United States Patent Office

3,639,432

Patented Feb. 1, 1972

3,639,432

2-HYDROXY-1,4-NAPHTHOQUINONE AMINOBENZOATES

Giancarlo Berti, Pisa, Italy, assignor to Finanz und Kompensations Anstalt, Vaduz, Leichtenstein, Germany

No Drawing. Continuation-in-part of application Ser. No. 493,245, Oct. 5, 1965. This application June 12, 1968, Ser. No. 736,285

Claims priority, application Austria, Oct. 5, 1964, 8,472/64

Int. Cl. C07c *79/46, 101/62*

U.S. Cl. 260—396 R 14 Claims

ABSTRACT OF THE DISCLOSURE

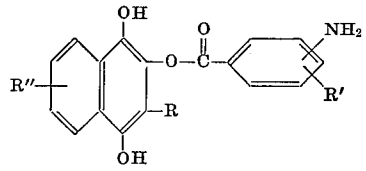
2 - hydroxy - 1,4 - naphthohydroquinone aminobenzoates, prepared by catalytically hydrogenating the condensation product of a 2-hydroxy-1,4-naphthoquinone and a nitrobenzoyl halide, are useful as antihaemorrhagic and capillary protective agents.

RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 493,245 filed Oct. 5, 1965 now abandoned.

SUMMARY

The present invention is directed to antihaemorrhagic and capillary protective agents of the formula



(I)

wherein

R is either hydrogen or lower alkyl, e.g. methyl, ethyl, propyl, isopropyl and butyl; and

each of R′ and R″ is, independently, either hydrogen; lower alkyl, e.g. methyl, ethyl, propyl, isopropyl and butyl; or lower alkoxy, e.g. methoxy, ethoxy, propoxy and butoxy;

to a process for the preparation of said agents and to intermediates formed in the preparation of said agents.

The preferred compounds of this invention are those wherein each of R′ and R″ is hydrogen and R is either hydrogen or methyl. When R″ is other than hydrogen, it is preferably in the 6- or 7-position. The amino group is preferably in the para-position.

It is an object of the subject invention to provide therapeutically active compounds having low acute and subacute toxicity. A further object is to produce compounds having a marked antihaemorrhagic activity and which can be administered orally. Another object is to obtain compounds which provide a capillary protective action. An additional object is to synthesize compounds having the noted properties. Still further objects will be apparent from the description and examples.

UTILITY

The compounds of this invention (esters I) have such a low toxicity that no deaths resulted from administering per os up to 2.0 grams/kilogram of body weight to mice, rats and rabbits. Said compounds produce a marked antihaemorrhagic activity in dosages of as little as 0.2 mg./kg. and retain such action when administered in doses up to 50 mg./kg. or higher. The consequent utility as antihaemorrhagic agents is confirmed by standard pharmacological tests in rabbits and mice.

Compounds I are also useful as capillary protective agents. For this purpose they are administered, e.g., orally in doses of from 0.2 to 20 mg./kg. The capillary protective action has been confirmed by standard tests on albino rabbits.

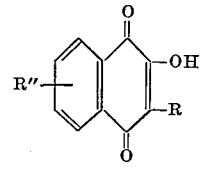
Compounds I are administered to mammals orally in standard dosage forms, e.g. tablets and capsules. The average daily dose varies, but is ordinarily within the range of from 0.2 to 50 milligrams (mg.) per kilogram (kg.) of body weight. It may be administered either as a single dose or in divided doses at regular intervals from two to four times per day.

Each of the compounds of this invention may be, e.g., incorporated, for oral administration, in a tablet as the sole active ingredient. A typical tablet is constituted by from 1 to 3 percent binder, e.g. tragacanth; from 3 to 10 percent disintegrating agent, e.g. corn starch; from 2 to 10 percent lubricant, e.g. talcum; from 0.25 to 1.0 percent lubricant, e.g. magnesium stearate; an average dosage of active ingredient; and q.s. 100 percent of filler, e.g. lactose; all percentages being by weight. Tablets are prepared according to standard tabletting techniques, which are well-known in the art, employing the necessary amounts of conventional granulating liquids, e.g. alcohol SD–30 and purified water. An exemplary tabletting formulation is:

	Parts
2 - (p - aminobenzoyloxy) - 1,4 - dihydroxynaphthalene	50
Tragacanth	2
Lactose	39.5
Corn starch	5
Talcum	3
Magnesium stearate	0.5
Alcohol SD–30, purified water, q.s.	

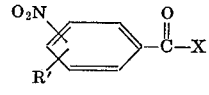
DETAILS

Esters I are prepared by reacting a 2-hydroxy-1,4-naphthoquinone of the formula



(II)

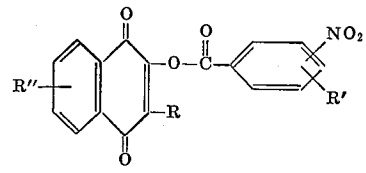
with a nitrobenzoyl halide of the formula



(III)

wherein X is halo, e.g. bromo and iodo, but preferably chloro;

in an inert solvent, e.g. benzene, chloroform and tetrahydrofuran, and in contact with a tertiary amine, e.g. pyridine, triethylamine and dimethylaniline. (In Formulae II and III and, in the absence of a contrary indication, throughout the disclosure, each of R, R′ and R″ has its aboveascribed definition.) The resulting corresponding nitrobenzoic esters of the formula



(IV)

are obtained in yields ranging from 80 to 95 percent, based on the weight of the starting materials.

Compounds II and III are either known compounds or are prepared according to published procedures from available starting materials. Exemplary Compounds II include:

3-isopropyl-2-hydroxy-1,4-naphthoquinone,
3-butyl-2-hydroxy-6-methyl-1,4-naphthoquinone,
6-ethyl-2-hydroxy-1,4-naphthoquinone,
2-hydroxy-3-methyl-6-propyl-1,4-naphthoquinone,
3-ethyl-2-hydroxy-6-isopropyl-1,4-naphthoquinone,
6-butyl-2-hydroxy-1,4-naphthoquinone,
3,7-dimethyl-2-hydroxy-1,4-naphthoquinone,
3,6- or 3,7-diethyl-2-hydroxy-1,4-naphthoquinone,
2-hydroxy-3-isopropyl-7-propyl-1,4-naphthoquinone,
2-hydroxy-7-isopropyl-1,4-naphthoquinone,
7-butyl-2-hydroxy-3-methyl-1,4-naphthoquinone,
3-ethyl-2-hydroxy-6-methoxy-1,4-naphthoquinone,
2-hydroxy-7-methoxy-3-propyl-1,4-naphthoquinone and
3-butyl-6- or 7-ethoxy-2-hydroxy-1,4-naphthoquinone.

Illustrative Compounds III are:

2-nitro-4-propoxybenzoyl chloride,
3-methyl-5-nitrobenzoyl chloride,
2-ethyl-4-nitrobenzoyl chloride,
2-nitro-4-propylbenzoyl chloride,
2-isopropyl-5-nitrobenzoyl chloride,
3-butyl-4-nitrobenzoyl chloride,
5-methoxy-2-nitrobenzoyl chloride,
2-ethoxy-3-nitrobenzoyl chloride and
3-methoxy-4-nitrobenzoyl bromide.

The nitrobenzoic acid esters IV are catalytically reduced with hydrogen in an inert solvent, e.g. dioxane and tetrahydrofuran, at a pressure of from 1 to 10 atmospheres and at a temperature of from 20° to 60° C. The catalyst employed for the catalytic reduction is a finely divided metal catalyst, e.g. platinum, palladium and nickel, which is in intimate contact with said nitrobenzoic acid esters during the reduction.

The naphthoquinonic system is thus first reduced to the corresponding naphthohydroquinonic system with the absorption of one mole of hydrogen per mole of ester, yielding the corresponding 2 - (nitrobenzoyloxy)-1,4-dihydroxy-naphthalene. On continuation of the reduction, a further three moles of hydrogen, per mole of ester, are absorbed, corresponding to the reduction of the nitro group to primary amino, to produce the corresponding Compound I with yields in the order of from 70 to 80 percent.

PREFERRED EMBODIMENTS

The following examples are merely illustrative. Reactions wherein R, R', R'' and X have any particular meaning or are designated as in a specified position are exemplary of corresponding reactions and the preparation of corresponding intermediates and final products wherein said R, R', R'' and X have any other meaning within the scope contemplated by this invention.

Example I

In a 1 litre flask fitted with a cooler having a calcium chloride closure, a solution of 50 grams (g.) of dry 2-hydroxy-3-methyl-1,4-naphthoquinone, 55 g. of p-nitrobenzoyl chloride and 30 g. of pyridine (dried by distilling over NaOH) in 300 milliliters (ml.) of benzene (dried over sodium) is refluxed for one hour. After cooling, the precipitate is collected by suction filtering and washed with 2 portions of 50 ml. of benzene. The filtrate is concentrated to 50 ml. by distillation, is filtered again, washing the precipitate with two portions of 20 ml. of benzene. Both combined precipitates are suspended in 500 ml. of distilled water; the suspension is stirred for 10 minutes in order to dissolve the pyridinium chloride completely; the resulting product is then collected by suction filtering and washed with distilled water until chloride-reaction free. The 90° C. stove-dried product is formed at 84 g. of 2 - hydroxy - 3-methyl-1,4-naphthoquinone p-nitrobenzoate; yellow crystals; melting point (M.P.) 178°–182° C. The product is re-crystallized by solution in boiling chloroform, followed by dilution in ethanol, melting then at 180°–182° C.

A solution of 50 g. of 2-hydroxy-3-methyl-1,4-naphthoquinone p-nitrobenzoate in 500 ml. of pure dioxane is admixed with 0.5 g. of platinum dioxide and stirred in the presence of hydrogen under normal pressure and at the temperature of 50° C., measuring the gas absorption. Absorption is stopped after 13 litres of gas have been absorbed, which takes 3–4 hours. The catalyst is removed by filtering, and the filtrate is diluted with 2 litres of petroleum ether (M.P. 40°–70° C.). An oily layer is separated; the supernatant liquid is decanted and the residue taken up in 200 ml. of benzene, heating a few minutes to boiling. After cooling, the precipitate is collected by suction filtering and washed with 100 ml. of benzene, thus obtaining 2-hydroxy-3-methyl-1,4-naphthohydroquinone 2 - (p - aminobenzoate) [2-(p-aminobenzoyloxy)-3-methyl - 1,4 - naphthohydroquinone] containing a molecule of crystal dioxane, which is removed by vacuum drying at 80° C. The residue is a greyish white powder melting with decomposition between 214° and 218° C. Said residue can be re-crystallized from an acetone and cyclohexane mixture.

Replacing the 2-hydroxy-3-methyl-1,4-naphthoquinone with an equivalent of either

3-ethyl-2-hydroxy-1,4-naphthoquinone,
2-hydroxy-3-propyl-1,4-naphthoquinone,
2-hydroxy-3-isopropyl-1,4-naphthoquinone or
2-hydroxy-3-(n-octyl)-1,4-naphthoquinone

results in the preparation, in similar manner, of

2-(p-aminobenzoyloxy)-3-ethyl-1,4-naphthohydroquinone,
2-(p-aminobenzoyloxy)-3-propyl-1,4-naphthohydroquinone,
2-(p-aminobenzoyloxy)-3-isopropyl-1,4-naphthohydroquinone or
2 - (p-aminobenzoyloxy)-3-(n-octyl)-1,4-naphthoquinone,

respectively.

Stopping the catalytic hydrogenation after the absorption of one mole of hydrogen (per mole of naphthoquinone-p-nitrobenzoate) yields the intermediate, 3-methyl-2-(p-nitrobenzoyloxy)-1,4-naphthohydroquinone.

Example II

A solution of 10 g. of 2-hydroxy-1,4-naphthoquinone, 12 g. of p-nitrobenzoyl chloride and 8 ml. of pyridine in 100 ml. of benzene is refluxed for 45 minutes. The same procedure used in Example I is successively repeated and, after treatment with water, 16.2 g. of 2-hydroxy-naphthoquinone p-nitro-benzoate as yellow prisms are recovered; the same, re-crystallized from chloroform, melt at 190°–192° C.

10 g. of this product in 100 ml. of dioxane are hydrogenated in the presence of 0.1 g. of platinum dioxide under the pressure of 5 atmospheres and at the temperature of 40° C. After the absorption of four molar equivalents of hydrogen is completed, the product is filtered and the filtrate evaporated in a rotating evaporator under a pressure of 15 millimeters (mm.) of mercury. The residue is taken up in 50 ml. of benzene and vacuum dried at 60° C. 8.5 g. of 2-hydroxy-1,4-naphthohydroquinone-2-(p-aminobenzoate) as a light pink powder are recovered; M.P. 200°–202° C. with decomposition.

Replacing the p-nitrobenzoyl chloride with an equivalent of either 2-methyl-4-nitrobenzoyl chloride, 3-methoxy-4-nitrobenzoyl chloride, 3-ethyl-4-nitrobenzoyl chloride or 3-ethoxy-5-nitrobenzoyl chloride results in the preparation, in similar manner, of 2-(2'-methyl-4'-nitrobenzoyloxy)-1,4 - naphthohydroquinone, 2 - (3'-methoxy-4'-nitrobenzoyloxy) - 1,4 - naphthohydroquinone, 2 - (3' - ethyl-4'-nitrobenzoyloxy) - 1,4 - naphthohydroquinone or 2-(3'-

ethoxy-5'-nitrobenzoyloxy)-1,4-naphthohydroquinone, respectively.

Example III

A solution of 30 g. of 2-hydroxy-3-methyl-1,4-naphthoquinone, 35 g. of m-nitrobenzoyl chloride and 20 ml. of anhydrous pyridine in 250 ml. of dry tetrahydrofuran is refluxed for 30 minutes. The solution is hot filtered to remove the insoluble pyridinium chloride. The filtrate is dry distilled over a water bath, and the residue is taken up in 100 ml. of ethanol by boiling for 10 minutes. After cooling, a yellow crystalline precipitate of 2-hydroxy-3-methyl-1,4-naphthoquinone-m-nitrobenzoate, M.P. 167°–169° C., is formed and collected. A 10 g. solution of this compound in 200 ml. of pure and dry tetrahydrofuran is hydrogenated in the presence of 1 g. of palladium on 10% carbon at normal temperature (20° C.) and pressure (1 atmosphere). When hydrogen absorption stops (after about two hours), the product is filtered and the filtrate evaporated to dryness at reduced pressure in a nitrogen stream. Residue is taken up in 100 ml. of benzene, collected by filtering and vacuum dried at 70° C., thus obtaining as a white powder, 2 - hydroxy - 3 - methyl-1,4-naphthohydroquinone-2-(m-aminobenzoate), M.P. 174°–178° C. with decomposition.

Replacing the 2-hydroxy-3-methyl-1,4-naphthoquinone with an equivalent of either 2-hydroxy-3,5-, 3,6- 3,7- or 3,8-dimethyl-1,4-naphthoquinone, 2-hydroxy-6-methoxy-3-methyl-1,4-naphthoquinone or 7-ethoxy-2-hydroxy-1,4-naphthoquinone results in the preparation, in similar manner, of 2-(m-aminobenzoyloxy)-3,5-, 3,6-, 3,7-, or 3,8-dimethyl - 1,4 - naphthohydroquinone, 2-(m-aminobenzoyloxy)-6-methoxy-3-methyl-1,4-naphthohydroquinone or 2-(m - aminobenzoyloxy) - 7 - ethoxy - 1,4 - naphthohydroquinone, respectively.

Example IV

From 10 g. of 2-hydroxy-1,4-naphthoquinone, 12 g. of m-nitrobenzoyl chloride and 8 ml. of anhydrous pyridine there are obtained, according to the procedure described in Example I, 2-hydroxy-naphthoquinone-m-nitrobenzoate as yellow crystals, M.P. 187°–189° C. Reduction of this product is carried out as described in Example II, but using 200 ml. of dioxane and 0.2 g. of platinum dioxide for 10 g. of nitro-ester; 2-hydroxy-1,4-naphthohydroquinone-2-(m-aminobenzoate), M.P. 214°–216° C. with decomposition, is thus obtained.

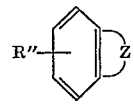
Example V

From 10 g. of 2-hydroxy-3-methyl-1,4-naphthoquinone, 11 g. of o-nitrobenzoyl chloride, 6 g. of pyridine and 100 ml. of benzene, operating according to Example I, 2-hydroxy - 3 - methyl-1,4-naphthoquinone-o-nitrobenzoate, M.P. 178–180° C., is obtained. 10 g. of this product in 100 ml. of dioxane are reduced as described in Example I, providing 2 - hydroxy-3-methyl-1,4-naphthohydroquinone-2-(o-aminobenzoate), M.P. 168°–172° C. with decomposition.

Each of the final products prepared according to this invention is useful as an antihaemorrhagic agent, the final products prepared as per the specific examples are merely exemplary. The corresponding nitrobenzoates and naphthoquinones are useful as intermediates in the preparation of said final products.

What is claimed is:

1. A compound of the formula



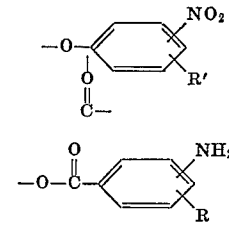
wherein

Z is a member selected from the group consisting of (a)

—CO—C(Y)=C(R)—CO— and (b)

—C(OH)=C(Y)—C(R)=C(OH)—

Y is a member selected from the group consisting of (c) and (d)

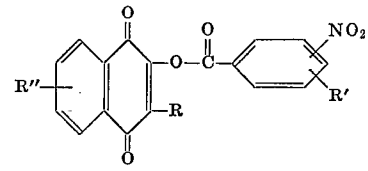


Y being (d) only when Z is (b);

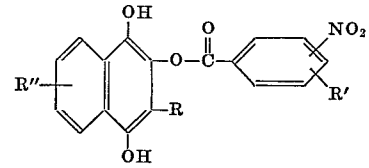
R is a member selected from the group consisting of hydrogen and lower alkyl; and

each of R' and R'' is, independently, a member selected from the group consisting of hydrogen, lower alkyl and lower alkoxy.

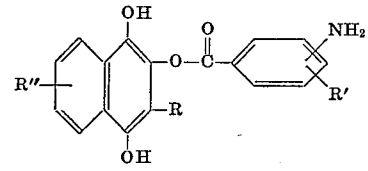
2. A compound according to claim 1 of the formula



3. A compound according to claim 1 of the formula



4. A compound according to claim 1 of the formula



5. A compound according to claim 4 wherein each of R' and R'' is hydrogen.

6. A compound according to claim 5 wherein R is hydrogen.

7. The compound according to claim 6 which is 2-hydroxy-1,4-naphthohydroquinone-2-(p-aminobenzoate).

8. The compound according to claim 6 which is 2-hydroxy-1,4-naphthohydroquinone-2-(m-aminobenzoate).

9. A compound according to claim 5 wherein R is methyl.

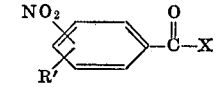
10. The compound according to claim 9 which is 2-(p-aminobenzoyloxy)-3-methyl-1,4-naphthohydroquinone.

11. The compound according to claim 9 which is 2-hydroxy - 3 - methyl - 1,4 - naphthohydroquinone-2-(m-aminobenzoate).

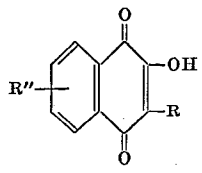
12. The compound according to claim 9 which is 2-hydroxy - 3 - methyl - 1,4 - naphthohydroquinone-2-(o-aminobenzoate).

13. A process for preparing compounds as defined in claim 1, which comprises:

(a) reacting a compound of the formula



wherein X is halo, with a hydroxynaphthoquinone of the formula



in an inert solvent and in the presence of a tertiary amine to obtain the corresponding nitrobenzoate and

(b) subjecting the obtained nitrobenzoate to catalytic hydrogenation in an inert solvent at a pressure of from 1 to 10 atmospheres and at a temperature of from 20 to 60° C., in the presence of a finely divided metal hydrogenation catalyst, the period of hydrogenation being so regulated as to produce the 1,2,4-trihydroxynaphthalene 2 - (nitrobenzoate) upon the

absorption of one mole of hydrogen per mole of ester, or the corresponding 2 - (aminobenzoate) after absorption of four mole of hydrogen per mole of ester.

14. A process according to claim **13** wherein X is chloro.

References Cited

Fieser, L. F. et al.: Organic Chemistry (1956), 3rd Ed. Pub. by Reinhold Publishing Corp. New York, pp. 181–182 and 596 relied on; QD 257 F5 (1956).

LORRAINE A. WEINBERGER, Primary Examiner

L. A. THAXTON, Assistant Examiner

U.S. Cl. X.R.

260—471 R; 424—309, 310