 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

The following compounds can be prepared in an analogous manner using suitable amines:

Example 24

(7-Chloro-quinolin-4-yl)-[2-(4-methyl-piperidin-1-yl)-ethyl]-amine

2.72 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 154-156°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.96 (d, J = 6 Hz, 3H), 1.28 (m, 2H), 1.43 (m, 1H), 1.68 (m, 1H), 2.06 (m, 2H), 2.73 (m, 2H), 2.90 (m,2H), 3.29 (m, 2H), 6.10 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.36

This is the replacement sheet

Date: 31 OCT 1996

(dd, J = 3 Hz and 9 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

Example 25

(7-Chloro-quinolin-4-yl)-[2-(3,3-dimethyl-piperidin-1-yl)-ethyl]-amine

2.1 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolin-amine hydrochloride; colourless crystals from acetonitrile, m.p.: 151-153°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.98 (s, 6H), 1.29 (m, 2H), 1.66 (m, 1H), 2.12 (m, 2H), 2.45 (m, 2H), 2.69 (t, J = 6 Hz, 2H), 3.28 (m, 2H), 6.20 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 7.96 (d, J = 3 Hz, 1H), 8.52 (d, J = 6 Hz, 1H).

Example 26

(RS)-(7-Chloro-quinolin-4-yl)-[2-(2-methyl-piperidin-1-yl)-ethyl]-amine

1.4 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolin-amine hydrochloride; colourless crystals from acetonitrile, m.p.: 133-134°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.12 (d, J = 6.5 Hz,6H), 1.30-1.75 (m, 6H), 2.17 (dt, J = 4 Hz and 10 Hz, 2H), 2.45-2.55 (m, 2H), 2.86 (tm, 1H), 3.1-3.3 (m, 3H), 6.13 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.38 (dd, J = 3 Hz and 9 Hz, 1H), 7.67 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

[illegible] the replacement sheet

Date: [illegible]

Example 27

(RS)-(7-Chloro-quinolin-4-yl)-[2-(2-ethyl-piperidin-1-yl)-ethyl]-amine

1.52 g from N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 115-117°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.93 (t, J = 7.5Hz, 3H), 1.3-1.75 (m, 8H), 2.21 (m, 2H), 2.39 (m, 2H), 2.57 (m, 1H), 2.85 (m, 1H), 3.16 (m, 1H), 3.26 (m, 2H), 5.17 (broad 1H), 6.36 (d, J = 6 Hz, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.65 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.52 (d, J = 6 Hz, 1H).

Example 28

(2R,6S)-(7-Chloro-quinolin-4-yl)-[2-(2,6-dimethyl-piperidin-1-yl)-ethyl]-amine

0.4 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 138-139°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.14 (d, J = 6.5 Hz, 6H), 1.2-1.7 (m, 6H), 2.57 (m, 2H), 2.94 (t, J = 7 Hz, 2H), 3.31 (m, 2H), 5.85 (broad, 1H), 6.38 (d, J = 6 Hz, 1H), 7.37 (dd, J = 2.5 Hz and 9.5 Hz, 1H), 7.70 (d, J = 9.5 Hz, 1H), 7.95 (d, J = 2.5 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 29

(7-Chloro-quinolin-4-yl)-[2-(3,5-dimethyl-piperidin-1-yl)-ethyl]-amine

0.67 g (isomer mixture cis:trans = 3:1) from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 142-143°C.

31 OCT 1996

^{1}H-NMR in $CDCl_3$; δ (ppm): 0.88 and 1.00(d, J = 6.5 Hz, 6H; ratio 3:1), 1.3-2.0 (several m, 4H), 2.2-2.84 (several m, 6H), 3.29 (m, 2H), 6.12 and 6.20 (broad, 1H; ratio 3:1), 6.37 (d, J = 6 Hz, 1H), 7.37 (dd, J = 3 Hz and 9 Hz, 1H), 7.66 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 30

(7-Chloro-quinolin-4-yl)-[2-(2,5-dimethyl-pyrrolidin-1-yl)-ethyl]-amine

0.35 g (isomer mixture cis:trans = 15:1) from 1.3 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; yellowish crystals from acetone, m.p.: 127-130°C.

^{1}H-NMR in DMSO-D_6; δ (ppm): 0.94 and 1.06(d, J = 6.5 Hz, 6H; ratio 15:1), 1.29 (m, 2H), 1.80 (m, 2H), 2.67 (m, 2H), 2.79 (m, 2H), 3.34 (m, 2H),), 6.47 (d, J = 6 Hz, 1H), 7.05 (br.t, 1H), 7.46 (dd, J = 3 Hz and 9 Hz, 1H), 7.78 (d, J = 3 Hz, 1H), 8.19 (d, J = 9 Hz, 1 H), 8.40 (d, J = 6 Hz, 1H).

Example 31

(7-Chloro-quinolin-4-yl)-[2-octahydro-indol-1-yl)-ethyl]-amine

0.3 g from 2.2 g of N-(2-chloroethyl)-7-chloro-4-quinolin-amine hydrochloride; colourless crystals from ethyl acetate, m.p.: 115-117°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.1 - 2.0 (m, 11H), 2.15 - 2.45 (m, 2H), 2.95 (m, 1H), 3.18 (m, 1H), 3.36 (m, 4H), 6.48 (d, J = 6 Hz, 1H), 7.22 (t, J = 6 Hz, 1H), 7.45 (dd, J = 3 Hz and 9 Hz, 1H), 7.91 (d, J = 3.Hz, 1H), 8.19 (d, J = 9 Hz, 1 H), 8.40 (d, J = 6 Hz, 1H).

This is the replacement sheet

Date: 31 OCT 1996

Example 32

2-(3-Azabicyclo[3.2.2]nonan-3-yl)-ethyl]-(7-chloro-quinolin-4-yl)-amine

0.45 g from 1.48 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; yellowish crystals from ethanol, m.p.: 205 - 207°C.

^{1}H-NMR in $CDCl_3$; δ (ppm): 1.60-1.82 (m, 8H), 1.95 (br.s, 2H), 2.66 (d, J = 4.5 Hz, 4H), 2.81 (m, 2H), 3.27 (m, 2H), 6.30 (broad, 1H), 6.36 (d, J = 6 Hz, 1H), 7.39 (dd, J = 3 Hz and 9 Hz, 1H), 7.69 (d, J = 9 Hz, 1H), 7.95 (d, J = 3 Hz, 1 H), 8.53 (d, J = 6 Hz, 1H).

Example 33

N_1-Allyl-N_2-(7-chloro-quinolin-4-yl)-N_1-methyl-ethane-1,2-diamine

0.56 g from 2.5 g of N-(2-chloroethyl)-7-chloro-4-quinolinamine hydrochloride; colourless crystals from acetonitrile, m.p.: 91-93°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 2.24 (s,3H),), 2.62 (t, J = 7 Hz, 2H), 3.04 (d, J = 7 Hz, 2H), 3.37 (m, 2H), 5.1-5.2 (m, 2H), 5.84 (m, 1H), 6.49 (d, J = 6 Hz, 1H), 7.21 (t, J = 6 Hz, 1H), 7.45 (dd, J = 3 Hz and 9 Hz, 1H), 7.78 (d, J = 3 Hz, 1H), 8.22 (d, J = 9 Hz, 1 H), 8.40 (d, J = 6 Hz, 1H).

Example 33a

(R,S)-(7-Chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-3-yl)-amine

0.42 g of (R,S)-(7-chloro-quinolin-4-yl)-(pyrrolidin-3-yl)-amine dihydrobromide is boiled under reflux overnight in 2 ml of formic acid and 2 ml of 37% formalin solution. Thereafter, 10 ml of water are added, the mixture is adjusted to pH 2 with conc. hydrochloric acid and extracted three times with 20 ml of

This is the replacement sheet

Date:

ethyl acetate each time. Thereafter, the aqueous phase is adjusted to pH 12 by the addition of conc. sodium hydroxide solution and extracted three times with 20 ml of ethyl acetate each time. After evaporation of the solvent the residue is recrystallized from tert.-butyl methyl ether and acetone and there are obtained 20 mg of colourless crystals, m.p.: 150-152°C.

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.75-2 (m, 1H), 2.29 (s,3H), 2.3-2.8 (multiple m, 5H), 4.13 (m, 1H), 6.47 (d, J = 6 Hz, 1H), 7.29 (d, J = 6.5 Hz, 1H), 7.45 (dd, J = 3 Hz and 9 Hz, 1H), 7.78 (d, J = 3 Hz, 1H), 8.39 (d, J = 6 Hz, 1 H), 8.40 (d, J = 9 Hz, 1H).

Example 33b

N_1-(7-Chloro-quinolin-4-yl)-2,N_2,N_2-trimethyl-propane-1,2-diamine

30 g of N_1-(7-chloro-quinolin-4-yl)-2-methyl-propane-1,2-diamine are boiled under reflux for 3 hours in 21.6 ml of aqueous formaldehyde solution (37%) and 45.3 ml of formic acid. Thereafter, the mixture is evaporated to dryness in a vacuum and the residue is taken up in 100 ml of water and adjusted to pH 12 using conc. potassium hydroxide solution. The precipitated product is recrystallized from 250 ml of acetonitrile and gives 25.1 g, m.p.: 114-116°C.

$C_{11}H_{20}ClN_3$ (277.80):

Calc.: C 64.85%, H 7.26%, Cl 12.76%, N 15.13%

Found: C 64.64%, H 7.18%, Cl 12.79%, N 15.07%

^{1}H-NMR in DMSO-d_6; δ (ppm): 1.09 (s, 6H), 2.22 (s, 6H), 3.18 (d, J = 5.5 Hz, 2H), 6.46 (t, J = 5.5 Hz, 1H), 6.51 (d, J = 6 Hz, 1H), 7.48 (dd, J = 2 Hz and 9.5 Hz, 1H), 7.82 (d, J = 2.5 Hz, 1H), 8.07 (d, J = 9.5 Hz, 1 H), 8.42 (d, J = 6 Hz, 1H).

31 OCT 1996

Example 33c

(S)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine

19 g of (S)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride are dissolved in 190 ml of dimethylamine solution (33% in ethanol) and held at 110°C in an autoclave for 15 hrs. After cooling and evaporation the residue is dissolved in 200 ml of dichloromethane and extracted with 200 ml of 1N NaOH. The basic aqueous phase is back-extracted with 200 ml of dichloromethane. The dichloromethane phases are dried and evaporated. The crude product is chromatographed on neutral aluminium oxide (act. II) in hexane/ethyl acetate 2:1, then in ethyl acetate alone. The resulting oil is triturated with 100 ml of diethyl ether and, after crystallization has taken place, diluted with 50 ml of hexane. There are obtained 13.5 g (79%) of white crystals; m.p. 110°C, $[\alpha]_D$ = +115° (c = 1.0, MeOH).

For the preparation of the dihydrochloride, 19.8 g of free base are dissolved in 200 ml of acetone, cooled in ice and then treated with 75 ml of 2N HCl and stirred for 10 min. After evaporation the residue is treated with 200 ml of toluene and again evaporated. The resulting oil is dissolved in 200 ml of ethanol while warming, filtered and, after crystallization has taken place, diluted with 50 ml of diethyl ether. There are obtained 23.7 g (94%) of white crystals; m.p.: >260°C, $[\alpha]_D$ = +136.5° (c = 1.0, MeOH).

^{1}H-NMR (250 MHz) in d_6-DMSO, signals at δ (ppm): 1.31 (d, J = 6.3, 3H), 2.81 (s, 6H), 3.39 (dd, 1H), 4.00 (dd, 1H), 4.73 (m, 1H), 7.08 (d, J = 7, 1H), 7.75 (dd, J_1 = 9, J_2 = 2, 1H), 8.15 (d, J = 2, 1H), 8.65 (d, J = 7, 1H), 9.06 (d, J = 9, 1H), 9.67 (d, J = 9, 1H), 10.5 (br, 1H), 15.0 (br, 1H)

This is the replacement sheet

Date: 31 OCT 1996

Example 33d

(R)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine

Analogously to Example 33c, starting from (R)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride there is prepared (R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine hydrochloride; white crystals; m.p.: >260°C, $[\alpha]_D$ = -132° (c = 1.0, MeOH).

Example 33e

(S)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine

15 g of (S)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride are dissolved in 100 ml of methanol and 50 ml of diethylamine and held at 125°C in an autoclave for 15 hrs. After cooling and evaporation the residue is dissolved in 200 ml of dichloromethane and extracted with 200 ml of 1N NaOH. The basic aqueous phase is back-extracted with 200 ml of dichloromethane. The dichloromethane phases are dried and evaporated. The crude product is chromatographed on neutral aluminium oxide (act. II) in hexane/ethyl acetate 2:1. The resulting oil is dissolved in 40 ml of diethyl ether and diluted slowly with 200 ml of hexane. There are obtained 10.3 g (69%) of white crystals; m.p.: 89°C, $[\alpha]_D$ = +122.6° (c = 1.0, MeOH).

For the preparation of the dihydrochloride, 18.1 g of free base are dissolved in 190 ml of acetone, cooled in ice and then treated with 62.5 ml of 2N HCl and stirred for 10 min. After evaporation the residue is treated with 200 ml of toluene and again evaporated. The resulting oil is dissolved in 200 ml of ethanol while warming, filtered, concentrated to 100 ml and, for crystallization, diluted with 2 x 50 ml of diethyl ether. There are obtained 21.8 g (96%) of white crystals; m.p.: 165-170°C, $[\alpha]_D$ = +150.6° (c = 1.0, MeOH).

...the replacement sheet
...OF ...
Date:

^{1}H-NMR (250 MHz) in d_6-DMSO, signals at δ (ppm): 1.26 (t, J = 7, 6H), 1.36 (d, J = 6.3, 3H), 3.17 (q, J = 7, 4H), 3.35 (dd, 1H), 4.01 (dd, 1H), 4.72 (m, 1H), 7.10 (d, J = 7, 1H), 7.75 (dd, J_1 = 9, J_2 = 2, 1H), 8.17 (d, J = 2, 1H), 8.65 (d, J = 7, 1H), 9.08 (d, J = 9, 1H), 9.81 (d, J = 9, 1H), 10.5 (br, 1H), 15.0 (br, 1H)

Example 33f

(R)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine

Analogously to Example 33e, starting from (R)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride there is prepared (R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine hydrochloride; white crystals, mp.: 165-170°C, $[\alpha]_D$ = -140.3° (c = 1.0, MeOH).

Example 33g

2.2 g of (S)-N_2,N_2-dimethyl-1,2-propanediamine and 2 g of 4,7-dichloroquinoline in 4 ml of 1-methyl-2-pyrrolidone are held at 150°C in an autoclave for 6.5 hrs. After cooling the reaction mixture is poured into 20 ml of 3N HCl and extracted with 4 x 20 ml of dichloromethane. The acidic-aqueous phase is made basic with 28% NaOH and then extracted with 3 x 20 ml of dichloromethane. The crude product is chromatographed on neutral aluminium oxide (act. II) in hexane/ethyl acetate 10:3. 1.25 g of yellow oil are obtained. This is dissolved in 10 ml of ethanol and converted into the dihydrochloride with ethanolic HCl solution. There are obtained 450 mg of white crystals; m.p.: 165°C, $[\alpha]_D$ = +15.1° (c = 1.0, MeOH).

^{1}H-NMR (250 MHz) in d_6-DMSO, signals at δ (ppm): 1.34 (d ,J = 6.1, 3H), 2.79 (s, 6H), 3.80 (m, 2H), 4.01 (m, 1H), 7.16 (d, J = 7, 1H), 7.78 (dd, J_1 = 9, J_2 = 2, 1H), 8.17 (d, J = 2, 1H), 8.65 (d, J = 7, 1H), 8.93 (d, J = 9, 1H), 9.92 (br, 1H), 11.1 (br, 1H), 15.0 (br, 1H)

3 1 OCT 1996

Example 33h

(R)-N_1-(7-Chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine

Analogously to Example 33g, starting from (R)-N_2,N_2-dimethyl-1,2-propanediamine hydrochloride there is prepared (R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine hydrochloride; white crystals, m.p.: 250°C, $[\alpha]_D$ = -9.4° (c = 1.0, MeOH).

$C_{14}H_{19}Cl_3N_3$ (336.69):

Calc.: C 49.94%, H 5.99%, Cl 31.59%, N 12.48%

Found: C 49.69%, H 6.18%, Cl 31.85%, N 12.28%

Preparation of intermediates

Example 34

(7-Chloro-quinolin-4-yl)-(2-chloro-ethyl)-amine

20 ml of thionyl chloride are slowly added dropwise while stirring to a suspension of 12.3 g of 2-(7-chloro-quinolin-4-amino)-ethanol [prepared according to R.C.Elderfield et al., J.Am.Chem.Soc. 68, 1250 (1946)] in such a manner that the temperature can be held at about 30°C without external cooling. The mixture is stirred at RT for one hour and thereafter evaporated to dryness. The residue is crystallized from 120 ml of glacial acetic acid. There are obtained colourless crystals which, after suspension in 250 ml of toluene, are dried at 50°C under a water-jet vacuum. 9.75 g of colourless crystalline product, m.p. 239-240°C, are obtained.

^{1}H-NMR in $CDCl_3$; δ (ppm): 3.97 (s, 4H), 7.02 (d, J = 8 Hz, 1H), 7.80 (dd, J = 3 Hz and 9 Hz, 1H), 8.14 (d, J = 3 Hz, 1H), 8.60 (d, J = 8 Hz, 1 H), 8.75 (d, J = 9 Hz, 1H), 9.85 (br.s, 1H), 14.63 (br.s, 1H).

This is the replacement sheet

Date: 31 OCT 1996

Example 35

4-Bromo-7-chloro-quinoline

83.9 g of 7-chloro-4-hydroxyquinoline are added portion-wise at 60° to 150 g of phosphorus oxybromide and the mixture is thereafter heated to 140°C for 6 hours. After cooling the mixture is treated with 3 l of ice-water and extracted with 2 x 1.5 l of dichloromethane. After evaporation of the solvent and crystallization from 1.3 l of hexane 34 g of product are obtained as colourless crystals, m.p.: 102-103°C.

Example 36

1-Methyl-2-pyrrolidin-1-yl-ethylamine

15 ml of aqueous formaldehyde solution (37%) are added dropwise at 5°C within one hour to 16.5 ml of pyrrolidine. Thereafter, 57.2 ml of nitroethane are added and the mixture is stirred at RT overnight. 150 ml of ethyl acetate and 400 ml of saturated sodium chloride solution are added, the organic phase is separated and is distilled in a water-jet vacuum. The product, 1-(2-nitropropyl)-pyrrolidine (18.5 g), passes over at 85-87°C.

13.1 g of this intermediate are then hydrogenated in 100 ml of methanol under 100 bar and at 80°C after the addition of 0.65 g of Raney-nickel. The product, 1-methyl-2-pyrrolidin-1-yl-ethylamine, is obtained by distillation at 49-52°C in a water-jet vacuum (4.7 g; colourless liquid).

The following diamines can be prepared in an analogous manner using the corresponding amines:

1-Methyl-2-piperidin-1-yl-ethylamine;
N,N-diethyl-propane-1,2-diamine;
N,N-dimethyl-propane-1,2-diamine.

[illegible] replacement sheet

Date: [illegible]

Example 37

N,N-Diethyl-cyclohexane-1,2-diamine

30 g of cyclohexene oxide are reacted with 44.8 g of diethylamine and 32.6 g of lithium perchlorate in 300 ml of acetonitrile overnight while stirring and under reflux. Thereafter, 200 ml of water are added and the product is extracted with 3 x 150 ml of ethyl acetate. After evaporation of the solvent 30.4 g of 2-(diethylamino)-cyclohexanol remain behind. This is dissolved in 150 ml of tetrahydrofuran without further purification. After the addition of 38.6 g of phthalimide and 68.7 g of triphenylphosphine 45.9 g of diethyl azodicarboxylate are added dropwise at a temperature of 10-15°C and the mixture is stirred at RT overnight. Thereafter, the mixture is evaporated, the residue is suspended in dilute hydrochloric acid (200 ml, pH 1) and washed with 3 x 150 ml of ethyl acetate. The pH is then adjusted to 12-13 by adding concentrated sodium hydroxide solution and the intermediate is extracted using 3 x 200 ml of ethyl acetate. After evaporation of the solvent N,N-diethyl-2-phthalimido-cyclohexylamine (36.8 g) remains behind in the form of yellow crystals.

These are saponified overnight in 250 ml of concentrated hydrochloric acid under reflux. After three-fold washing using 200 ml of dichloromethane each time the pH is adjusted to 13-14 by adding concentrated sodium hydroxide solution and the product is extracted using 3 x 200 ml of ethyl acetate and, after evaporation of the solvent, is obtained as a yellowish oil (13.4 g) which is processed without further purification.

2-Pyrrolidin-1-yl-cyclohexylamine is prepared in an analogous manner using pyrrolidine in place of diethylamine.

In an analogous manner, from cyclopentene oxide and diethylamine there is obtained N,N-diethyl-cyclopentane-1,2-diamine and from cyclopentene oxide and pyrrolidine there is obtained 2-pyrrolidin-1-yl-cyclopentylamine.

Example 38

1,1-Dimethyl-2-pyrrolidin-1-yl-ethylamine

18 ml of 2-nitropropane and 16.5 ml of pyrrolidine are dissolved in 60 ml of dioxan. 15 ml of aqueous formaldehyde solution (37%) and 8 ml of 2% sodium hydroxide solution are added at 5°C. The mixture is heated to 90°C while stirring for 1 hour, cooled and thereafter extracted with 3 x 150 ml of ethyl acetate. Upon distillation in a water-jet vacuum there are obtained 19 g of 1-(2-nitro-2-methylpropyl)-pyrrolidine.

This intermediate is then hydrogenated in 100 ml of methanol under 100 bar and at 80°C after the addition of 1.5 g of Raney-nickel. The product, 1,1-dimethyl-2-pyrrolidin-1-yl-ethylamine, is obtained by distillation in a water-jet vacuum at 52-57°C (13.1 g; colourless liquid).

1,1-Dimethyl-2-piperidin-1-yl-ethylamine can be prepared in an analogous manner using piperidine in place of pyrrolidine.

Example 39

3-Piperidin-1-yl-propylamine

3.7 g of piperidine and 2.3 g of acrylonitrile are pooled and heated to 100°C for 3 hours. After cooling the mixture is taken up in 40 ml of isopropanol and the 3-(1-piperidino)-propionitrile is precipitated using 12.8 ml of 3.6N isopropanolic hydrochloric acid (colourless crystals, m.p. 186-190°C, 6.68 g).

This intermediate is hydrogenated in 31 ml of 25% HCl and 31 ml of glacial acetic acid in the presence of 0.13 g of platinum dioxide at RT under 10 bar. After evaporation of the hydrogenation solution the residue is taken up in 50 ml of water, adjusted to pH 13 using concentrated sodium hydroxide solution and extracted with 3 x 150 ml of ethyl acetate. 3-Piperidin-1-

This is the replacement sheet

Date: 31 OCT 1996

yl-propylamine is obtained as a colourless oil, b.p. 45-50°C/0.1 mm Hg, by distillation.

Example 40

(R,S)-(7-Chloro-quinolin-4-yl)-(pyrrolidin-3-yl)-amine

9.85 g of 3-aminopyrrolidine are benzoylated with 16 g of benzoyl chloride at 0°C in 90 ml of dichloromethane, 17.7 ml of N,N-dimethylformamide and 25.5 ml of triethylamine. After warming to room temperature the mixture is filtered and the filtrate is evaporated to dryness. The residue is taken up in 100 ml of water (pH 8), filtered and again evaporated to dryness. The residue is digested in succession with in each case 90 ml of toluene, ethyl acetate and dichloromethane, the solution being decanted off each time from initially oily, but later crystalline, residue. The organic solutions are combined and evaporated. The dark coloured oil obtained (2.7 g) is then reacted at 140°C overnight with 2.1 g of 4,7-dichloroquinoline and 2.1 g of phenol. The reaction mixture is taken up with 50 ml of water, adjusted to pH 2 by the addition of conc. hydrochloric acid and extracted three times with 50 ml of ethyl acetate each time. Thereafter, the aqueous phase is adjusted to pH 12 using conc. sodium hydroxide solution and extracted three times with 50 ml of ethyl acetate each time. After evaporation of the solvent the residue is crystallized from 10 ml of ethyl acetate/toluene. The resulting product (0.6 g) is then saponified to (R,S)-(7-chloro-quinolin-4-yl)-(pyrrolidin-3-yl)-amine dihydrobromide by boiling in 10 ml of 48% HBr for 12 hours.

Example 41

N_1-(7-Chloro-quinolin-4-yl)-2-methyl-propane-1,2-diamine

52.8 g of 4,7-dichloroquinoline and 30.85 g of 1,2-diamino-2-methylpropane are stirred in 530 ml of N-methyl-2-pyrrolidone under argon at 150°C for 5 hours. Thereafter, the

... this replacement sheet

Date. 31 OCT 1996

solvent is evaporated in a vacuum and the residue is taken up in 1250 ml of water. After adjustment to pH 1 using conc. hydrochloric acid the mixture is extracted once with 200 ml of ethyl acetate and twice with 100 ml of ethyl acetate each time and subsequently treated with about 170 ml of 30% potassium hydroxide solution until the pH has reached 12. Thereby, 88 g of N_1-(7-chloro-quinolin-4-yl)-2-methyl-propane-1,2-diamine separate in crystalline form; m.p.: 169-171°C.

Example 42

(S)-2-Amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane

23 g of L-alaninol and 57.4 g of 4,7-dichloroquinoline in 100 ml of 1-methyl-2-pyrrolidone are held at 150°C for 6 hrs. After cooling the reaction mixture is poured into 500 ml of cold 2N HCl and extracted with 3 x 200 ml of dichloromethane. The acidic-aqueous phase is made basic with 28% NaOH, whereby the crude product precipitates. After stirring in an ice bath for 30 min. it is filtered off and then recrystallized from 300 ml of 2-propanol/150 ml of ethanol. There are obtained 51.2 g (74%) of (S)-2-amino-N-(7-chloro-quinolin-4-yl)-1-propanol; white crystals, m.p.: 225°C, $[\alpha]_D = +35^o$ (c = 1.0, MeOH).

^{1}H-NMR (250 MHz) in d_6-DMSO, signals at δ (ppm): 1.24 (d, J = 6.4, 3H), 3.45 (m, 1H), 3.58 (m, 1H), 3.73 (m, 1H), 4.87 (t, J = 5.6, 1H), 6.53 (d, J = 7, 1H), 6.84 (d, J = 7.7, 1H), 7.44 (dd, J_1 = 9, J_2 = 2, 1H), 7.78 (d, J = 2, 1H), 8.35 (d, J = 7, 1H), 8.39 (d, J = 9, 1H)

27.3 g of (S)-2-amino-N-(7-chloro-quinolin-4-yl)-1-propanol are suspended in 270 ml of chloroform. Then, a solution of 72 ml of thionyl chloride in 70 ml of chloroform are added dropwise over 30 min. while cooling with ice, whereby the temperature should not exceed 25°C. Subsequently, the mixture is stirred at room temperature for a further 30 min. and at 70°C for 90 min. The reaction mixture is cooled and evaporated, then treated with toluene and again evaporated. The resulting foam is dissolved in 500 ml of ethanol while warming, filtered and

concentrated to about 300 ml, whereupon crystallization occurs. There are obtained 31.6 g (94%) of (S)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane hydrochloride as white crystals; m.p.: 210°C, $[\alpha]_D$ = +90° (c = 1.0, MeOH).

The R enantiomer, (R)-2-amino-1-chloro-N-(7-chloro-quinolin-4-yl)-propane, can be obtained as the hydrochloride starting from D-alaninol; white crystals, m.p.: 210°C, $[\alpha]_D$ = -88° (c = 1.0, MeOH).

1H-NMR (250 MHz) in d6-DMSO, signals at d (ppm): 1.41 (d, J = 6.5, 3H), 3.88-4.06 (m, 2H); 4.48 (m, 1H), 7.03 (d, J = 7.3, 1H), 7.79 (dd, J_1 = 9, J_2 = 2, 1H), 8.15 (d, J = 2, 1H) 8.59 (d, J = 7.3, 1H), 8.89 (d, J = 9, 1H), 9.44 (d, J = 8.4, 1H), 14.66 (s, 1H)

Example 43

(S)-N_2,N_2-Dimethyl-1,2-propanediamine

7.6 g of L-alaninol are stirred at 90°C for 14 hrs. in 20 ml of formic acid and 20 ml of 37% formaldehyde solution. After cooling the reaction mixture is poured on to 100 g of ice and 60 ml of 28% NaOH and extracted with 3 x 100 ml of dichloro-methane. After drying and evaporating the dichloromethane phases the crude produce is distilled at normal pressure. There are obtained 7.8 g of (S)-2-dimethylamino-1-propanol as a colourless oil; b.p. 147°C, $[\alpha]_D$ = +2.7° (c = 1.0, MeOH).

7.3 g of (S)-2-dimethylamino-1-propanol, 37 g of triphenylphospine and 20.8 g of phthalimide are suspended in 70 ml of tetrahydrofuran under argon and cooled in an ice bath. Then, 24 ml of diethyl azodicarboxylate are added dropwise over 30 min. and the mixture is stirred at room temperature for a further 5 hrs. Then, the mixture is poured into 200 ml of ice-cold 1N HCl and extracted with 3 x 200 ml of ethyl acetate. The acidic-aqueous phase is made basic with 28% NaOH and then extracted with 3 x 200 ml of dichloromethane. After drying and evaporating the dichloromethane phases the 12 g of crude

This is the replacement sheet
31 OCT 1996
Date:

product (GC 78% + 16% regioisomer) are chromatographed on silica gel in ethyl acetate. There are obtained 6 g of yellow oil which solidifies (regioisomer not separated). This 6 g of product are boiled at reflux in 50 ml of conc. HCl for 20 hrs. After cooling the precipitated phthalic acid is filtered off. The filtrate is washed with 2 x 50 ml of dichloromethane and then made basic cautiously with solid KOH while cooling in an ice bath and finally extracted with 3 x 80 ml of dichloromethane. After drying and evaporating the dichloromethane phases the crude product is distilled at normal pressure. There are obtained 1.2 g of (S)-N_2,N_2-dimethyl-1,2-propanediamine as a colourless oil; b.p.: 127°C.

^{1}H-NMR (250MHz) in $CDCl_3$, signals at d (ppm): 0.89 (d, J = 6.4, 3H), 1.37 (s, 2H), 2.22 (s, 6H), 2.48 - 2.67 (m, 3H)

The R enantiomer, (R)-N_2,N_2-dimethyl-1,2-propanediamine, can be prepared in an analogous manner starting from D-alaninol.

Example A

(RS)-N_2-(7-Chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine can be formulated as the active ingredient according to methods known per se to give pharmaceutical preparations of the following composition:

1. 500 mg tablets	
Active ingredient	500 mg
Powd. lactose.	149 mg
Polyvinylpyrrolidone	15 mg
Dioctyl sodium sulphosuccinate	1 mg
Na carboxymethylstarch	30 mg
Magnesium stearate	5 mg
	700 mg

This is the replacement sheet
Date. 31 OCT 1996

2. 50 mg tablets	
Active ingredient	50 mg
Powd. lactose	50 mg
Microcrystalline cellulose	82 mg
Na carboxymethylstarch	15 mg
	200 mg

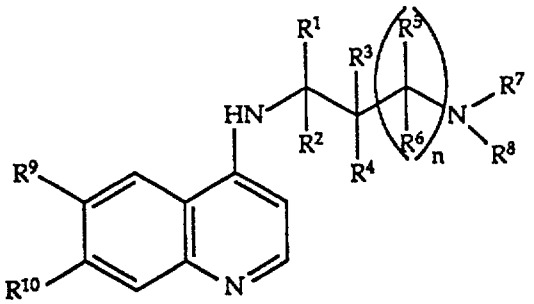
3. 100 mg capsules	
Active ingredient	100.0 mg
Powd lactose	104.7 mg
Corn starch	70.0 mg
Hydroxypropylmethylcellulose	10.0 mg
Dioctyl sodium sulphosuccinate	0.3 mg
Talc	12.0 mg
Magnesium stearate	3.0 mg
	300.0 mg

4. 500 mg suppositories	
Active ingredient	500 mg
Suppository mass	ad 2000 mg

5. 100 mg soft gelatine capsules	
Active ingredient	100 mg
Medium chain triglyceride	300 mg
	400 mg

Claims

1. The use of aminoquinoline derivatives of the general formula



I

wherein the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, octahydroindole or 3-azabicyclo[3,2,2]nonane and n = 0 or 1 or

wherein the symbols R^1 and R^3 signify tri- or tetramethylene, all remaining symbols to R^6 signify hydrogen, n = 0 and R^7 and R^8 have the above significances or

wherein the symbols R^1 and R^7 signify methylene or dimethylene and n = 1,
R^1 and R^7 signify di- or trimethylene and n = 0,
R^3 and R^7 signify di- or trimethylene and n = 1
R^3 and R^7 signify tri- or tetramethylene and n = 0
R^5 and R^7 signify tri- or tetramethylene and n = 1
R^1 and R^5 signify di- or tri-methylene and n = 1, all remaining substituents signify hydrogen, except R^8 which signifies alkyl, alkenyl or alkynyl or

wherein the symbols R^3 and R^5 signify tri- or tetramethylene and n = 1, all remaining substituents to R^6 signify hydrogen and R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl,

R^9 signifies hydrogen or halogen and R^{10} signifies halogen or trifluoromethyl,

as well as pharmaceutically acceptable salts of basic compounds of general formula I for the manufacture of medicaments for the control of not only chloroquine-resistant malaria pathogens, but also chloroquine-sensitive malaria pathogens.

2. The use of compounds of formula I according to claim 1 in which the symbols R^1 to R^6 signify hydrogen or one or two thereof signifies (signify) alkyl and the others signify hydrogen, R^7 and R^8 signify alkyl, alkenyl or aralkyl or together with the N atom signify pyrrolidine or piperidine, optionally substituted by alkyl, and n = 0 or 1.

3. The use of (S)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine according to claim 2.

4. The use of (R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine according to claim 2.

5. The use of N_1-(7-chloro-quinolin-4-yl)-2,N_2,N_2-trimethyl-propane-1,2-diamine according to claim 2.

6. The use of N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine according to claim 2.

7. The use of (RS)-(7-chloro-quinoline-4-yl)-(1-methyl-piperidine-3-yl)amine according to claim 2.

8. The use of (RS)-(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-3-yl)-amine according to claim 2.

9. The use of (RS)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,2-diamine,

(RS)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

* C L M S *

This is the replacement sheet

Date: 31 OCT 1996

(S)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(R)-N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,2-diamine,

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-2-pyrrolidin-1-yl-ethyl)-amine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

(R)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine,

(S)-N_1-(7-chloro-quinolin-4-yl)-N_2,N_2-dimethyl-propane-1,2-diamine and

(RS)-(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine

according to claim 2.

10. Compounds of general formula I defined in claim 1, except

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-ethane-1,2-diamine,

N_2-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-ethane-1,2-diamine,

* C L M S *

31 OCT 1996

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-dimethyl-propane-1,3-diamine,

N_3-(7-chloro-quinolin-4-yl)-N_1,N_1-diethyl-propane-1,3-diamine,

(7-chloro-quinolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine,

(7-chloro-quinolin-4-yl)-[(1-ethyl-pyrrolidin-2-yl)-methyl]-amine,

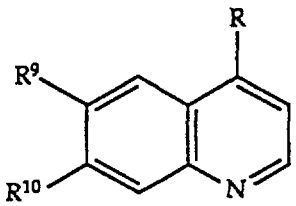
(7-chloro-quinolin-4-yl)-(1-methyl-pyrrolidin-2-yl-methyl)-amine,

(7-chloro-quinolin-4-yl)-(1-methyl-piperidin-2-yl-methyl)-amine and

(7-chloro-quinolin-4-yl)-(1-ethyl-piperidin-3-yl)-amine.

11. A process for the manufacture of compounds according to claim 10, which process comprises

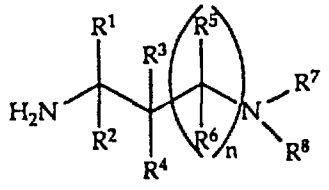
a) reacting quinoline derivatives of the general formula



II

wherein R^9 and R^{10} have the significances given in claim 1 and R signifies a leaving group,

with amino compounds of the general formula



III

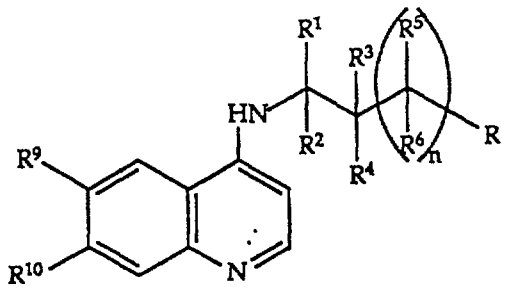
This is the replacement sheet

Date:

wherein the substituents R^1 to R^8 have the significances given in claim 1,

or

b) reacting alkylamino-quinoline derivatives of the general formula



IV

wherein R^1 to R^6 and R^9 and R^{10} have the significances given in claim 1 and R signifies a leaving group,

with amines of the formula

$$HNR^7R^8 \qquad V$$

wherein R^7 and R^8 have the significances given in claim 1,

or

c) reacting compounds of formula I in which R^1 to R^6 as well as R^9 and R^{10} have the significances given in claim 1 and R^7 and R^8 signify hydrogen or one of them signifies hydrogen and the other signifies an alkyl group with alkylating agents which are suitable for the alkylation of amino groups,

and

d) if desired, converting a basic compound of formula I into a pharmaceutically usable salt by means of an acid.

12. Compounds according to claim 10 for use as therapeutically active substances.

13. Compounds according to claim 10 for use as active substances against not only chloroquine-resistant malaria pathogens, but also chloroquine-sensitive malaria pathogens.

Title to the replacement sheet

* C L M S *

Date: 31 OCT 1996

14. The use of compounds according to claim 10 in the control of diseases or in the improvement of health.

15. A medicament containing one or more compounds according to claim 10 and a therapeutically inert excipient.

16. A medicament according to claim 15 for the treatment or prevention of malaria.

* C L M S *

This is the replacement sheet

Date: 31 OCT 1996

Abstract

Aminoquinoline derivatives for use against chloroquine-resistant and chloroquine-sensitive malaria pathogens

The present invention relates to novel aminoquinoline derivatives which have an equally good effect not only against chloroquine-sensitive malaria pathogens, but also against chloroquine resistant pathogens. The compounds, describe in the present invention, exhibit no cross-resistants with chloroquine.

This is the replacement sheet

Date: