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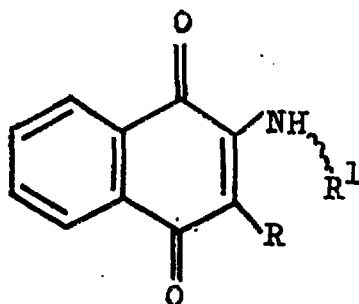


(54) NAPHTHOQUINONE DERIVATIVES AND A PROCESS
 FOR THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESSELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

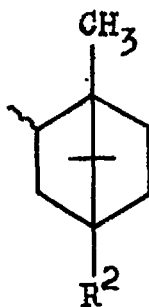
The present invention is concerned with naphthoquinone derivatives and a process for the manufacture thereof.

The naphthoquinone derivatives provided by the present invention have the following general formula



(I)

wherein R represents a hydrogen or halogen atom or a lower alkoxy group and R¹ represents a grouping of the formula



(a)

or



(b)

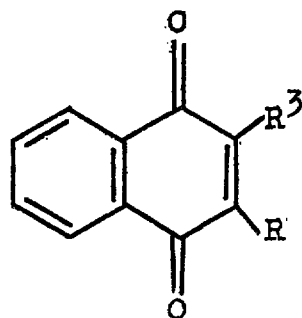
in which R^2 represents a hydrogen atom, a lower alkyl group, a phenyl group which may be substituted by halogen, nitro, amino or hydroxy, or a phenyl-(lower alkyl) group.

As used in this description and in the accompanying claims, the term "lower alkyl" denotes a straight-chain or branched-chain alkyl group containing from 1 to 7 carbon atoms for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, amyl, hexyl, and heptyl.

As stated above, there may be present as substituents on the phenyl group: halogen (preferably bromine or chlorine), nitro, amino and hydroxy. The substituent is preferably present in the para-position of the phenyl group. The term "phenyl-(lower-alkyl)" denotes a phenyl-alkyl group containing from 1 to 4 carbon atoms in the alkyl group. The 2-phenylethyl group is the preferred phenyl-(lower alkyl) group. The term "lower alkoxy" denotes an alkoxy group containing from 1 to 4 carbon atoms such as, for example, methoxy, ethoxy, propoxy and butoxy.

One preferred class of naphthoquinone derivatives of formula I hereinbefore comprises those in which R^1 represents a grouping of formula (a), particularly those in which R^2 in said grouping represents a hydrogen atom, the methyl, n-propyl or n-heptyl group, the phenyl group or the phenethyl group. The naphthoquinone derivatives of formula I in which R^1 represents a grouping of formula (b) also constitute a preferred class. When R in formula I represents a halogen atom, chlorine and bromine are preferred and when R represents a lower alkoxy group the methoxy group is preferred.

According to the process provided by the present invention, the naphthoquinone derivatives aforesaid are manufactured by reacting a compound of the general formula



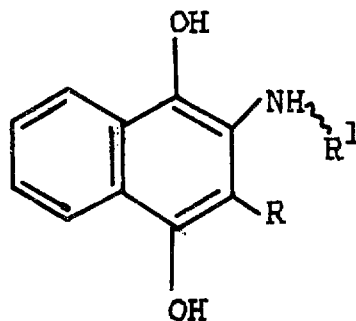
(II)

, wherein R has the significance given earlier and R^3 represents a hydrogen atom or a leaving atom or group (as hereinafter defined), with an amine of the general formula



(III)

, wherein R^1 has the significance given earlier, or by oxidising a compound of the general formula



(IV)

, wherein R and R^1 have the significance given earlier,

and, in either case if desired, converting a naphthoquinone derivative of formula I obtained in which R represents a hydrogen atom or a halogen atom other than a chlorine atom into a corresponding derivative in which R represents a chlorine atom.

As used in this description and in the accompanying claims, the expression "leaving atom or group" denotes an acyloxy group, for example, acetoxy, or propionyloxy, an alkoxy group for example methoxy, or ethoxy, an aryloxy group for example phenyloxy, an aralkoxy group for example benzyloxy, an arylsulphonyloxy group for example tosyloxy, an alkylsulphonyloxy group for example mesyloxy, an arylthio group, an aralkylthio group, the hydroxy group or a halogen atom for example bromine or chlorine.

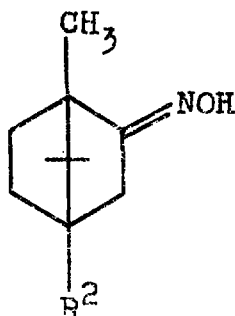
According to one embodiment of the process provided by the present invention the naphthoquinone derivatives of formula I are manufactured by reacting a compound of formula II with an amine of formula III.

The starting materials of formula II are known and can be prepared in a manner known per se.

The amine starting materials of formula III in which R^1 represents a grouping of formula (b) are known and can be prepared according to methods known per se; for example, by reduction of the corresponding oximes.

The amine starting materials of formula III in which R^1 represents a grouping of formula (a) are new with the exception of those in which R^2 in the grouping of formula (a) represents a hydrogen atom.

The amine starting materials of formula III in which R^1 represents a grouping of formula (a) can be prepared, for example, by reducing an oxime of the general formula



(V)

, wherein R^2 has the significance given earlier, optionally resolving a stereoisomer mixture thus obtained and converting a base obtained into an acid addition salt if desired.

The reduction of an oxime of formula V can be carried out in a manner known for the reduction of oximes to primary amines. Suitable reduction methods are catalytic hydrogenation (for example, in the presence of ammonia such as hydrogenation in the presence of Raney-nickel in alcoholic ammonia), hydrogenation in the presence of platinum in glacial acetic acid or reduction in a chemical manner such as, for example, with sodium in alcohol, zinc in acetic acid, lithium aluminium hydride in ether.

The amine starting materials of formula III occur in two stereoisomeric forms, namely in the exo and the endo form. Depending on the nature of the agent used to effect the reduction of the oxime group in the preparation of such amines, there is obtained a mixture of both forms or predominantly the endo or the exo form. Thus, for example, when an oxime of formula V is reduced with sodium in alcohol there is predominantly obtained the endo form, when the reduction is carried out with lithium aluminium hydride there is obtained the practically pure exo form and when the reduction is carried out by catalytic hydrogenation there is obtained a mixture of the exo and the endo form in a proportion of about 3:7.

Where a mixture of the two stereoisomeric forms is obtained, these can be separated from each other in a known manner, for example on the basis of the different rates of crystallisation of different salts, i.e. by fractional crystallisation, especially of the acetates.

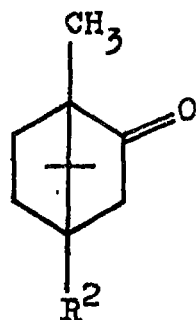
The amine starting materials of formula III in which R^1 represents a grouping of formula (a) are chiral and are therefore obtained in the form of racemates. If desired,

these racemates can be resolved into the optical antipodes according to methods which are known per se; for example, by fractional crystallization of the salts with optically active acids.

5 The amine starting materials of formula III are bases and can be converted into acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and with organic acids such as acetic acid, tartaric acid, maleic acid, fumaric acid, citric acid, oxalic acid and toluenesulphonic acid.

10 The oximes of formula V hereinbefore are likewise new with the exception of those in which R^2 represents a hydrogen atom, the methyl or propyl group or the unsubstituted phenyl group.

The oximes of formula V can be obtained, for example, by heating a compound of the general formula



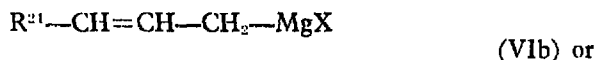
(VI)

15 , wherein R^2 has the significance given earlier, with, for example, hydroxylamine hydrochloride and sodium ethylate in ethanol.

The compounds of formula VI are likewise new with the exception of those in which R^2 represents a hydrogen atom, the methyl, ethyl or propyl group or an optionally substituted phenyl group.

20 The compounds of formula VI in which R^2 represents a substituent other than a hydrogen atom can be obtained, for example, as follows starting from camphor:

Camphor is reacted with a metal-organic compound of the general formula



25 , wherein R^{20} represents the methyl group, an optionally substituted phenyl group or the benzyl group, R^{21} represents a lower alkyl group containing from 1 to 4 carbon atoms, R^{22} represents a hydrogen atom, a lower alkyl group containing from 1 to 5 carbon atoms, the phenyl group or a phenyl-(lower alkyl) group containing 1 or 2 carbon atoms in the lower alkyl group, M represents the group-
30 ing MgX or sodium, potassium or lithium and X represents a halogen atom, and the reaction product is hydrolysed. The hydrolysis product, if necessary after hydrogenation of any double- or triple-bond which may be present and if desired after dehydration, is subsequently converted into the corresponding exo acid amide by reaction with a cyano compound [Ritter reaction: Org. Reactions; Vol. 17, 213—
35 325 (1969)]. This exo acid amide is subsequently hydrolysed to the corresponding exo amine in a manner known per se; for example, by heating with an acid or base, preferably with an acid and expediently at the reflux temperature of the hydrolysis mixture.

40 The foregoing exo amine can then be dehydrogenated to the corresponding imine; for example, by reaction with tert.butyl hypochlorite in an inert organic solvent such as ether to give the corresponding N-chloro compound and treatment of this with an inorganic or organic base such as, for example, sodium methoxide.

The resulting imine is subsequently hydrolysed to a compound of formula VI in a manner known per se; for example, by treatment with a dilute mineral acid.

The compounds of formula VI in which R² represents the methyl or phenyl group can also be obtained, for example, as follows starting from camphor.

Camphor is reacted with a Grignard compound of the general formula



wherein R²³ represents the methyl or phenyl group.

The reaction product is hydrolysed, then dehydrated and the dehydration product is subsequently treated with glacial acetic acid in the presence of an acid such as, for example, sulphuric acid, hydrochloric acid and the corresponding R²³ substituted isobornyl acetate is obtained. This is saponified with alkali and the 4-R²³-isoborneol obtained is oxidised to the 4-R²³-camphor.

Those amine starting materials of formula II in which R² in the grouping of formula (a) represents a substituted phenyl group can be prepared, for example, by introducing the desired substituent into the unsubstituted phenyl ring of a corresponding acid amide in a manner known per se and hydrolysing the acid amide obtained. Thus, for example, a nitro group can be introduced by nitration with nitric acid. The nitro group can be reduced in a manner known per se to the amino group and a methoxy group can be converted into the hydroxy group in a manner known per se; for example, with hydrobromic acid.

The reaction of a compound of formula II with an amine of formula III is expediently effected in an organic solvent which is inert under the reaction conditions; for example an alcohol such as methanol or ethanol, an aliphatic hydrocarbon, a halogenated aliphatic hydrocarbon (e.g. methylene chloride), an aromatic hydrocarbon (e.g. benzene), nitrobenzene, dioxan, tetrahydrofuran, dimethylformamide.

The reaction can be carried out at a temperature of from about room temperature up to about 150°C. The reaction is preferably carried out at an elevated temperature, especially at about 60° to 100°C.

The reaction is expediently carried out using an excess of amine of formula III in order to bind the acid which may be released. An organic base which is inert under the reaction conditions such as, for example, a tertiary organic amine (e.g. triethylamine, pyridine) can also be used in order to bind the acid which may be released.

According to another embodiment of the process provided by the present invention, the naphthoquinone derivatives of formula I hereinbefore are manufactured by oxidising a compound of formula IV hereinbefore.

The starting materials of formula IV are novel. They can be prepared, for example, by reducing a naphthoquinone derivative of formula I hereinbefore. The reduction is preferably carried out catalytically; for example, using palladium/charcoal, platinum, Raney-nickel and the like as the catalyst.

The oxidation of a compound of formula IV can be carried out in a manner known per se; for example, by passing air or oxygen through a solution of a compound of formula IV or by shaking a solution of a compound of formula IV with dilute hydrogen peroxide or by treatment with iron (III) salts.

The conversion of a naphthoquinone derivative of formula I in which R represents a hydrogen atom or a halogen atom other than a chlorine atom into a corresponding derivative of formula I in which R represents a chlorine atom can expediently be carried out by heating in a suitable solvent with, for example, lithium chloride or by passing chlorine gas through a solution of the appropriate derivative of formula I. The heating is expediently effected at a temperature of from about 50°C to 150°C, preferably at about 80°—120°C.

Depending on the amine starting material of formula III used, the naphthoquinone derivatives of formula I can be obtained in two diastereomeric forms and in the form of racemates or in optically active form.

When racemic amine starting materials of formula III are used, there are obtained racemic naphthoquinone derivatives of formula I. When the individual optical antipodes of formula III are used, there are obtained the corresponding optical antipodes of formula I. When the endo or the exo form of an amine of formula III is used, there is obtained the endo or the exo form of a naphthoquinone derivative of formula I.

The naphthoquinone derivatives of formula I possess amoebicidal and bacteriostatic activity, especially against gram-negative bacteria such as, for example, *Escherichia coli*, *Shigella sonnei* and/or *Shigella flexneri*.

Thus, for example, racemic 2-(2-exo-bornylamino)-3-chloro-1,4-naphthoquinone has, in mouse, an LD₅₀ of over 5000 mg/kg p.o. and a CD₅₀ of 4 mg/kg p.o. against

Escherichia coli, of 8 mg/kg p.o. against Shigella flexneri and of 7 mg/kg p.o. against Shigella sonnei.

In the mouse, (-)-2-[(1R)-2-exo-bornylamino]-3-chloro-1,4-naphthoquinone has an LD₅₀ of over 5000 mg/kg p.o. and a CD₅₀ of ca 50 mg/kg p.o. against Shigella sonnei and Shigella flexneri.

In the mouse, (+)-2-[(1R)-2-endo-bornylamino]-3-bromo-1,4-naphthoquinone has an LD₅₀ of over 5000 mg/kg p.o. and a CD₅₀ of ca 50 mg/kg p.o. against Shigella sonnei and Escherichia coli.

The CD₅₀ values mentioned hereinbefore were obtained in accordance with the following method:

Groups each consisting of 5 mice are dewormed for 4 days. At the same time, they are placed on a carbohydrate-rich diet (popcorn). On the 5th day, no nourishment is administered. From the 6th day until the end of the experiment they receive drinking water which contains 4 g of dihydrostreptomycin, 100 mg of erythromycin and 400,000 units of mycostatin per litre. On the 6th day they again receive popcorn. On the 7th day, once more no nourishment is administered. Likewise, on the 8th day no nourishment is administered and the mice are infected orally with 100 million streptomycin-, erythromycin- and mycostatin-resistant germs of Shigella sonnei, Shigella flexneri or Escherichia coli. From the 9th day, the mice receive popcorn until the end of the experiment and the derivative to be tested is administered for the first time 24 hours after the oral infection. In the case of Shigella sonnei and Escherichia coli, the derivative to be tested is administered 3 times and in the case of Shigella flexneri 5 times at 24-hour intervals. The mice infected with Shigella flexneri are killed one day and the animals infected with Shigella sonnei or Escherichia coli three days after the last treatment.

A piece of large intestine together with the contents (ca 200 mg) is isolated and homogenised. 6 different dilutions thereof (1/10,000; 1/50,000; 1/100,000; 1/500,000; 1/1,000,000; 1/2,000,000) are prepared.

A drop from each dilution is streaked on an agar plate. After incubation for 48 hours, the number of colonies is counted and with the corresponding dilutions there is calculated the germ count per gram of piece of intestine for each mouse. By comparison of the individual germ counts for 5 mice with the average germ counts of 5 untreated mice there is calculated the percentage germ reduction in each mouse. The results are stated in CD₅₀ values.

The naphthoquinone derivatives provided by this invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier. This can be an organic or inorganic inert carrier material which is suitable for enteral or parenteral application such as, for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gum arabic, polyalkylene glycols, or petroleum jelly. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilized and/or may contain additives such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers.

The naphthoquinone derivatives provided by this invention are preferably administered orally, that is to say, in pharmaceutical dosage forms usual for oral administration such as, for example, dragées, tablets, capsules. Particularly preferred are tablets which can contain about 100 mg, 200 mg or 250 mg of naphthoquinone derivative. Daily doses up to about 1000 mg, corresponding to about 14 mg/kg/day, can be administered in several individual doses. However, it will be appreciated that the doses stated hereinbefore are only given by way of example and can be varied according to the severity of the case to be treated and the judgement of the treating physician.

The following Examples illustrate the process provided by the invention:

Example 1

33.7 g of rac.-2-endo-bornanamine dissolved in 50 ml of absolute alcohol are added dropwise with stirring at room temperature to a suspension of 22.7 g of 2,3-dichloro-1,4-naphthoquinone in 200 ml of absolute alcohol. After the addition, the reaction mixture is boiled at reflux for 4 hours, there resulting a dark-red solution. The reaction mixture is then evaporated under reduced pressure, the residue taken up in 300 ml of chloroform, the chloroform solution successively shaken out with 100 ml of water, three times with 100 ml of 1-N hydrochloric acid each time and four times with 100 ml of water each time. After drying over sodium sulphate, the organic phase is concentrated, treated with active charcoal and evaporated. After crystallisa-

tion from n.hexane, there are obtained 30.3 g of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone of melting point 110°—111°C.

Example 2

5 4.54 g of 2,3-dichloro-1,4-naphthoquinone are suspended in 30 ml of absolute benzene and treated with 2.226 g of triethylamine. At room temperature, a solution of 3.218 g of rac.-2-endo-bornanamine in 10 ml of absolute benzene is added drop-
wise with stirring during 35 minutes. After stirring for 2 hours, the dark-red coloured suspension is filtered off from insolubles, the filtrate evaporated, the residue dissolved in methylene chloride. The solution is washed with water, 1-N hydrochloric acid and
10 water, dried over sodium sulphate, filtered and evaporated. The residue is treated in hexane with active charcoal and the rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone crystallised. 2.9 g of red crystals of melting point 109°—110°C are obtained.

Example 3

15 In an analogous manner to that described in Example 1 or Example 2, the following naphthoquinone derivatives are manufactured:

- from 2,3-dichloro-1,4-naphthoquinone and (+)-(1R)-2-endo-bornanamine, (+)-2-[(1R)-2-endo-bornylamino]-3-chloro-1,4-naphthoquinone.
Melting point 113°—115°C (from hexane).
20 $[\alpha]_D^{25} = +120^\circ$ (c=0.01 in alcohol).
- from 2,3-dichloro-1,4-naphthoquinone and (—)-(1R)-2-exo-bornanamine, (—)-2-[(1R)-2-exo-bornylamino]-3-chloro-1,4-naphthoquinone.
Melting point 97°—98°C (from hexane).
 $[\alpha]_D^{25} = -175^\circ$ (c=0.03 in alcohol).
- 25 from 2,3-dibromo-1,4-naphthoquinone and (+)-(1R)-2-endo-bornanamine, (+)-2-[(1R)-2-endo-bornylamino]-3-bromo-1,4-naphthoquinone.
Melting point 102°—104°C (from hexane/petroleum ether).
 $[\alpha]_D^{25} = +104^\circ$ (c=0.1 in alcohol).
- 30 from 2,3-dibromo-1,4-naphthoquinone and rac.-2-endo-bornanamine, rac.-2-(2-endo-bornylamino)-3-bromo-1,4-naphthoquinone. Melting point 82°—84°C (from hexane/petroleum ether).
- 35 from 1,4-naphthoquinone and rac.-2-endo-bornanamine, rac.-2-(2-endo-bornylamino)-1,4-naphthoquinone. Melting point 181°—182°C (from chloroform/petroleum ether).
from 2,3-dichloro-1,4-naphthoquinone and rac.-2-endo-norbornanamine, rac.-2-chloro-3-(2-endo-norbornylamino)-1,4-naphthoquinone. Melting point 100°—102°C (from chloroform/petroleum ether).
- 40 from 2,3-dichloro-1,4-naphthoquinone and rac.-2-exo-norbornanamine, rac.-2-chloro-3-(2-exo-norbornylamino)-1,4-naphthoquinone. Melting point 112°—114°C (from chloroform/petroleum ether).
- from 1,4-naphthoquinone and rac.-2-exo-bornanamine, rac.-2-(2-exo-bornylamino)-1,4-naphthoquinone. Melting point 163°—164°C (from methylene chloride/petroleum ether).
- 45 from 2,3-dibromo-1,4-naphthoquinone and rac.-2-exo-bornanamine, rac.-2-(2-exo-bornylamino)-3-bromo-1,4-naphthoquinone. Melting point 85°—87°C (from hexane/petroleum ether).
- from 2,3-dimethoxy-1,4-naphthoquinone and rac.-2-endo-bornanamine, rac.-2-(2-endo-bornylamino)-3-methoxy-1,4-naphthoquinone.
- 50 from 2,3-dimethoxy-1,4-naphthoquinone and rac.-2-exo-bornanamine, rac.-2-(2-exo-bornylamino)-3-methoxy-1,4-naphthoquinone.

Example 4

192.6 mg of 3-chloro-1,4-naphthoquinone are dissolved in 25 ml of absolute dioxan and treated dropwise at room temperature with stirring with 153.3 mg of rac.-2-endo-bornanamine dissolved in 5 ml of absolute dioxan. The dark-red reaction mixture is boiled at reflux for 70 minutes. The solvent is thereafter evaporated in a vacuum, the residue taken up in 30 ml of chloroform, washed with 10 ml of water, 5 ml of 1-N hydrochloric acid and water, dried over sodium sulphate, filtered and evaporated. The residue (321 mg) is resolved on 10 g of silica gel (0.2—0.5 mm) using methylene chloride as eluting agent. 14 fractions each comprising 2—3 ml of eluate are collected. Fractions 4—7 contain the desired product. These fractions are further washed in methylene chloride with water, then dried over sodium sulphate, filtered and evaporated. The residue is crystallised from isopropyl ether. 30.4 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone are obtained. Melting point 110°—111°C.

Example 5

11.13 g of 2-chloro-3-methoxy-1,4-naphthoquinone are suspended in 100 ml of absolute methanol and, with stirring at 20°C, treated dropwise during 20 minutes with 8.9 g of rac.-2-endo-bornanamine dissolved in 20 ml of absolute methanol. After boiling at reflux for 30 minutes, the deep-red reaction mixture is concentrated under reduced pressure, the residue dissolved in 200 ml of chloroform, shaken out with 100 ml of 1-N hydrochloric acid and washed neutral with water. The organic phase is dried over sodium sulphate, filtered and evaporated. The substance is recrystallised from n-hexane. There are obtained 15.05 g of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone of melting point 110°—111°C.

Example 6

1.35 g of rac.-2-endo-bornanamine dissolved in 10 ml of absolute alcohol are added dropwise with stirring at 20°C during 5 minutes to a suspension of 1.0 g of 2-acetoxy-3-chloro-1,4-naphthoquinone in 20 ml of absolute alcohol. The reaction mixture is boiled at reflux for 20 minutes. After evaporation of the alcoholic solution, the residue is chromatographed on 20 g of silica gel (0.2—0.5 mm) with methylene chloride as eluting agent. In so doing, 12 fractions each comprising 5 ml are collected. Fractions 5—8 contain 300 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone which melts at 109°—111°C after crystallisation from isopropyl ether.

Example 7

208.6 mg of 2-chloro-3-hydroxy-1,4-naphthoquinone are suspended in 5 ml of absolute alcohol and, with stirring at room temperature, treated with 168.6 mg of rac.-2-endo-bornanamine dissolved in 3 ml of absolute alcohol. After stirring at room temperature for 60 minutes, the dark-red solution is evaporated in a vacuum, the residue treated with isopropyl ether and the insoluble part filtered off. After evaporating off the mother liquor, the residue (90.6 mg) is chromatographed on 3 g of silica gel (0.2—0.5 mm) with methylene chloride as eluting agent. 15 fractions each comprising 1 ml are collected. Fractions 5—12 give 55.0 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone of melting point 109°—110°C after crystallisation from methanol.

Example 8

388.3 mg of rac.-2-(2-endo-bornylamino)-3-bromo-1,4-naphthoquinone (manufactured in accordance with Example 3) are heated to 100°C with 848.0 mg of lithium chloride in 50 ml of absolute dimethylformamide. After 24 hours, the mixture is concentrated to dryness, the residue taken up in ether and the solution washed with water, dried over sodium sulphate, filtered and evaporated. In methylene chloride solution, the residue is filtered over 6 g of silica gel (0.2—0.5 mm). The product obtained after evaporating off the eluate is crystallized from isopropyl ether. There are obtained 280 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone. Melting point 110°—111°C.

Example 9

A) The preparation of the starting material:
3.43 g of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone are dissolved in 100 ml of absolute alcohol and hydrogenated at room temperature in the presence of 500 mg of palladium/charcoal (5%). After the uptake of hydrogen, the hydro-

generation mixture is separated from the catalyst under nitrogen, the solution is concentrated and the residue is crystallised from hexane to give rac.-2-(2-endo-bornylamino)-3-chloro-1,4-dihydroxy-naphthalene of melting point 152°—154°C.

B) The process:

100 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-dihydroxy-naphthalene are dissolved in 20 ml of absolute alcohol. Oxygen gas is conducted through the solution for 2 hours. The red solution is thereafter evaporated in a vacuum and the residue crystallised from n-hexane. 86.5 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone are obtained. Melting point 109°—111°C.

Example 10

Dry chlorine gas is conducted for 2 minutes through a solution of 1.545 g of rac.-2-(2-endo-bornylamino)-1,4-naphthoquinone (manufactured in accordance with Example 3) in 25 ml of absolute dimethylformamide. There thereby results a light-yellow solution and the mixture slightly warms. After stirring at room temperature for 90 minutes, the mixture is evaporated in a vacuum and the dark-red residue taken up in chloroform. The solution is washed neutral with water, dried over sodium sulphate, filtered and evaporated. The residue is coarsely resolved on silica gel (0.2—0.5 mm) with methylene chloride and the enriched fractions are once more chromatographed on 15 g of silica gel (0.2—0.5 mm) with methylene chloride as eluting agent (34 fractions of 1 ml). After crystallisation from methanol, fractions 16—27 give 122 mg of rac.-2-(2-endo-bornylamino)-3-chloro-1,4-naphthoquinone of melting point 109°—110°C.

Example 11

A) The preparation of the starting material:

140 g of rac.-1,4,7,7-tetramethyl-2-norbornyl oxime are dissolved in 1700 ml of absolute alcohol and hydrogenated in the presence of 1.4 g of ammonium carbonate and 14 g of Raney-nickel at 170 atmospheres hydrogen pressure and 110°C for 5 hours (inclusive of heating-up time). The solution, separated from the catalyst, is made congo-acidic with alcoholic hydrochloric acid and concentrated under reduced pressure. The crude hydrochloride salt is crystallised from alcohol/ether. Melting point over 300°C; yield: 130.6 g.

The 130.6 g of hydrochloride salt are dissolved in water and the amines are released with the calculated amount of sodium hydroxide. The precipitated base is taken up in ether, washed with water, dried over sodium sulphate, filtered and concentrated. There are obtained 117.4 g of crude base.

By means of nuclear resonance spectroscopy it can be established that the amine mixture consists of 4-methyl-2-endo-bornanamine and 4-methyl-2-exo-bornanamine in the proportion 7:3.

The two stereoisomers are separated by fractional crystallisation of their acetates as follows:

117.4 g of amine are dissolved in 1000 ml of absolute ether and cooled to -20°C. 29.6 g of glacial acetic acid in 100 ml of absolute ether are added dropwise thereto with stirring during 45 minutes. After the addition, the mixture is stirred for a further 10 minutes and the precipitated acetate filtered off, washed with absolute ether and dried. There are obtained 111.7 g of acetate of the endo compound. The acetate of the exo compound remains in the mother liquor.

The 111.7 g of acetate of the endo compound are dissolved in 500 ml of water and the base is released with the calculated amount of sodium hydroxide. The precipitated amine is taken up in ether, washed with water, dried over sodium sulphate and concentrated. According to thin layer chromatography, the crude residue (86.5 g) is rac.-1,4,7,7-tetramethyl-2-endo-norbornanamine enriched to 90%.

The 86.5 g of amine are dissolved in 850 ml of absolute ether and cooled to -20°C. 24.82 g of glacial acetic acid in 100 ml of absolute ether are added dropwise thereto with stirring during 45 minutes. The precipitated acetate is filtered off and dried. There are obtained 93 g of acetate of the endo compound; the acetate of the exo compound remaining in the mother liquor.

The 93 g of acetate of the endo compound are dissolved in water and the base is released with the calculated amount of sodium hydroxide. The base is taken up in ether, washed with water, dried over sodium sulphate and filtered. The filtrate is treated with ca 100 ml of alcohol and made congo-acidic with alcoholic hydrochloric acid. After evaporation of the solution and crystallisation from alcohol/ether, there are obtained 77.8 g of rac.-1,4,7,7-tetramethyl-2-endo-norbornanamine hydrochloride with a melting point of over 300°C.

The rac.-1,4,7,7-tetramethyl-2-exo-norbornanamine can be isolated from the respective mother liquors.

B) The process:

11.35 g of 2,3-dichloro-1,4-naphthoquinone are suspended in 100 ml of absolute alcohol and, with stirring, treated during 15 minutes with 16.73 g of rac.-2-endo-1,4,7,7-tetramethylnorbornanamine dissolved in 50 ml of absolute alcohol. The dark-red solution is boiled at reflux for two hours. The reaction mixture is thereafter evaporated under reduced pressure. The residue is dissolved in 200 ml of methylene chloride and successively shaken out with 100 ml of water, three times with 50 ml of 1-N hydrochloric acid each time and three times with 100 ml of water each time. After drying over sodium sulphate, the methylene chloride solution is concentrated, treated with active charcoal and evaporated. After crystallisation from methylene chloride/n.hexane, there are obtained 9.95 g of rac.-2-chloro-3-[(1,4,7,7-tetramethyl-2-endo-norbornyl)-amino]-1,4-naphthoquinone of melting point 114°—115°C.

Example 12

A) The preparation of the starting material:

The rac.-2-exo-1,4,7,7-tetramethylnorbornanamine used as the starting material can be isolated from the mother liquors obtained in Example 11(A).

B) The process:

4.42 g of 2,3-dichloro-1,4-naphthoquinone are suspended in 50 ml of absolute alcohol and treated with 6.5 g of rac.-2-exo-1,4,7,7-tetramethylnorbornanamine in 50 ml of absolute alcohol. The mixture is subsequently boiled at reflux for 3 hours, there resulting a dark-red solution. After evaporation, the residue is dissolved in 100 ml of methylene chloride and shaken out with 50 ml of water, three times with 25 ml of 3-N hydrochloric acid each time and four times with 50 ml of water each time. The organic phase is thereafter dried over sodium sulphate, filtered, concentrated, treated with active charcoal and evaporated. The residue is recrystallised from n.hexane/petroleum ether (40°—45°C). In this manner there are obtained 5.30 g of rac. - 2 - chloro - 3 - [(1,4,7,7 - tetramethyl - 2 - exo - norbornyl)amino] - 1,4-naphthoquinone of melting point 127°—129°C.

Example 13

A) The preparation of the starting material:

rac.-4-Propyl-2-exo-bornanamine hydrochloride can be obtained from the corresponding oxime in a manner analogous to that described in Examples 11(A) and 12(A).

B) The process:

A suspension of 4.54 g of 2,3-dichloro-1,4-naphthoquinone in 100 ml of methylene chloride is treated at room temperature with 4.45 g of triethylamine. 5.564 g of rac.-4-propyl-2-exo-bornanamine hydrochloride are added to the resulting brownish-green suspension and the resulting mixture is boiled under reflux for 24 hours and subsequently worked up. The methylene chloride solution is washed with water, 1-N hydrochloric acid and again with water, dried over sodium sulphate, filtered and evaporated. The residue is recrystallised from alcohol to yield 6.54 g of crude crystals with a melting point of 109°—111°C. From the mother liquor, after recrystallisation from alcohol there are obtained a further 0.72 g of product having a melting point of 108°—110°C. The total yield of rac.-2-chloro-3-[(4-propyl-2-exo-bornyl)amino]-1,4-naphthoquinone amounts of 7.26 g.

Example 14

A) The preparation of the starting material:

12.16 g of magnesium turnings are overlaid with 350 ml of absolute ether and, with stirring, treated over a period of 70 minutes with a solution of 55.6 g of ethyl bromide in 50 ml of absolute ether. The resulting mixture is heated under reflux for a further 60 minutes, then cooled to room temperature and treated dropwise over a period of 60 minutes with a solution of 48.9 g of 1-heptyne in 50 ml of absolute ether. The resulting mixture is boiled under reflux for 18 hours, treated dropwise over a period of 60 minutes with a solution of 76.1 g of racemic camphor in 50 ml of absolute ether, boiled under reflux for 20 hours, cooled in an ice-bath and treated with 50 ml of water and 200 ml of hydrochloric acid (1:1). The ethereal phase is washed neutral with five 150 ml portions of water, dried over sodium sulphate, filtered and

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evaporated. The residue (114.5 g) is subjected to a steam-distillation, 1.8 litres of distillate being collected. The distillation residue is treated with 300 ml of ether and the ether phase is separated off, washed with three 150 ml portions of water, dried over sodium sulphate, filtered and evaporated to yield 71.4 g of rac.-2-heptynyl-2-borneol having a boiling point of 99°—100°C/0.01 mm Hg.

70.3 g of rac.-2-heptynyl-2-borneol in 300 ml of glacial acetic acid are hydrogenated in the presence of 1 g of platinum dioxide while shaking at room temperature under normal pressure. After 3 hours, 12.75 litres of hydrogen have been taken up and the reaction comes to a standstill. The catalyst is filtered off and the filtrate is concentrated on a rotary evaporator in water-jet vacuum. The residue is dissolved in 300 ml of ether and the solution is washed with eight 100 ml portions of water, dried over sodium sulphate, filtered and evaporated to yield 62.9 g of rac.-2-heptyl-2-borneol having a boiling point of 103°—105°C/0.01 mm Hg.

50 ml of glacial acetic acid are treated with 4.22 g of concentrated sulphuric acid ($d=1.84$) and heated to 60°, then treated dropwise with stirring over a period of 20 minutes with a mixture of 10.1 g of rac.-2-heptyl-2-borneol and 3.61 g acetonitrile in 30 ml of glacial acetic acid. The resulting mixture is stirred at 60°C for 19 hours, again treated with 4.22 g of concentrated sulphuric acid ($d=1.84$) and 3.61 g of acetonitrile, heated at 60°C for a further 23 hours, cooled to room temperature, poured onto ca 300 g of ice and allowed to stand for 1 hour. The oil which separates out is taken up in ca 200 ml of ether and the ethereal solution is washed with two 100 ml portions of water, two 50 ml portions of saturated sodium carbonate solution and three 150 ml portions of water, dried over sodium sulphate, filtered and evaporated. The crude residue (8.55 g) is chromatographed on 260 g of silica gel (0.2—0.5 mm) with methylene chloride as eluting agent, 180 fractions of 10 ml being collected. Fractions 148—160 contain 5.65 g of rac.-N-(4-heptyl-2-exo-bornyl)-acetamide which melts at 94°—96°C after crystallisation from methanol.

13.8 g of rac.-N-(4-heptyl-2-exo-bornyl)-acetamide are boiled under reflux with stirring for 48 hours with 140 ml of 6-N hydrochloric acid and 70 ml of ethanol. The resulting mixture is cooled in an ice-bath and the precipitated crystals are filtered off, dried and crystallised from ether/(petroleum ether) to yield 9.25 g of material having a melting point of 242°—244°C. A further 1.8 g of material having a melting point of 242°—244°C can be obtained from the ether/(petroleum ether) mother liquor. The total yield of rac.-4-heptyl-2-exo-bornanamine hydrochloride amounts to 11.05 g.

B) The process:

A suspension of 2.27 g of 2,3-dichloro-1,4-naphthoquinone in 50 ml of methylene chloride is treated at room temperature with 2.43 g of triethylamine. 3.455 g of rac.-4-heptyl-2-exo-bornanamine hydrochloride are added to the resulting brownish-green suspension and the resulting mixture is boiled under reflux for 17 hours, then washed with water, 1-N hydrochloric acid and again with water, dried over sodium sulphate, filtered and evaporated. The residue is crystallised from alcohol to yield 4.07 g of rac.-2-chloro-3-[(4-heptyl-2-exo-bornyl)amino]-1,4-naphthoquinone of melting point 80°—82°C.

Example 15

A) The preparation of the starting material:

rac.-4-Phenyl-2-exo-bornanamine can be obtained from the corresponding oxime in a manner analogous to that described in Examples 11(A) and 12(A).

B) The process:

A solution of 2.3 g of rac.-4-phenyl-2-exo-bornanamine and 1.38 ml of triethylamine in 50 ml of methylene chloride is added dropwise over a period of 80 minutes at reflux temperature to a solution of 2.3 g of 2,3-dichloro-1,4-naphthoquinone in 50 ml of methylene chloride. After an hour, a further 0.458 g of rac.-4-phenyl-2-exo-bornanamine are added and the resulting mixture is boiled at reflux for a further 4 hours, cooled, washed 3 times with water, dried over sodium sulphate and evaporated in vacuum. The residue is crystallised from ether/hexane and recrystallised from (methylene chloride)/hexane to yield 3.7 g of rac.-2-chloro-3-[(4-phenyl-2-exo-bornyl)amino]-1,4-naphthoquinone in the form of red crystals of melting point 121°—122°C.

Example 16

A) The preparation of the starting material:

61 g of phenethyl-borneol are boiled at reflux for 4 hours with 60 ml of acetic anhydride. The resulting mixture is evaporated in vacuum and the residue is treated

with benzene and water and neutralised with sodium bicarbonate. The phases are separated, and the aqueous phase is extracted twice with benzene. The combined benzene phases are dried with sodium sulphate, filtered and evaporated. The residue is distilled in high vacuum (0.01 mm Hg) to yield 40 g of rac.-2-(1-phenylethylidene)-camphane.

A mixture of 72 g of rac.-2-(1-phenylethylidene)-camphane and 24.6 g of acetonitrile is added dropwise over a period of 5 minutes to a solution, heated to 60°C, of 60 ml of concentrated sulphuric acid in 900 ml of glacial acetic acid. The resulting mixture is stirred at 60°C for 10 hours, then a further 24.6 g of acetonitrile are added and the mixture is stirred at 60°C for a further 10 hours, poured onto 1.5 kg of ice and exhaustively extracted with methylene chloride. The combined methylene chloride phases are washed with aqueous sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated. The residue is crystallised from n-hexane/(methylene chloride) (1:2) to yield 19.6 g of rac.-N-(4-phenethyl-3-exo-bornyl)-acetamide having a melting point of 169°—171°C. Working up of the mother liquors yields a further 6.5 g of the same substance having a melting point of 166°—169°C.

8.1 g of rac.-N-(4-phenethyl-2-exo-bornyl)-acetamide are boiled under reflux for 60 hours with 800 ml of 6-N hydrochloric acid and 400 ml of ethanol, then the resulting mixture is evaporated in vacuum. The residue is crystallised from methanol/water to yield 4.1 g of rac.-4-phenethyl-2-exo-bornanamine hydrochloride of melting point 277°—278°C.

B) The process:

A solution of 2.6 g of rac.-4-phenethyl-2-exobornanamine and 1.38 ml of triethylamine in 50 ml of benzene is added dropwise at 50°C to 2.3 g of 2,3-dichloro-1,4-naphthoquinone in 50 ml of benzene. The resulting mixture is stirred at 60°C for 24 hours, then a further 0.51 g of rac.-4-phenethyl-2-exo-bornanamine are added and the mixture is stirred at 60°C for a further 24 hours, allowed to cool, washed with water, and evaporated. The residue is crystallised from (methylene chloride)/n-hexane to yield 3.3 g of rac.-2-chloro-3-[(4-phenethyl-2-exo-bornyl)amino]-1,4-naphthoquinone in the form of red crystals of melting point 133°—134°C.

Example 17

A) The preparation of the starting material:

34.5 g of 2-phenyl-borneol and 15.8 ml of acetonitrile are added dropwise over the course of a few minutes at 60°C to a solution of 32 g of concentrated sulphuric acid in 450 ml of glacial acetic acid. After 6 hours at 60°C, a further 15.8 ml of acetonitrile are added and the resulting mixture is stirred at 60°C for a further 15 hours, then poured onto ice and extracted with methylene chloride. The extract is washed with saturated sodium hydrogen carbonate solution, dried over sodium sulphate and evaporated. The residue is crystallised from (methylene chloride)/hexane to yield 15.3 g of rac.-N-(4-phenyl-2-exo-bornyl)-acetamide of melting point 151°—152°C. Chromatography of the mother liquors on silica gel with methylene chloride yields a further 6.6 g of rac.-N-(4-phenyl-2-exo-bornyl)-acetamide.

21.6 g of rac.-N-(4-phenyl-2-exo-bornyl)-acetamide are treated with 120 ml of concentrated nitric acid. The resulting mixture is treated dropwise with stirring at -10°C with 72 ml of concentrated sulphuric acid, held at -10°C for 25 hours, allowed to warm to 0°C, poured onto 1 kg of ice and extracted with methylene chloride. The extract is dried over sodium sulphate and evaporated. The residue is crystallised from acetone/n-hexane to yield 14.9 g of rac.-N-[4-(p-nitro-phenyl)-2-exo-bornyl]-acetamide of melting point 205°—206°C.

6.32 g of rac.-N-[4-(p-nitro-phenyl)-2-exo-bornyl]-acetamide are boiled at reflux for 72 hours with 300 ml of ethanol and 600 ml of 6-N hydrochloric acid. The resulting mixture is evaporated in vacuo and the residue crystallised from methanol/water to yield 5.2 g of rac.-4-(p-nitro-phenyl)-2-exo-bornanamine hydrochloride of melting point 347°C (with decomposition).

B) The process:

A solution of 2.7 g of rac.-4-(p-nitro-phenyl)-2-exo-bornanamine and 1.38 ml of triethylamine in 50 ml of methylene chloride is added dropwise over the course of 80 minutes to a boiling solution of 2.3 g of 2,3-dichloro-1,4-naphthoquinone in 50 ml of methylene chloride; after 3 hours, a solution of a further 0.35 g of rac.-4-(p-nitro-phenyl)-2-exo-bornanamine in a small amount of methylene chloride is added. The stirred mixture is heated at reflux for a total of 72 hours. It is subsequently washed four times with a small amount of water, dried over sodium sulphate, treated with

n-hexane until a turbidity begins to form, and allowed to stand in a refrigerator. Resulting crystals are recrystallised from (methylene chloride)/n-hexane to yield 2.9 g of rac.-2-chloro-3-[4-(p-nitro-phenyl)-2-exo-bornylamino]-1,4-naphthoquinone of melting point 180°—181°C.

The following Examples are illustrative of pharmaceutical preparations containing the naphthoquinone derivatives provided by the invention:

Example A

Capsules of the following composition are manufactured in a conventional manner:

rac.-2-(2-exo-Bornylamino)- 3-chloro-1,4-naphthoquinone	200 mg
Lactose	110 mg
Corn starch	35 mg
Talc	5 mg

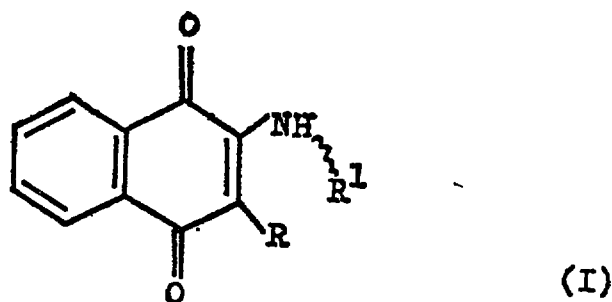
Example B

Tablets of the following composition are manufactured in a conventional manner:

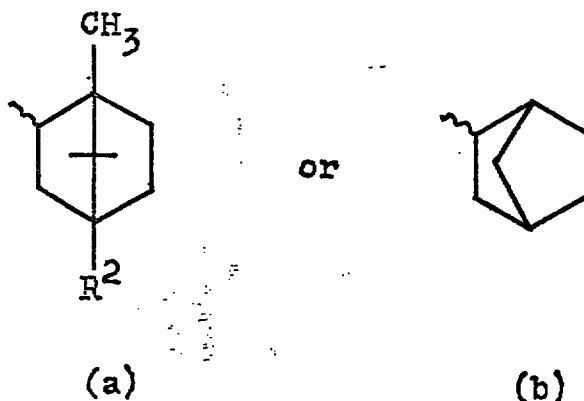
rac.-2-(2-exo-Bornylamino)- 3-chloro-1,4-naphthoquinone	100 mg
Lactose	50 mg
Corn starch	23 mg
Calcium stearate	2 mg

WHAT WE CLAIM IS:—

1. Naphthoquinone derivatives of the general formula



wherein R represents a hydrogen or halogen atom or a lower alkoxy group and R¹ represents a grouping of the formula



in which R² represents a hydrogen atom, a lower alkyl group, a phenyl group which may be substituted by halogen, nitro, amino or hydroxy, or a phenyl-(lower) alkyl) group.

2. Naphthoquinone derivatives in accordance with claim 1, wherein R¹ represents a grouping of formula (a).

3. Naphthoquinone derivatives in accordance with claim 2, wherein R² in the grouping of formula (a) represents a hydrogen atom.



(21)

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n-hexane until a turbidity begins to form, and allowed to stand in a refrigerator. Resulting crystals are recrystallised from (methylene chloride)/n-hexane to yield 2.9 g of rac.-2-chloro-3-[4-(p-nitro-phenyl)-2-exo-bornylamino]-1,4-naphthoquinone of melting point 180°—181°C.

5 The following Examples are illustrative of pharmaceutical preparations containing the naphthoquinone derivatives provided by the invention: 5

Example A

Capsules of the following composition are manufactured in a conventional manner:

10	rac.-2-(2-exo-Bornylamino)- 3-chloro-1,4-naphthoquinone	200 mg	10
	Lactose	110 mg	
	Corn starch	35 mg	
	Talc	5 mg	

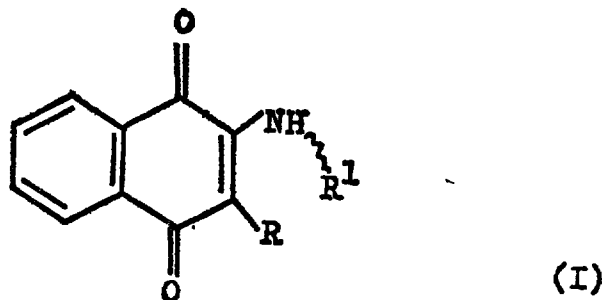
Example B

15 Tablets of the following composition are manufactured in a conventional manner: 15

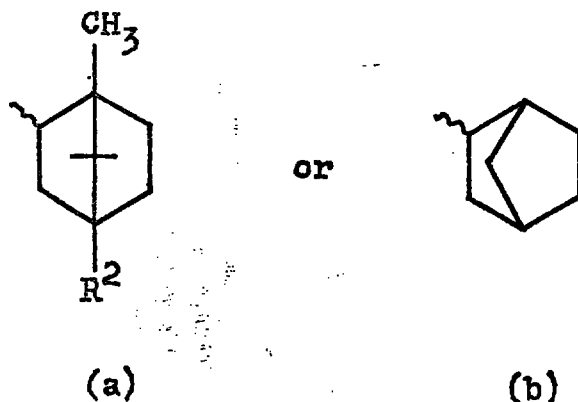
	rac.-2-(2-exo-Bornylamino)- 3-chloro-1,4-naphthoquinone	100 mg	
	Lactose	50 mg	
20	Corn starch	23 mg	20
	Calcium stearate	2 mg	

WHAT WE CLAIM IS:—

1. Naphthoquinone derivatives of the general formula



25 wherein R represents a hydrogen or halogen atom or a lower alkoxy group and 25
R¹ represents a grouping of the formula

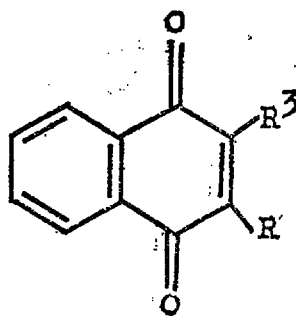


30 in which R² represents a hydrogen atom, a lower alkyl group, a phenyl group which may be substituted by halogen, nitro, amino or hydroxy, or a phenyl- (lower) alkyl group. 30

2. Naphthoquinone derivatives in accordance with claim 1, wherein R¹ represents a grouping of formula (a).

3. Naphthoquinone derivatives in accordance with claim 2, wherein R² in the grouping of formula (a) represents a hydrogen atom.

4. Naphthoquinone derivatives in accordance with claim 2, wherein R^2 in the grouping of formula (a) represents the methyl group.
5. Naphthoquinone derivatives in accordance with claim 2, wherein R^2 in the grouping of formula (a) represents the n-propyl group.
- 5 6. Naphthoquinone derivatives in accordance with claim 2, wherein R^2 in the grouping of formula (a) represents the n-heptyl group. 5
7. Naphthoquinone derivatives in accordance with claim 2, wherein R^2 in the grouping of formula (a) represents the phenyl group.
8. Naphthoquinone derivatives in accordance with claim 2, wherein R^2 in the grouping of formula (a) represents the phenethyl group.
- 10 9. Naphthoquinone derivatives in accordance with claim 1, wherein R^1 represents a grouping of formula (b). 10
10. Naphthoquinone derivatives in accordance with any one of claims 1 to 9 inclusive, wherein R represents a hydrogen atom.
- 15 11. Naphthoquinone derivatives in accordance with any one of claims 1 to 9 inclusive, wherein R represents a halogen atom. 15
12. Naphthoquinone derivatives in accordance with claim 11, wherein R represents a bromine atom.
13. Naphthoquinone derivatives in accordance with claim 11, wherein R represents a chlorine atom.
- 20 14. Naphthoquinone derivatives in accordance with any one of claims 1 to 9 inclusive, wherein R represents a lower alkoxy group. 20
15. Naphthoquinone derivatives in accordance with claim 14, wherein R represents the methoxy group.
- 25 16. rac.-2-(endo-Bornylamino)-3-chloro-1,4-naphthoquinone. 25
17. (+)-2-[(1R)-2-endo-Bornylamino]-3-chloro-1,4-naphthoquinone.
18. (-)-2-[(1R)-2-exo-Bornylamino]-3-chloro-1,4-naphthoquinone.
19. (+)-2-[(1R)-2-endo-Bornylamino]-3-bromo-1,4-naphthoquinone.
20. rac.-2-(2-endo-Bornylamino)-3-bromo-1,4-naphthoquinone.
- 30 21. rac.-2-(2-endo-Bornylamino)-1,4-naphthoquinone. 30
22. rac.-2-Chloro-3-(2-endo-norbornylamino)-1,4-naphthoquinone.
23. rac.-2-Chloro-3-(2-exo-norbornylamino)-1,4-naphthoquinone.
24. rac.-2-(2-exo-Bornylamino)-3-chloro-1,4-naphthoquinone.
25. rac.-2-(2-exo-Bornylamino)-1,4-naphthoquinone.
- 35 26. rac.-2-(2-exo-Bornylamino)-3-bromo-1,4-naphthoquinone. 35
27. rac.-2-(2-endo-Bornylamino)-3-methoxy-1,4-naphthoquinone.
28. rac.-2-(2-exo-Bornylamino)-3-methoxy-1,4-naphthoquinone.
29. rac - 2 - Chloro - 3 - [2 - endo - (1,4,7,7 - tetramethylnorbornyl) - amino] - 1,4 - naphthoquinone.
- 40 30. rac. - 2 - Chloro - 3 - [2 - exo - (1,4,7,7 - tetramethylnorbornyl) - amino] - 1,4 - naphthoquinone. 40
31. rac.-2-Chloro-3-[(4-propyl-2-exo-bornyl)-amino]-1,4-naphthoquinone.
32. rac.-2-Chloro-3-[(4-n-heptyl-2-exo-bornyl)amino]1,4-naphthoquinone.
33. rac.-2-Chloro-3-[(4-phenyl-2-exo-bornyl)-amino]-1,4-naphthoquinone.
- 45 34. rac.-2-Chloro-3-[(4-phenethyl-2-exo-bornyl)-amino]-1,4-naphthoquinone. 45
35. A pharmaceutical preparation comprising a naphthoquinone derivative as set forth in any one of claims 1 to 34 inclusive in admixture with a compatible pharmaceutical carrier.
36. A process for the manufacture of the compounds claimed in claim 1, which process comprises reacting a compound of the general formula
- 50 50



(II)



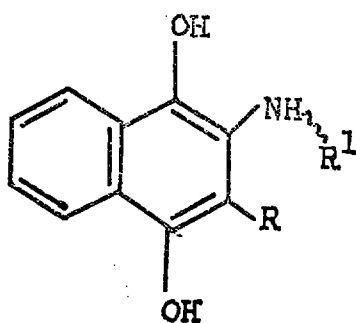
, wherein R has the significance given in claim 1 and R³ represents a leaving atom or group (as hereinbefore defined), with an amine of the general formula



(III)

5 , wherein R¹ has the significance given in claim 1, or oxidising a compound of the general formula

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(IV)

- 10 , wherein R and R¹ have the significance given in claim 1, and, in either case if desired, converting a naphthoquinone derivative of formula I obtained in which R represents a hydrogen atom or a halogen atom other than a chlorine atom into a corresponding derivative in which R represents a chlorine atom.
37. A process according to claim 36, wherein an amine starting material of formula III in which R¹ represents a grouping of formula (a) is used.
- 15 38. A process according to claim 37, wherein an amine starting material of formula III in which R² in the grouping of formula (a) represents a hydrogen atom or the methyl group is used.
39. A process according to claim 36, wherein an amine starting material of formula III in which R¹ represents a grouping of formula (a) is used.
- 20 40. A process according to any one of claims 36 to 39 inclusive, wherein a starting material of formula II in which R represents a halogen atom is used.
41. A process according to claim 40, wherein a starting material of formula II in which R represents a bromine or chlorine atom is used.
- 25 42. A process according to any one of claims 36 to 39 inclusive, wherein a starting material of formula II in which R represents a hydrogen atom is used.
43. A process according to any one of claims 36 to 39 inclusive, wherein a starting material of formula II in which R represents a lower alkoxy group is used.
44. A process according to claim 43, wherein a starting material of formula II in which R represents the methoxy group is used.
- 30 45. A process according to any one of claims 36 to 44 inclusive, wherein the reaction of a compound of formula II with an amine of formula III is carried out in an inert organic solvent.
46. A process according to any one of claims 36 to 45 inclusive, wherein the reaction of a compound of formula II with an amine of formula III is carried out at a temperature of from about room temperature to about 150°C.
- 35 47. A process according to claim 36, wherein a starting material of formula IV in which R represents a halogen atom and R¹ represents a grouping of formula (a) in which R² represents a hydrogen atom is used.
48. A process according to claim 36 or claim 47, wherein the oxidation of a compound of formula IV is carried out by conducting oxygen through a solution of a compound of formula IV.
- 40 49. A process according to any one of claims 36 to 48 inclusive, wherein the conversion of a naphthoquinone derivative of formula I in which R represents a hydrogen atom or a halogen atom other than a chlorine atom into a corresponding derivative in which R represents a chlorine atom is carried out by means of lithium chloride.



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50. A process for the manufacture of the naphthoquinone derivatives of formula I in claim 1, substantially as hereinbefore described with reference to Examples 1 to 17.

5 51. Naphthoquinone derivatives of formula I in claim 1, when manufactured by the process claimed in any one of claims 36 to 50 inclusive.

5

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