

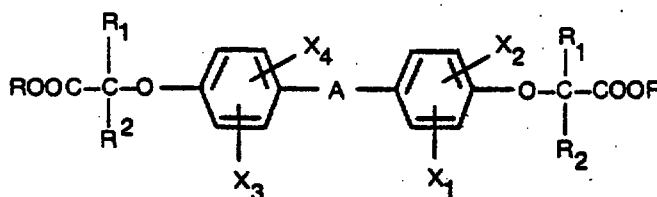
Novel substituted arylene compounds and processes for their production

This invention relates to novel substituted arylene compounds and processes for their production.

Elevated levels of blood cholesterol and blood lipids are conditions which are believed related to the onset of arteriosclerosis. Thus, compounds capable of reducing the levels of these blood constituents are recognized as potentially useful anti-arteriosclerotic agents. The prior art contains many materials which are characterized as potentially useful anti-arteriosclerotic agents. These prior art agents and intermediates thereto, which the applicants believe are most closely structurally related to the compounds of the present invention are as follows:

United States Patent Specification No. 3,686,271 discloses a class of arylene bis alpha-alkoxyacetic acids and certain derivatives; and United States Patent Specification No. 3,769,436 discloses a class of arylenebisoxyceticacids and certain derivatives.

Also, United States Patent No. 4,148,915 disclosed derivatives of bis(2-phenoxyalkane carboxylic acids) of the formula



in which

R represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms,

R₁ represents a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms,

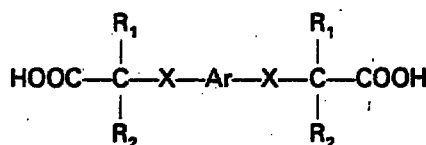
R₂ represents a hydrogen atom or an alkyl group having from 1 to 12 carbon atoms,

A represents O, S, SO or SO₂, and

X₁, X₂, X₃ and X₄, any two or more of which may be the same or different, each represents a hydrogen or halogen atom or an alkyl group having from 1 to 3 carbon atoms.

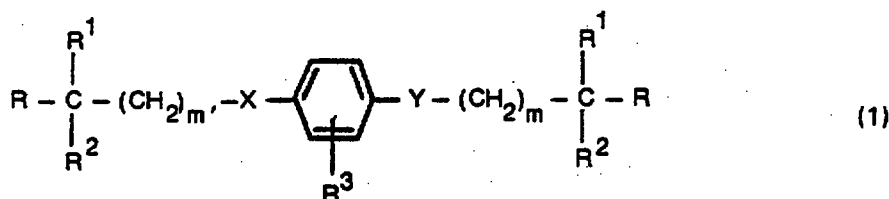
Such derivatives are useful in the treatment of hyperlipemia and arteriosclerosis, and US-4,148,915 contains data relating to investigations made on hypocholestermic activity, hypolipemic activity and the uricosuric activity of the derivatives.

Moreover, German Offenlegungsschrift No. 2,038,628 discloses compounds having the formula:



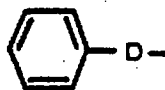
where X is O or NH, Ar is a mono- or bicyclo aryl radical such as phenyl, biphenylene or naphthylene, and each of R₁ and R₂ is a hydrogen atom or a lower alkyl radical containing up to 2 carbon atoms. These compounds have alleged, but unqualified, activity for the treatment of arteriosclerosis and coronary arteries.

One aspect of the present invention provides a compound having one of the formulae 1 to 5:—

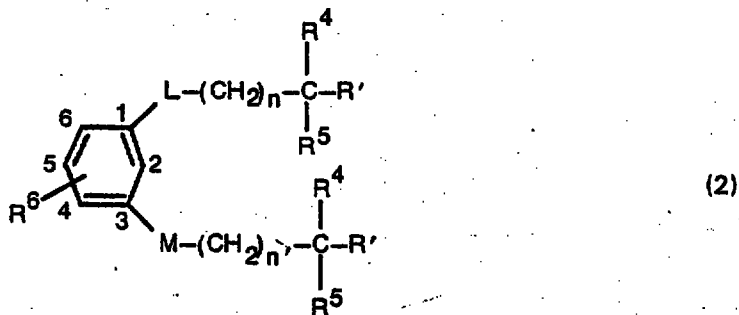


wherein X and Y are the same or different and are oxygen, sulfur, sulfone or sulfoxide; m and m' are the same or different and are integers in the range from 2 to 5; each R is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation; each of R¹ and R², which are the same or different, is an alkyl radical having from 1 to 6 carbon atoms, or R¹ when taken together with the R² which shares the same carbon atom represents —(CH₂)₃₋₅—; and R³ is a hydrogen or halogen atom, an alkyl radical having from 1 to 6 carbon atoms, methoxy, phenyl, trifluoromethyl, 2,5-dichloro, 2,5-dimethyl, 2,3,5-trimethyl, carboxylic acyl of from 1 to 6 carbon atoms, alpha-hydroxyalkyl having

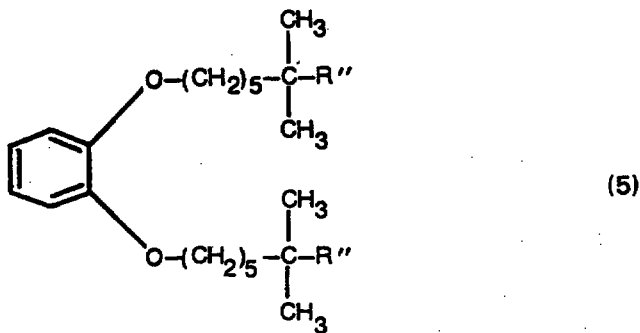
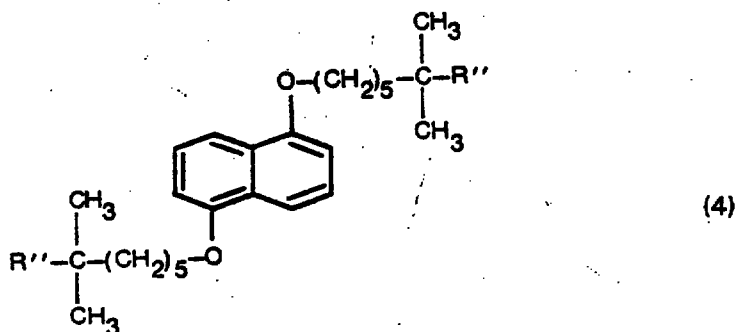
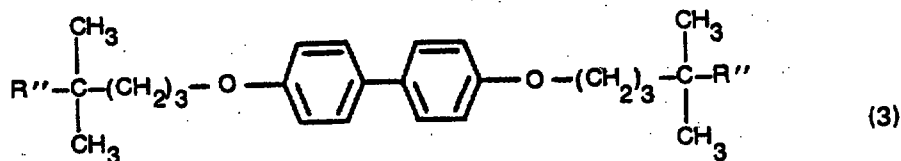
from 1 to 6 carbon atoms, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-methoxyphenyl, 2-tolyl, 4-tolyl or



wherein D is O, CO, S, SO, SO₂, CH₂, or CHO; provided that R³ is not a hydrogen atom when all of the following conditions are satisfied, namely when X and Y are both oxygen atoms, m and m' are both 2, R¹ and R² are both CH₃, and R is CO₂H:



wherein L and M are the same or different and are oxygen, sulfur, sulfone or sulfoxide; n and n' are the same or different and are integers in the range from 2 to 5; each of R⁴ and R⁵ which are the same or different is an alkyl radical having from 1 to 6 carbon atoms; R' is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl of from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation; and R⁶ is a hydrogen atom, 4-formyl, 2-nitro, 2-methyl, 5-methyl, 4-benzoyl or 4-chloro:



wherein, in formula 3, 4 or 5, each R'' is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation:

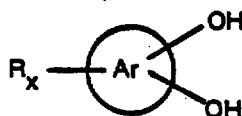
or, when R, R' or R'' is COOH in any such compound, a pharmaceutically acceptable salt of that compound.

The compounds of the present invention are useful as hypocholesterolemic agents and possess the additional advantage of elevating the high density lipoprotein fraction of cholesterol (HDL-cholesterol), which is known to lower the risk factor of coronary heart disease (Gordon, T. et al., High Density Lipoprotein as a Protective Factor Against Coronary Heart Disease, May 1977, The American Journal of Medicine, Vol 62, pp. 707—714). Certain compounds of the invention also reduce the low density lipoprotein fraction of cholesterol (LDL-cholesterol), thus further reducing the risk factor of coronary heart disease.

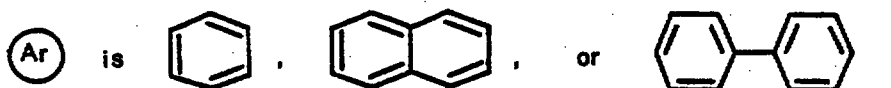
The invention also provides pharmaceutical compositions comprising a plasma high density lipoprotein increasing amount of a compound as described above as well as the pharmaceutically acceptable acid-addition salts thereof and mixtures thereof.

The compounds of the present invention may be prepared by several processes in accordance with another aspect of the present invention. These processes, which are equivalent for the purposes of the present invention, are described hereinbelow with specific reference to the dioxyphenylene compounds of the invention. This description is utilized merely for convenience and those skilled in the art will recognize that the analogous sulfur-containing compounds can be prepared by substituting sulfur-containing starting materials or utilizing substantially identical reactions or obvious variations thereof. Those skilled in the art will also recognize that the sulfur compounds can be utilized to prepare corresponding sulfone and sulfoxide compounds by art-recognized oxidation techniques.

In the preferred method of the invention, a compound of the formula I



wherein



and R_x represents any of the hereinbefore defined substituents R³ and R⁶, is reacted with a compound (an alkylating agent) of the formula II



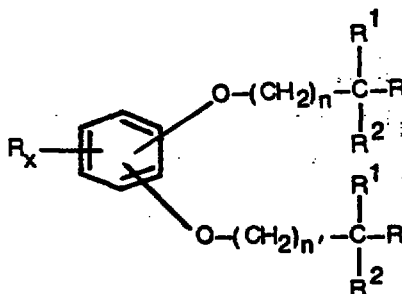
wherein n, R, R¹ and R² are as hereinabove defined. In formula I



and in formula II n is preferably 3, R is preferably CO₂CH₃ and R¹ and R² are preferably CH₃.

Q is a substituent known to those skilled in the art as a "leaving group" [C. H. Snyder and A. R. Soto, J. Org. Chem., 30, 673 (1965)]. For purposes of the present invention, the halogens are suitable leaving groups and the preferred halogen is bromine. Other suitable leaving groups such as *p*-toluene-sulfonyloxy will be known to those skilled in the art. The reaction is usually carried out in the presence of a base, examples of which are the alkali metal hydrides, amides, hydroxides, alkoxides and carbonates such as sodium hydride, potassium amide, potassium hydroxide, sodium methoxide, potassium *t*-butoxide and sodium carbonate. The preferred bases are the alkali metal hydrides, especially sodium hydride. The reaction is conducted usually in an anhydrous, non-protic solvent such as an ether, a hydrocarbon or a tertiary amide; examples of such solvents are dimethoxyethane, dioxane, tetrahydrofuran, pentane, cyclohexane, benzene, xylene, and N,N-dimethylformamide. Other suitable solvents will suggest themselves to those skilled in the art. The preferred solvent is N,N-dimethylformamide. The time and temperature ranges for conducting the foregoing reaction may be varied, and in general, a temperature range of about 20°C to about 70°C and a time range of about 2 to about 24 hours can be used. The preferred ranges are about 60°—70°C for about 4—5 hours. The ranges can vary depending on the reactants, the solvent and the base being utilized, and it is within the

skill of the art to choose these ranges to optimize the yield for a specific reaction. When carrying out the above-described reaction, it is preferred to use slightly more than two equivalents of the alkylating agent, II, and slightly more than two equivalents of base per mole of the compound I. The use of a greater excess of base, for example from 4 to 10 equivalents, is desirable when an alkali metal carbonate such as sodium or potassium carbonate is utilized. The product of the reaction, represented by the preferred structure III,

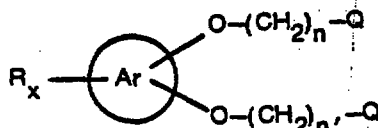


III

may be isolated by standard procedures, for example, addition of the reaction mixture to water, separating the organic phase when present, extracting the aqueous phase with a water-immiscible solvent such as diethyl ether, washing the combined organic phases with water, drying the washed organic phase with, for example, MgSO_4 , evaporating the solvent and purifying the product by, for example, vacuum distillation. Alternatively, when R is an ester this function may be saponified, with, for example, methanolic sodium hydroxide, and the acid product may be isolated and purified by well-known methods. If desired, the ester functions may be saponified after the ester has been isolated and purified. The above described reaction of compounds I and II will produce products, III, wherein n and n' are the same. When it is desired to prepare a compound of formula III wherein n and n' are different, those skilled in the art will understand that the reaction can be performed in two separate stages, i.e., each step utilizing substantially one equivalent of alkylating agent II, and substantially one equivalent of base for each mole of compound I.

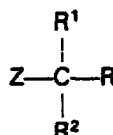
The compounds I, and the alkylating agents II, are either commercially available or are readily prepared. The preferred alkylating agent, methyl 5-bromo-2,2-dimethylpentanoate may be prepared from 2,2-dimethyl-4-pentenoic acid [J. Am. Chem. Soc., 77, 1092 (1955)] by the addition of hydrogen bromide in the presence of benzoyl peroxide.

A second process for preparing the compounds of the invention comprises the reaction of an arylenebis(oxy)alkyl compound of formula IV



IV

wherein Ar , n, n', R_x and Q are as previously defined with a compound of formula V



V

wherein R, R^1 and R^2 are as previously defined. Z is an alkali metal which is preferably lithium, R is preferably CO_2A , wherein A' is sodium or lithium, and



is preferably



Preferred solvents for use in this reaction are anhydrous polar solvents such as tetrahydrofuran, tetrahydropyran, dimethoxy ethane, diethylene glycol dimethyl ether and dimethyl sulfoxide. Tetrahydrofuran is the preferred solvent at temperatures, up to about 40°C whereas diethylene glycol dimethyl ether is the preferred solvent at temperatures above 40°C . The reaction solvent can also be a

hydrocarbon such as pentane, heptane, benzene or toluene, as well as mixtures thereof.

The time and temperature for conducting the reaction are dependent on the particular reactants and the solvent that is used. In general a temperature from about -10°C to about 60°C and a reaction time of from about one hour to about 24 hours can be used. According to the preferred method, the reaction is carried out at a temperature between 0°C to about 30°C for about 16 hours. When reacting compounds IV and V, a ratio of 2 equivalents of V to 1 mole of IV is normally utilized, but it is preferred to use a slight excess of the arylenebis(oxy)alkyl compound, IV.

The product may be isolated and purified by standard procedures, such as those described hereinabove for compound III. When the product is in the form of the diester, it may be saponified, if desired, for example with dilute base either before or after its isolation and purification. The starting arylenebis(oxy)alkyl compounds, IV, may be prepared by well-known methods such as by reaction of the corresponding compound, I, with a compound of the formula VI [R. Adams and L. N. Whitehill, J. Am. Chem. Soc., 63, 2073 (1949)].



VI

wherein Q and Q' are leaving groups which may be the same or different and are defined hereinabove, n is also as previously defined. For purposes of the invention, Q and Q' are preferably different, for example Q may be chlorine when Q' is bromine. The reaction of compound I with VI is performed in substantially the same manner as that described hereinabove for the reaction of compound II with compound I.

Certain of the compounds may be prepared by aromatic ring substitution. Thus, the benzene ring of a compound of formula III wherein



is



and R_x is hydrogen may be, for example, halogenated.

The compounds of the invention wherein R is CHO may be prepared by reduction of the corresponding acid or by oxidation of the corresponding alcohol. These compounds can also be prepared by using starting materials such as II or V wherein R is a protected CHO group such as in the form of an ethylene acetal. The protecting group is subsequently removed, for example, by dilute acid hydrolysis of the ethylene acetal.

The compounds of the invention wherein R is CH_2OH can also be prepared from the corresponding aldehyde, free acid or ester by, for example, reduction with lithium aluminum hydride. The carboxylic acids of the invention, i.e., the compounds of formula III wherein R, R' and R'' are CO_2H , form carboxylate salts with any of a variety of inorganic and organic bases. Suitable bases for purposes of the invention, are those which form pharmaceutically-acceptable salts such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, calcium hydroxide, ammonia and amines. The salts are converted back to their respective carboxylic acids by treatment with an acid such as dilute hydrochloric acid. The carboxylic acids and their respective salts differ in certain physical properties such as solubility properties but they are otherwise equivalent for purposes of the invention.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, these solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of the invention are new chemical substances, of value as pharmacological agents which increase the high density lipoprotein fraction of cholesterol (HDL-cholesterol) at the expense of the low density lipoprotein fraction of cholesterol (LDL-cholesterol). In addition, many of the compounds of the invention reduce total plasma cholesterol levels. The risk of coronary heart disease is thereby reduced. The effectiveness of the compounds of the invention was established by the screening procedure described in Maxwell, R. E., Nawrocki, J. W., and Uhlendorf, P. D., Artery, 4, 303 (1978).

A compound is considered active in this procedure if it increases the HDL fraction of cholesterol by at least 50%. The test results obtained for compounds of the invention are shown in the following table.

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TEST RESULTS

Compound of Example	Dose mg/kg	Percent Change		
		Plasma Cholesterol	HDL Cholesterol	HDL/LDL Electro- Phoretic
1A	50	-30	347	435
1B	50	0	381	318
1D	50	-30	385	595
1G	50	0	480	—
1K	50	0	628	—
1M	50	0	674	—
1O	50	0	723	—
1P	50	+39	1100	—
1Q	50	0	421	—
1R	50	-30	686	—
1S	50	+32	428	—
2	50	-26	566	871
2A	50	-37	743	1009
2B	50	-45	728	1311
4	50	-27	1410	2432
4	25	—	741	1798
4	12.5	—	518	945
5	50	-45	791	2472
5A	50	0	1477	1722
5D	50	-55	384	1091
5E	50	-62	348	377
5F	50	-53	753	1443
5F	25	—	206	493
5F	12.5	—	94	242
5I	50	-52	294	794
5J	50	-28	383	510
5K	50	-37	317	556
5L	50	0	276	274
5M	50	-44	628	785

TEST RESULTS (Continued)

	Compound of Example	Dose mg/kg	Percent Change		
			Plasma Cholesterol	HDL Cholesterol	HDL/LDL Electro-Phoretic
5					
10	5M	25	—	232	302
	5M	12.5	—	74	101
	6	50	-33	289	388
15	7	50	0	907	703
	8	50	-27	525	509
20	10	50	-44	389	—
	11	50	—	410	—
	12	50	+40	319	—
25	13	50	+61	1292	—
	14	—	—	—	—
30	17	50	0	947	—

The compounds of the invention can be administered either orally or parenterally. They can be combined with a solid or liquid carrier or diluent and made available in varying amounts in such pharmaceutical forms as tablets, capsules, powders, and aqueous and non-aqueous suspensions and solutions. The preferred daily dosage is from about 10 to about 250 mg/kg which may be administered in either single or divided dosage units.

The starting materials for preparing the compounds of the invention are either commercially available or can be readily prepared by published literature procedures; for example: 2,5-Dioxybenzophenone is prepared according to J. Herzig and Br. Hofmann, Ber, 41, 143 (1908); Phenylthio-benzohydroquinone is prepared according to O. Dimroth, L. Kraft, and K. Aichinger, Ann. der Chemie, 545, 124 (1940). All the substituted phenylhydroquinones are prepared according to D. E. Kvalnes, J. Am. Chem. Soc., 56, 2478 (1934). Fluorohydroquinone and trifluoromethylhydroquinone are prepared according to the procedure of A. E. Feiring, and W. A. Sheppard, J. Org. Chem., 40, 2543 (1975).

The invention is illustrated by the following examples.

Example 1

A solution of 3.32 g of *t*-butylhydroquinone in 15 ml of dimethylformamide is added dropwise to a suspension of 2.4 g of 50% sodium hydride in 25 ml of dimethylformamide, and allowed to stir for $\frac{1}{2}$ an hour at room temperature. 11.2 g of methyl 5-bromo-2,2-dimethylpentanoate is added followed by heating the mixture at 60—70°C for 6 hrs. Dimethylformamide is distilled off, the residue is poured into water and the organic material is extracted with ether. The ether extract is washed with water until neutral, dried over anhydrous magnesium sulfate and the ether is evaporated. The residue is purified by distillation yielding the product, dimethyl 5,5'-[[2-(1,1-dimethylethyl)1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] b.p. 200°C at 0.5 mm of Hg; yield 4 g.

Following the general procedure of Example 1, with the substitution of an equivalent amount of the specified diphenol, the following products are obtained:

A. From fluorohydroquinone, the product obtained is dimethyl 5,5'-[(2-fluoro-1,4-phenylene)-bis(oxy)]bis[2,2-dimethylpentanoate], m.p. 33—35° following crystallization from ether-petroleum ether.

B. From 2,5-dihydroxyacetophenone, the product obtained is dimethyl 5,5'-[(2-acetyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate] b.p. 210°C at 0.1 mm of Hg.

- C. From 2,4-dihydroxybenzophenone, the product obtained is dimethyl 5,5'-[(4-benzoyl-1,3-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate], which is hydrolysed directly by refluxing with a solution of 2N methanolic sodium hydroxide to give the corresponding acid, 5,5'-[(4-benzoyl-1,3-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid] m.p. 125—126°C, following crystallization from tetrahydrofuran-isopropyl ether.
- D. From 2-methylresorcinol, the product obtained is dimethyl 5,5'-[(2-methyl-1,3-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate], b.p. 200°C at 0.3 mm of Hg.
- E. From 5-methylresorcinol, the product obtained is dimethyl 5,5'-[(5-methyl-1,3-phenylene)bis[2,2-dimethylpentanoate], b.p. 200°C at 0.3 mm of Hg.
- F. From 4-chlorobenzene 1,3-dithiol the product obtained is dimethyl 5,5'-[(4-chloro-1,3-phenylene)bis(thio)]bis[2,2-dimethylpentanoate] b.p. 200°C at 0.02 mm of Hg.
- G. From *o*-chlorophenylhydroquinone, the product obtained is 5,5'-[(2'-chloro[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 101—2°C, following crystallization from isopropyl ether.
- H. From *p*-anisylhydroquinone, the product obtained is 5,5'-[(4'-methoxy[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 69—73° (d), following crystallization from isopropyl ether.
- I. From *p*-chlorophenylhydroquinone, the product obtained is 5,5'-[(4'-chloro[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 110—111°C, following crystallization from tetrahydrofuran-petroleum ether.
- J. From *p*-tolylhydroquinone, the product obtained is 5,5'-[(4'-methyl[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 65—8°C, following crystallization from chloroform.
- K. From *o*-tolylhydroquinone, the product obtained is 5,5'-[(2'-methyl[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 65—8°C, following crystallization from isopropyl ether.
- L. From 2,5-dihydroxybenzaldehyde, the product obtained is dimethyl 5,5'-[(2-formyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate], b.p. 220°C at 0.1 mm of Hg.
- M. From trifluoromethylhydroquinone, the product obtained is 5,5'-[(2-trifluoromethyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 114—5°C, following crystallization from tetrahydrofuran-hexane.
- N. From 2,4-dichlorophenylhydroquinone, the product obtained is 5,5'-[(2',4'-dichloro[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 82—6°C, following crystallization from isopropyl ether.
- O. From 2,5-dihydroxypropiophenone, the product obtained is dimethyl 5,5'-[[2-(1-oxopropyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate]
- P. From 2,5-dihydroxybutyrophenone, the product obtained is dimethyl 5,5'-[[2-(1-oxobutyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate].
- Q. From 2,5-dihydroxybenzophenone, the product obtained is dimethyl 5,5'-[(2-benzoyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate].
- R. From 2,5-dimethylhydroquinone, the product obtained is dimethyl 5,5'-[2,5-dimethyl-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoate], m.p. 60—2°C, following crystallization from isopropyl ether.
- S. From phenylthiobenzohydroquinone, the product obtained is 5,5'-[(2-phenylthio)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 117—8°C, following crystallization from tetrahydrofuran-isopropyl ether.

Example 2

- A solution of 3.5 g of 2-methoxyhydroquinone in 35 ml of methanol is stirred with 3.0 g of sodium methoxide for thirty minutes. 12.3 g of methyl 5-bromo-2,2-dimethylpentanoate is added and

the mixture is refluxed for 24 hours. Methanol is removed under reduced pressure and the residue is poured into water. An oil separates, which is extracted with ether and the ether extract is washed with water, dried over anhydrous magnesium sulfate and the ether is evaporated. The residue is purified by distillation yielding the product, dimethyl 5,5'-[(2-methoxy-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate] b.p. 200°C at 0.2 mm of Hg; yield 6.6 g.

Following the general procedure of Example 2, with the substitution of an equivalent amount of the specified diphenol, the following products are obtained:

A. From methylhydroquinone the product obtained is dimethyl 5,5'-[(2-methyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate] b.p. 192°C at 0.15 mm of Hg.

B. From bromohydroquinone, the product obtained is dimethyl 5,5'-[(2-bromo-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate] b.p. 200°C at 0.3 mm of Hg.

Example 3

A suspension of 3.45 g of 2,4-dihydroxybenzaldehyde, 10.4 g of anhydrous potassium carbonate, 0.5 g of potassium iodide and 13.4 g of methyl 5-bromo-2,2-dimethylpentanoate in 70 ml of acetone is refluxed for 24 hours. The suspension is cooled, filtered and the solvent is evaporated. The residue is poured into water, and the organic material is extracted with ether. The ether extract is washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue is purified by distillation yielding the product, dimethyl 5,5'-[(4-formyl-1,3-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate], b.p. 210°C at 0.1 mm of Hg; yield 6.5 g.

A. From 2-nitroresorcinol the product obtained is dimethyl 5,5'-[(2-nitro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate] b.p. 230°C at 1.0 mm of Hg.

B. From 4,4'-biphenyldithiol, the product obtained is dimethyl 5,5'-[[1,1'-biphenyl]-4,4'-diylbis(thio)]bis[2,2-dimethylpentanoate], m.p. 46—7°, following crystallization from isopropyl ether.

Example 4

A solution of 60.0 g of phenylhydroquinone in 200 ml of dimethylformamide is added dropwise to a suspension of 27.5 g of 59% sodium hydride in 100 ml of dimethylformamide with stirring under N₂ blanket. The mixture is stirred for one hour at room temperature to complete the reaction. One hundred fifty-six ml of methyl 5-bromo-2,2-dimethylpentanoate is added dropwise at room temperature followed by heating the mixture at 80—85°C for 12—14 hours. The mixture is cooled, filtered from the inorganic residue and dimethylformamide is distilled under reduced pressure. The residue is treated with water and the organic material is extracted with ether. The ether extract is dried over anhydrous magnesium sulfate and ether removed leaving behind an oil. The unreacted alkyl bromide is removed by distillation under high vacuum and the residue is purified by chromatography over silica gel. The crude diester (160 g) is directly hydrolyzed by refluxing with 1600 ml of 2N methanolic sodium hydroxide for 3 hours. Methanol is removed and the residue is treated with water followed by acidification. The product obtained is 5,5'-[[1,1'-biphenyl]-2,5-diylbis(oxy)]bis[2,2-dimethylpentanoic acid], mp 139—140°C, following crystallization from tetrahydrofuran-isopropyl ether, yield 125 g.

Example 5

17.6 g of isobutyric acid is added dropwise to a stirred suspension of 10.6 g of 50% NaH and 20.6 g of diisopropylamine in 170 ml of anhydrous tetrahydrofuran at room temperature under nitrogen. The mixture is refluxed for 30 minutes followed by cooling to 0°C. At this time 138 ml of a solution of butyllithium in heptane is added slowly. The ice-bath is retained for 30 minutes followed by warming to 30—40° for another 30 minutes. The slightly turbid solution is cooled to 0°C and a solution of 26.3 g of 1,4-bis(3-chloropropoxy)benzene in 50 ml of dry tetrahydrofuran is added dropwise while the temperature was maintained below 10°C. After 30 minutes the mixture is allowed to warm to room temperature and stirring is continued for 16 hours. The mixture is cooled and hydrolysed with 250 ml of water and the aqueous phase is separated, washed with 100 ml of ether, and acidified with 6N hydrochloric acid yielding the product, 5,5'-[1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 168°C, following crystallization from tetrahydrofuran-isopropyl ether, yield 23 g.

Following the general procedure of Example 5, with the substitution of an equivalent amount of the specified starting material the following products are obtained:

A. From 1,4 bis(4-chlorobutoxy)benzene the product obtained is 6,6'-[1,4-phenylenebis(oxy)]bis[2,2-dimethylhexanoic acid], m.p. 158—159°C following crystallization from tetrahydrofuran-hexane.

B. From cyclobutane carboxylic acid the product obtained is 1,1'-[1,4-phenylenebis(oxy(4,1-butane-diyl))]biscyclobutanecarboxylic acid, m.p. 132—133°C following crystallization from tetrahydrofuran-petroleum ether.

C. From 1,4-bis(3-chloropropoxy)2,3,5-trimethylbenzene the product obtained is 5,5'-[(2,3,5-trimethyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 143°C following crystallization from diethyl ether.

D. From 1,4-bis(3-chloropropoxy)2,5-dichlorobenzene, the product obtained is 5,5'-[(2,5-dichloro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 162°C following crystallization from tetrahydrofuran-isopropyl ether.

E. From 1,4-bis(2-chloroethoxy)-2-chlorobenzene, the product obtained is 4,4'-[(2-chloro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylbutanoic acid], m.p. 135—137°C following crystallization from tetrahydrofuran-isopropyl ether.

F. From 1,4-bis(3-chloropropoxy)-2-chlorobenzene, the product obtained is 5,5'-[(2-chloro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 135°C following crystallization from tetrahydrofuran-isopropyl ether.

G. From 4,4'-bis(3-chloropropoxy)-1,1'-biphenyl, the product obtained is 5,5'-[(1,1'-biphenyl)-4,4'-diylbis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 201°C, following crystallization from tetrahydrofuran-hexane.

H. From 1,5-bis(3-chloropropoxy)naphthalene, the product obtained is 5,5'-[1,5-naphthalene-diylbis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 219°C following crystallization from dimethylformamide.

I. From 1,3-bis(3-chloropropoxy)benzene, the product obtained is 5,5'-[1,3-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 135—136°C, following crystallization from isopropyl ether.

J. From 1,3-bis(2-chloroethoxy)benzene, the product obtained is 4,4'-[1,3-phenylenebis(oxy)]bis[2,2-dimethylbutanoic acid], m.p. 104—105°C, following crystallization from diethyl ether-petroleum ether.

K. From 1,3-bis(4-chlorobutoxy)benzene, the product obtained is 6,6'-[1,3-phenylenebis(oxy)]bis[2,2-dimethylhexanoic acid], m.p. 85—86°C, following crystallization from isopropyl ether.

L. From 1,2-bis(5-chloropentoxy)benzene, the product obtained is 7,7'-[1,2-phenylenebis(oxy)]bis[2,2-dimethylheptanoic acid], m.p. 61°C, following crystallization from diethyl ether-petroleum ether.

M. From 1-(3-chloropropoxy)-4-[(3-chloropropyl)thio]benzene, the product obtained is 5-[[4-[(4-carboxy-4-methylpentyl)oxy]phenyl]thio]-2,2-dimethylpentanoic acid, m.p. 112°C following crystallization from chloroform-petroleum ether.

Example 6

A solution of 3.05 g of 5-[[4-(4-carboxy-4-methylpentyl)oxy]-2,5-dimethylphenyl]thio]-2,2-dimethylpentanoic acid in 10 ml of glacial acetic acid containing 0.9 ml of hydrogen peroxide is stirred at room temperature for 6 hrs. The solution is poured into water and extracted with ether. The ether extract is washed with water, dried over anhydrous magnesium sulfate and the solvent is evaporated. The residual oil solidifies on trituration with isopropyl ether and the product obtained is 5-[[4-[(4-carboxy-4-methylpentyl)oxy]phenyl]sulfinyl]-2,2-dimethylpentanoic acid, m.p. 98—100°C, following crystallization from tetrahydrofuran-isopropyl ether; yield 1.9 g.

Example 7

A solution of 6.56 g of 6,6'-[1,4-phenylene bis(oxy)]bis[2,2-dimethylhexanoic acid] in 25 ml of tetrahydrofuran is added to a stirred suspension of 1.1 g of lithium aluminum hydride in 75 ml of tetrahydrofuran followed by refluxing for 5—6 hours. The mixture is cooled, and the excess hydride is decomposed with saturated sodium sulfate solution, filtered from the inorganic solids and the filtrate is evaporated. The product obtained is, 6,6'-[1,4-phenylenebis(oxy)]bis[2,2-dimethyl-1-hexanol], m.p. 72°C following crystallization from tetrahydrofuran-hexane, yield 4 g.

Example 8

4.0 g of dimethyl 5,5'-[(1-acetyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate] is treated with 0.4 g of sodium borohydride in 40 ml of methanol at room temperature. After usual workup, the residue is hydrolyzed with 2N methanolic sodium hydroxide yielding the product, 5,5'-[2-(hydroxyethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 141—143°C, following

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crystallization from tetrahydrofuran-isopropyl ether, yield 1.2 g.

Example 9

5 A solution of 2.5 g of dimethyl 5,5'-[[2-(1-hydroxypropyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] in 25 ml of benzene was refluxed 8 hrs in the presence of catalytic amount of p-toluenesulfonic acid. After usual work up, the product obtained is dimethyl 5,5'-[2-(1-propenyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoate], yield 1.1 g.

Example 10

10 3.0 g of dimethyl 5,5'-[[2-benzoyl-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] is reduced catalytically and the crude ester saponified. The product thus obtained is 5,5'-[[2-(benzyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 140—141°C following crystallization from tetrahydrofuran-petroleum ether, yield 2.1 g.

Example 11

15 A solution of 2.09 g of dimethyl 5,5'-[[2-benzoyl-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] in 20 ml of 95% alcohol is refluxed with 2.0 g of Zn-dust and 2.0 g of sodium hydroxide. The suspension is filtered, acidified, and the product obtained is 5,5'-[2-(hydroxyphenylmethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 125—128°C, following crystallization from ether hexane, yield 1 g.

Example 12

25 3.8 g of dimethyl 5,5'-[[2-formyl-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] is treated with 0.5 g of sodium borohydride in 40 ml of methanol at room temperature. After usual work up, the residue is hydrolysed with 2N methanolic sodium hydroxide and the product obtained is 5,5'-[[2-(hydroxymethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 128—9°C, following crystallization from tetrahydrofuran-isopropyl ether, yield 2.7 g.

Example 13

30 3.65 g of dimethyl 5,5'-[[2-(1-oxobutyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] is reduced with 0.5 g of sodium borohydride in 40 ml of methanol at room temperature. After usual work up, the residue is hydrolysed with 2N methanolic sodium hydroxide and the product obtained is 5,5'-[[2-(1-hydroxybutyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 122—123°C, following crystallization from ether-isopropyl ether, yield 2.1 g.

Example 14

35 A solution of 2.8 g of 5,5'-[[2-phenylthio]-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid] in 25 ml of methylene chloride is stirred overnight with 1.0 g of *m*-chloroperbenzoic acid at room temperature. The separated solid is filtered, washed with methylene chloride and dried. The product obtained is 5,5'-[[2-(phenylsulfonyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 141—3°C, following crystallization from tetrahydrofuran-isopropyl ether, yield 1.3 g.

Example 15

45 2.4 g of 5,5'-[[2-(phenylthio)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid] is treated with 1.8 g of *m*-chloroperbenzoic acid in 75 ml of methylene chloride. The product obtained is 5,5'-[[2-(phenylsulfonyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 194—6°C, following crystallization from tetrahydrofuran-isopropyl ether, yield 1.8 g.

Example 16

50 A solution of 4.77 g of 5-[[4-[(4-carboxy-4-methylpentyl)oxy]-2,5-dimethylphenyl]thio]2,2-dimethylpentanoic acid in 20 ml of glacial acetic acid is treated with 4.9 ml of 30% hydrogen peroxide at 50°C in three portions followed by refluxing for two hours. The solution is poured into water and the solids are filtered, washed with water and dried. The product obtained is 5-[[4-[(4-carboxy-4-methylpentyl)oxy]phenyl]sulfonyl]-2,2-dimethylpentanoic acid, m.p. 106—7°C, following crystallization from tetrahydrofuran-isopropyl ether, yield 4.3 g.

Example 17

60 8.2 g of dimethyl 5,5'-[[2-(1-oxopropyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoate] is treated with 0.85 g of sodium-borohydride in 40 ml of methanol at room temperature. After usual work up, the residue is hydrolysed with 2N methanolic sodium hydroxide and the product is 5,5'-[2-(1-hydroxypropyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid], m.p. 112—113°C, following crystallization from tetrahydrofuran-petroleum ether, yield 4.1 g.

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1. A compound having one of the following formulae 1 to 5:—



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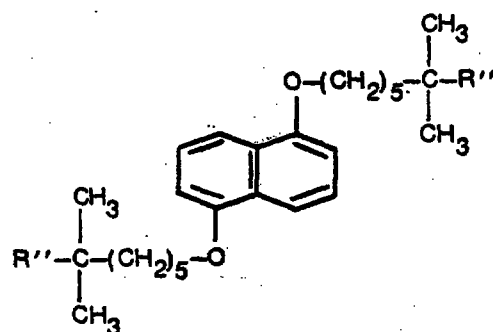
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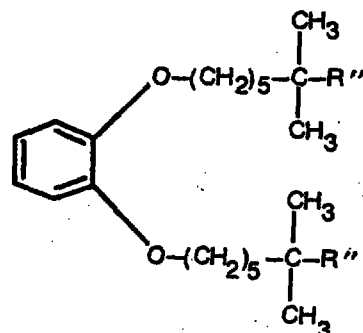
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(4)

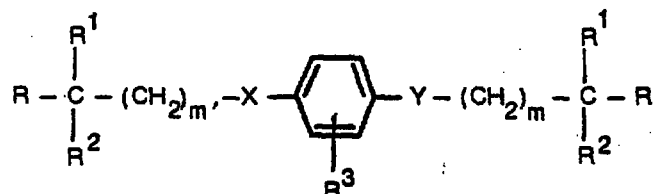


(5)

wherein, in formula 3, 4 or 5, each R'' is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation;

or, when R, R' or R'' is COOH in any such compound, a pharmaceutically acceptable salt of that compound.

2. A compound as claimed in claim 1 which has the formula:



(1)

wherein X and Y are the same or different and are oxygen, sulfur, sulfone or sulfoxide; m and m' are the same or different and are integers in the range from 2 to 5; each R is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation; each of R¹ and R², which are the same or different, is an alkyl radical having from 1 to 6 carbon atoms, or R¹ when taken together with the R² which shares the same carbon atom represents -(CH₂)₃₋₅-; and R³ is a hydrogen or halogen atom, an alkyl radical having from 1 to 6 carbon atoms, methoxy, phenyl, trifluoromethyl, 2,5-dichloro, 2,5-dimethyl, 2,3,5-trimethyl, carboxylic acyl of from 1 to 6 carbon atoms, alpha-hydroxyalkyl of from 1 to 6 carbon atoms 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-methoxyphenyl, 2-tolyl, 4-tolyl or

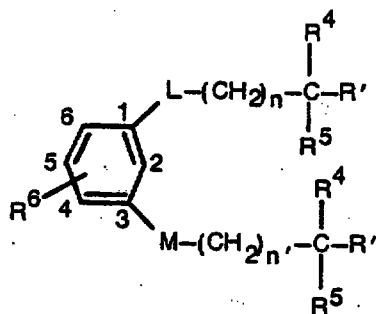


wherein D is O, CO, S, SO, SO₂, CH₂, or CHOH; provided that R³ is not a hydrogen atom when all the following conditions are satisfied, namely when X and Y are both oxygen, m and m' are both 2; R¹ and R² are both CH₃, and R is CO₂H;

or, when R is COOH, a pharmaceutically acceptable salt of the compound.

3. A compound as claimed in claim 1, which has the formula:





(2)

wherein L and M are the same or different and are oxygen, sulfur, sulfone or sulfoxide; n and n' are the same or different and are integers in the range from 2 to 5; each of R⁴ and R⁵, which are the same or different, is an alkyl radical having from 1 to 6 carbon atoms; each R' is CH₃, OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation; R⁶ is a hydrogen atom, 4-formyl, 2-nitro, 2-methyl, 5-methyl, 4-benzoyl or 4-chloro;

or, when R' is COOH, a pharmaceutically acceptable salt of that compound.

4. A compound as claimed in claim 1 and which is selected from: dimethyl 5,5'-[(2-fluoro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[(2-acetyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[(2-methyl-1,3-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

5,5'-[(2'-chloro[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[(2'-methyl[1,1'-biphenyl]-2,5-diyl)bis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[(2-trifluoromethyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid],

dimethyl 5,5'-[(2-(1-oxopropyl)-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[(2-(1-oxobutyl)-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[(2-benzoyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[2,5-dimethyl-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoate],

5,5'-[(2-phenylthio)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid],

dimethyl 5,5'-[(2-methoxy-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[(2-methyl-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

dimethyl 5,5'-[(2-bromo-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoate],

5,5'-[(1,1'-biphenyl)-2,5-diylbis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[(2,5-dichloro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[(2-chloro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[1,3-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[2-(hydroxyethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[2-(benzyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[2-(hydroxyphenylmethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[(2-hydroxymethyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[(2-(1-hydroxybutyl)-1,4-phenylene)bis(oxy)]bis[2,2-dimethylpentanoic acid],

5,5'-[2(phenylsulfinyl)-1,4-phenylene]bis(oxy)]bis[2,2-dimethylpentanoic acid], and

5,5'-[2-(1-hydroxypropyl)-1,4-phenylenebis(oxy)]bis[2,2-dimethylpentanoic acid].

5. A compound as claimed in Claim 1, which is

6,6'-[1,4-phenylenebis(oxy)]bis[2,2-dimethylhexanoic acid],

6,6'-[1,3-phenylenebis(oxy)]bis[2,2-dimethylhexanoic acid], or

6,6'-[1,4-phenylenebis(oxy)]bis[2,2-dimethyl-1-hexanol].

6. A compound as claimed in Claim 1, which is

4,4'-[(2-chloro-1,4-phenylene)bis(oxy)]bis[2,2-dimethylbutanoic acid], or

4,4'-[1,3-phenylenebis(oxy)]bis[2,2-dimethylbutanoic acid],

7. A compound as claimed in Claim 1, which is

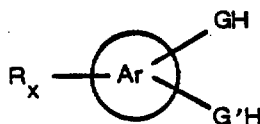
7,7'-[1,2-phenylenebis(oxy)]bis[2,2-dimethylheptanoic acid].

8. A compound as claimed in Claim 1, which is

5-[(4-[(4-carboxy-4-methylpentyl)oxy]phenyl)thio]-2,2-dimethylpentanoic acid, or

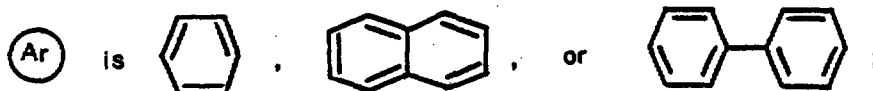
5-[(4-[(4-carboxy-4-methylpentyl)oxy]phenylsulfinyl)-2,2-dimethylpentanoic acid.

9. A process for preparing a compound as claimed in claim 1, which process comprises reacting a compound of the following general formula:—



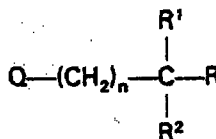
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wherein



each of G and G' which are the same or different is oxygen or sulfur; and R_x represents any of the substituents R³ and R⁶ as defined in claim 1; with a compound of the following general formula:—

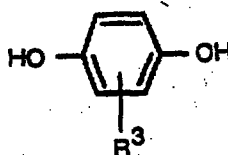
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15 wherein Q is a leaving group and n, R, R¹ and R² are as defined in claim 1; and either isolating the resulting product or, when either of G and G' is sulfur, oxidizing the coupled product and isolating the oxidized product.

10. A process according to claim 9, which comprises reacting a compound of the formula

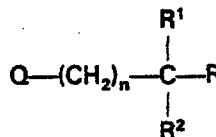
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wherein R³ is as defined in claim 1, with a compound of the formula

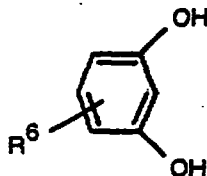
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35 wherein Q is a leaving group and n, R, R¹ and R² are as defined in claim 1; and isolating the resulting product.

11. A process according to claim 9, which comprises reacting a compound of the formula

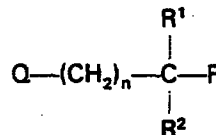
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where R⁶ is as defined in claim 1, with a compound of the formula

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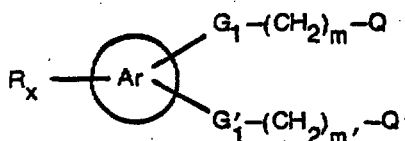


II

55 where Q is a leaving group and n, R, R¹ and R² are as defined in claim 1, and isolating the resulting product.

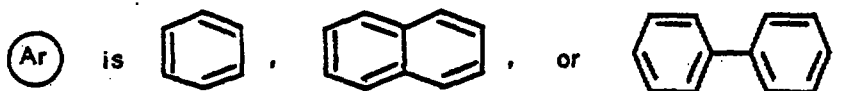
12. A process for producing a compound as claimed in claim 1, which process comprises reacting a compound of the following general formula:

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65 wherein



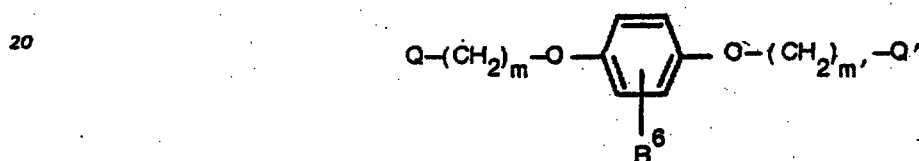


5 each of G₁ and G₁' which are the same or different is oxygen, sulfur, sulfone or sulfoxide; R_x represents any of the substituents R³ and R⁶ as defined in claim 1; Q and Q' are the same or different and are leaving groups; and m and m' are as defined in claim 1; with a compound of the following formula:



15 wherein R, R¹ and R² are as defined in claim 1, and Z is an alkali metal; and isolating the resulting product.

13. A process according to claim 12, which comprises reacting a compound of the formula



25 wherein Q and Q' are leaving groups and m, m' and R⁶ are as defined in claim 1; with a compound of the following formula



35 where R, R¹ and R² are as defined in claim 1; and isolating the resulting product.

14. A process according to claim 12, which comprises reacting a compound of the formula



45 where Q and Q' are leaving groups and m, m' and R⁶ are as defined in claim 1, with a compound of the following formula

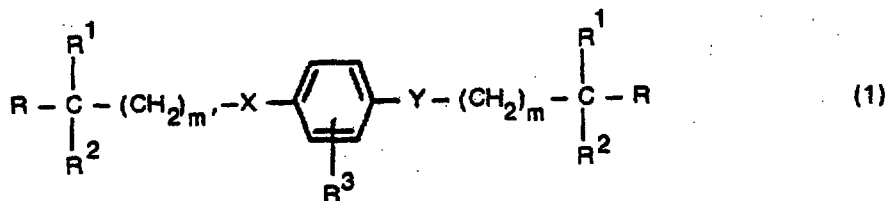


55 where R, R¹ and R² are as defined in claim 1, and isolating the resulting product.

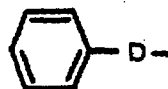


Claims for the Contracting State: AT

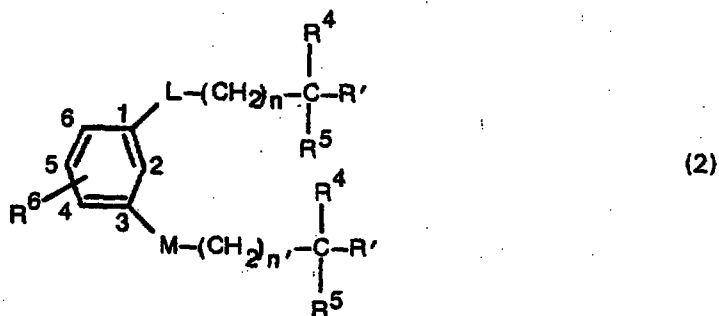
1. A process for producing a compound having one of the following formulae 1 to 5:—



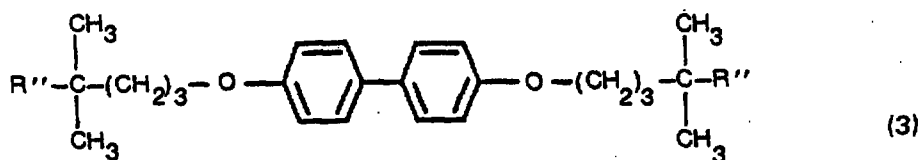
wherein X and Y are same or different and are oxygen, sulfur, sulfone or sulfoxide; m and m' are the same or different and are integers in the range from 2 to 5; R is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation; each of R¹ and R², which are the same or different is an alkyl radical having from 1 to 6 carbon atoms, or R¹ when taken together with the R² sharing the same carbon atom represents —(CH₂)₃₋₅—; and R³ is a hydrogen or halogen atom, an alkyl radical having from 1 to 6 carbon atoms, methoxy, phenyl, trifluoromethyl, 2,5-dichloro, 2,5-dimethyl, 2,3,5-trimethyl, a carboxylic acyl of from 1 to 6 carbon atoms, alpha-hydroxyalkyl having from 1 to 6 carbon atoms, 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-methoxyphenyl, 2-tolyl, 4-tolyl or

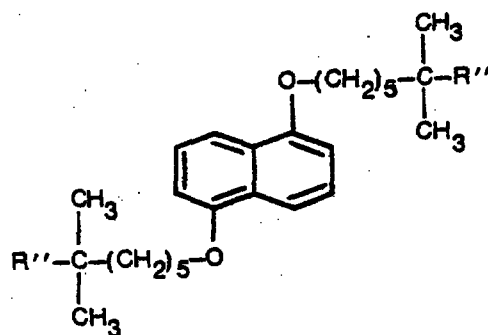


wherein D is O, CO, S, SO, SO₂, CH₂ or CHOH; provided that R³ is not a hydrogen atom when all of the following conditions are satisfied, namely when X and Y are both oxygen atoms, m and m' are both 2, R¹ and R² are both CH₃, and R is CO₂H:

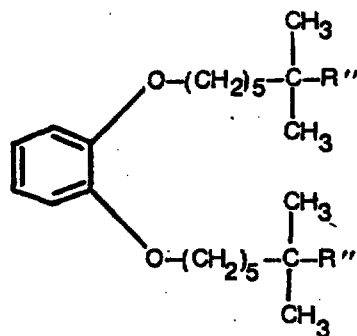


wherein L and M are the same or different and are oxygen, sulfur, sulfone or sulfoxide; n and n' are the same or different and are integers in the range from 2 to 5; each of R⁴ and R⁵ which are the same or different is an alkyl radical having from 1 to 6 carbon atoms; R' is CH₂OH, CHO or CO₂A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation; and R⁶ is a hydrogen atom, 4-formyl, 2-nitro, 2-methyl, 5-methyl, 4-benzoyl or 4-chloro:





(4)

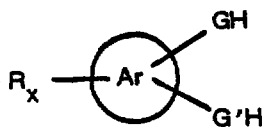


(5)

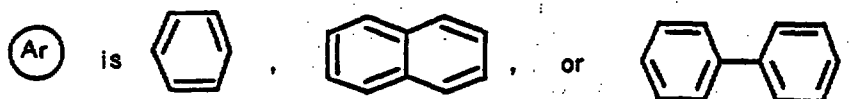
wherein, in formula 3, 4 or 5, each R'' is CH_2OH , CHO or CO_2A wherein A is a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, an alkali or alkaline earth metal cation, an organic amine cation or an ammonium cation:

or, when R, R' or R'' is COOH in any such compound, a pharmaceutically acceptable salt of that compound:

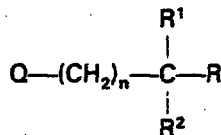
which process comprises reacting a compound of the following general formula:



wherein

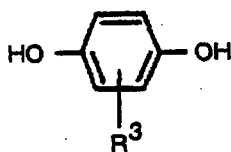


G and G' which are the same or different and are oxygen or sulfur; and R_x represents any of the substituents R^3 and R^6 as defined above; with a compound of the following general formula:—

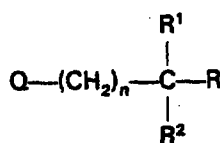


wherein Q is a leaving group and n, R, R^1 and R^2 are as defined above; and either isolating the resulting product or, when either of G and G' is sulfur, oxidizing the coupled product and isolating the oxidized product.

2. A process according to claim 1, which comprises reacting a compound of the formula

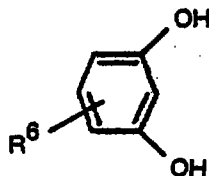


where R^3 is as defined in claim 1, with a compound of the formula

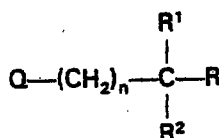


wherein Q, n, R, R^1 and R^2 are as defined in claim 1; and isolating the resulting product.

3. A process according to claim 1, which comprises reacting a compound of the formula

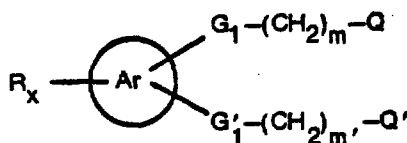


where R^6 is as defined in claim 1, with a compound of the formula

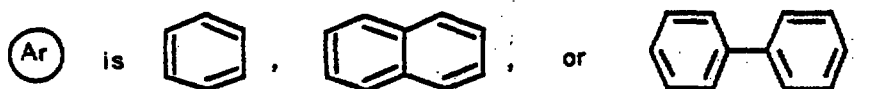


where Q, n, R, R^1 and R^2 are as defined in claim 1, and isolating the resulting product.

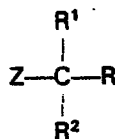
4. A process for producing a compound as claimed in claim 1, which process comprises reacting a compound of the following general formula:



wherein

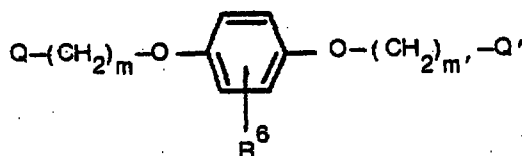


G_1 and G'_1 are the same or different and are oxygen, sulfur, sulfone or sulfoxide; R_x represents any of the substituents R^3 and R^6 as defined in claim 1; Q and Q' are the same or different and are leaving groups; and m and m' are as defined in claim 1; with a compound of the following formula:



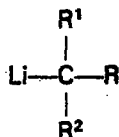
wherein Z is an alkali metal and R, R^1 and R^2 are as defined in claim 1; and isolating the resulting product.

5. A process according to claim 4, which process comprises reacting a compound of the formula



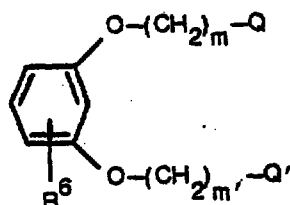
where Q and Q' are leaving groups and m, m' and R^6 are as defined in claim 1, with a compound of the formula



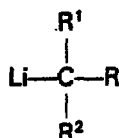


where R, R¹ and R² are as defined in claim 1; and isolating the resulting product.

6. A process according to claim 4, which process comprises reacting a compound of the formula



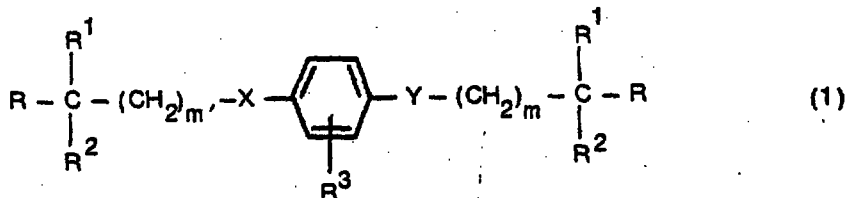
wherein Q and Q' are leaving groups and m, m' and R⁶ are as defined in claim 1, with a compound of the formula



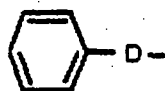
wherein R, R¹ and R² are as defined in claim 1; and isolating the resulting product.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

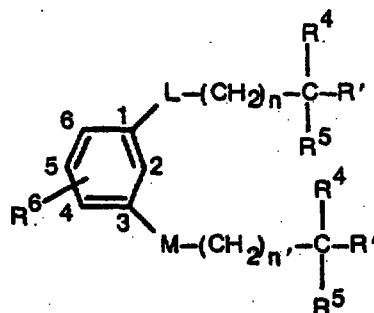
1. Verbindung mit einer der folgenden Formeln 1 bis 5:



worin X und Y gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; m und m' gleich oder verschieden sind und ganze Zahlen im Bereich von 2 bis 5 bedeuten; jedes R CH₂OH, CHO oder CO₂A ist, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischenamins oder ein Ammoniumkation bedeutet; jedes von R¹ und R², die gleich oder verschieden sind, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen bedeutet, oder R¹ zusammen mit dem R² am selben Kohlenstoffatom —(CH₂)₃₋₅— bedeutet; und R³ ein Wasserstoff- oder Halogenatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, Methoxy, Phenyl, Trifluormethyl, 2,5-Dichlor, 2,5-Dimethyl, 2,3,5-Trimethyl, ein Carboxyl-Acyl mit 1 bis 6 Kohlenstoffatomen, alpha-Hydroxyalkyl mit 1 bis 6 Kohlenstoffatomen, 2-Chlorphenyl, 4-Chlorphenyl, 2,4-Dichlorphenyl, 4-Methoxyphenyl 2-Tolyl, 4-Tolyl oder

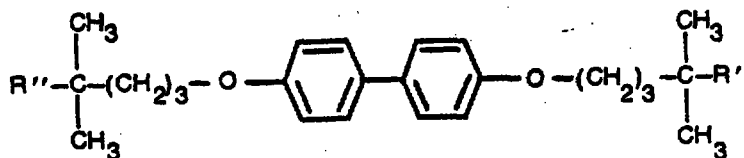


ist, worin D O, CO, S, SO, SO₂, CH₂ oder CHOH bedeutet; mit der Maßgabe, daß R³ kein Wasserstoffatom ist, wenn alle der folgenden Bedingungen erfüllt sind, nämlich wenn X und Y beide Sauerstoffatome sind, m und m' beide 2 bedeuten, R¹ und R² beide CH₃ bedeuten und R CO₂H ist:

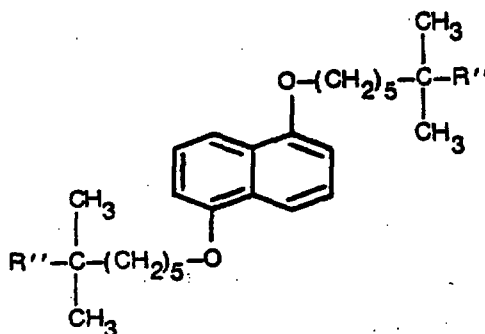


(2).

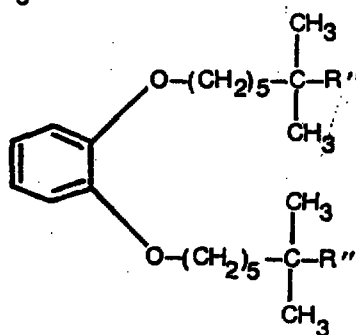
worin L und M gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; n und n' gleich oder verschieden sind un ganze Zahlen im Bereich von 2 bis 5 bedeuten; jedes von R⁴ und R⁵, die gleich oder verschieden sind, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen bedeutet; jedes R' CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischen Amins oder ein Ammoniumkation bedeutet; und R⁶ ein Wasserstoffatom, 4-Formyl, 2-Nitro, 2-Methyl, 5-Methyl, 4-Benzoyl oder 4-Chlor bedeutet:



(3)



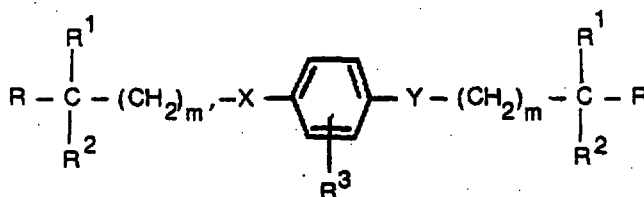
(4)



(5).

worin, in den Formeln 3, 4 oder 5, jedes R'' CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischen Amins oder ein Ammoniumkation bedeutet; oder, wenn R, R' oder R'' in irgendeiner dieser Verbindungen COOH bedeutet, ein pharmazeutisch akzeptables Salz dieser Verbindung.

2. Verbindung nach Anspruch 1 mit der Formel



(1).



5,5'-[2-(Hydroxyphenylmethyl)-1,4-phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
 5,5'-[(2-Hydroxymethyl)-1,4-phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
 5,5'-[[2-(1-Hydroxybutyl)-1,4-phenylen]-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
 5,5'-[[2-(Phenylsulfinyl)-1,4-phenylen]-bis-(oxy)]-bis-[2,2-dimethylpentansäure] und
 5,5'-[2-(1-Hydroxypropyl)-1,4-phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure].

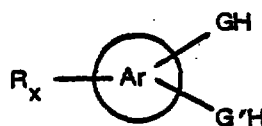
5. Verbindung nach Anspruch 1, welche
 6,6'-[1,4-Phenylen-bis-(oxy)]-bis-[2,2-dimethylhexansäure],
 6,6'-[1,3-Phenylen-bis-(oxy)]-bis-[2,2-dimethylhexansäure] oder
 6,6'-[1,4-Phenylen-bis-(oxy)]-bis-[2,2-dimethyl-1-hexanol] ist.

6. Verbindung nach Anspruch 1, welche
 4,4'-[(2-Chlor-1,4-Phenylen)-bis-(oxy)]-bis-[2,2-dimethylbutansäure] oder
 4,4'-[1,3-Phenylen-bis-(oxy)]-bis-[2,2-dimethylbutansäure] ist.

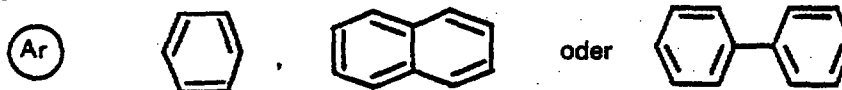
7. Verbindung nach Anspruch 1, welche
 7,7'-[1,2-Phenylen-bis-(oxy)]-bis-[2,2-dimethylheptansäure] ist.

8. Verbindung nach Anspruch 1, welche
 5-[[4-[(4-Carboxy-4-methylpentyl)oxy]-phenyl]-thio]-2,2-dimethylpentansäure oder
 5-[[4-[[4-carboxy-4-methylpentyl)oxy]-phenylsulfinyl]-2,2-dimethylpentansäure ist.

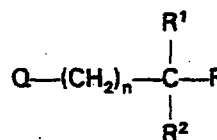
9. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches Verfahren gekennzeichnet ist durch Umsetzung einer Verbindung der folgenden allgemeinen Formel:



worin

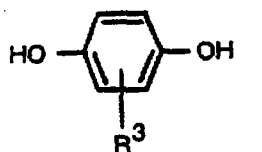


bedeutet; jedes von G und G', die gleich oder verschieden sind, Sauerstoff oder Schwefel ist; und R_x irgendeinen der Substituenten R^3 und R^6 , wie in Anspruch 1 definiert, bedeutet; mit einer Verbindung der folgenden allgemeinen Formel

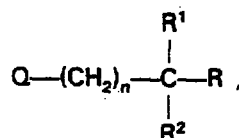


worin Q eine austretende Gruppe bedeutet und n, R, R^1 und R^2 der in Anspruch 1 gegebenen Definition entsprechen; und entweder Isolierung des resultierenden Produkts oder, wenn eines von G und G' Schwefel ist, Oxidation des gekuppelten Produkts und Isolierung des oxidierten Produkts.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß eine Verbindung der Formel

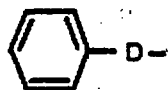


worin R^3 der in Anspruch 1 angegebenen Definition entspricht, mit einer Verbindung der Formel



32

worin X und Y gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; m und m' gleich oder verschieden sind und ganze Zahlen im Bereich von 2 bis 5 bedeuten; jedes R CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischenamins oder ein Ammoniumkation bedeutet; jedes von R¹ und R², die gleich oder verschieden sind, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen bedeutet, oder R¹ zusammen mit dem R² am selben Kohlenstoffatom —(CH₂)₃₋₅— bedeutet; und R³ ein Wasserstoff- oder Halogenatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, Methoxy, Phenyl, Trifluormethyl, 2,5-Dichlor, 2,5-Dimethyl, 2,3,5-Trimethyl, Carboxyl-Acyl mit 1 bis 6 Kohlenstoffatomen, alpha-Hydroxyalkyl mit 1 bis 6 Kohlenstoffatomen, 2-Chlorphenyl, 4-Chlorphenyl, 2,4-Dichlorphenyl, 4-Methoxyphenyl, 2-Tolyl, 4-Tolyl oder



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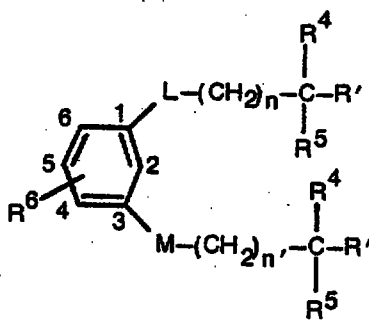
bedeutet, worin D O, CO, S, SO, SO₂, CH₂ oder CHOH bedeutet; mit der Maßgabe, daß R³ kein Wasserstoffatom ist, wenn alle der folgenden Bedingungen erfüllt sind, nämlich wenn X und Y beide Sauerstoff sind, m und m' beide 2 bedeuten, R¹ und R² beide CH₃ bedeuten und R CO₂H ist; oder, wenn R COOH bedeutet, ein pharmazeutisch akzeptables Salz der Verbindung.

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3. Verbindung nach Anspruch 1 mit der Formel

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(2),

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worin L und M gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; n und n' gleich oder verschieden sind und ganze Zahlen im Bereich von 2 bis 5 bedeuten; jedes von R⁴ und R⁵, die gleich oder verschieden sind, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen bedeutet; jedes R' CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischenamins oder ein Ammoniumkation bedeutet; R⁶ ein Wasserstoffatom, 4-Formyl, 2-Nitro, 2-Methyl, 5-Methyl, 4-Benzoyl oder 4-Chlor bedeutet; oder, wenn R' COOH bedeutet, ein pharmazeutisch akzeptables Salz der Verbindung.

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4. Verbindung nach Anspruch 1, ausgewählt aus:

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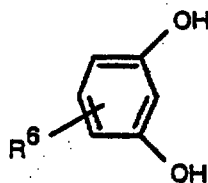
65

- Dimethyl-5,5'-[(2-fluor-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[(2-acetyl-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[(2-methyl-1,3-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- 5,5'-[(2'-Chlor-[1,1'-biphenyl]-2,5-diyl)-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[(2'-Methyl-[1,1'-biphenyl]-2,5-diyl)-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[(2-Trifluormethyl-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- Dimethyl-5,5'-[[2-(1-oxopropyl)-1,4-phenylen]-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[[2-(1-oxobutyl)-1,4-phenylen]-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[(2-benzoyl-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[2,5-dimethyl-1,4-phenylen-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- 5,5'-[(2-Phenylthio)-1,4-phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- Dimethyl-5,5'-[(2-methoxy-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[(2-methyl-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- Dimethyl-5,5'-[(2-brom-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentanoat],
- 5,5'-[(1,1'-Biphenyl)-2,5-diyl-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[1,4-Phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[(2-Dichlor-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[(2-Chlor-1,4-phenylen)-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[1,3-Phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[2-(Hydroxyäthyl)-1,4-phenylen-bis-(oxy)]-bis-[2,2-dimethylpentansäure],
- 5,5'-[[2-(Benzyl)-1,4-phenylen]-bis-(oxy)]-bis-[2,2-dimethylpentansäure],

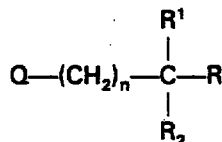


worin Q eine austretende Gruppe bedeutet und n, R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen, umgesetzt wird; und das resultierende Produkt isoliert wird.

11. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß eine Verbindung der Formel

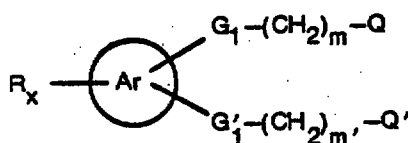


worin R⁶ der in Anspruch 1 gegebenen Definition entspricht, mit einer Verbindung der Formel



worin Q eine austretende Gruppe ist und n, R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen, umgesetzt wird und das resultierende Produkt isoliert wird.

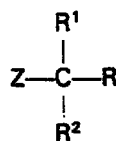
12. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches Verfahren gekennzeichnet ist durch Umsetzung einer Verbindung der folgenden allgemeinen Formel



worin

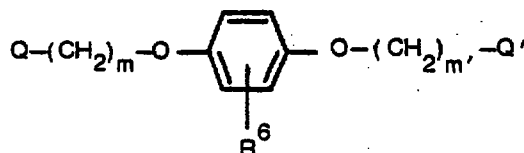


bedeutet; jedes von G₁ und G'₁, die gleich oder verschieden sind, Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeutet; R_x irgendeinen der Substituenten R³ und R⁶, wie in Anspruch 1 definiert, bedeutet; Q und Q' gleich oder verschieden sind und austretende Gruppen bedeuten; und m und m' der in Anspruch 1 angegebenen Bedeutung entsprechen; mit einer Verbindung der folgenden Formel



worin R, R¹ und R² der in Anspruch 1 angegebenen Bedeutung entsprechen und Z ein Alkalimetall ist; und Isolierung des resultierenden Produkts.

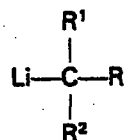
13. Verfahren nach Anspruch 12, gekennzeichnet durch Umsetzung einer Verbindung der Formel



worin Q und Q' austretende Gruppen sind und m, m' und R⁶ der in Anspruch 1 angegebenen Definition entsprechen; mit einer Verbindung der folgenden Formel

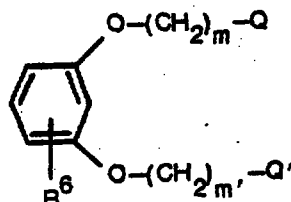


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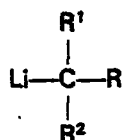


worin R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen; und Isolierung des resultierenden Produkts.

14. Verfahren nach Anspruch 12, dadurch gekennzeichnet, daß eine Verbindung der Formel



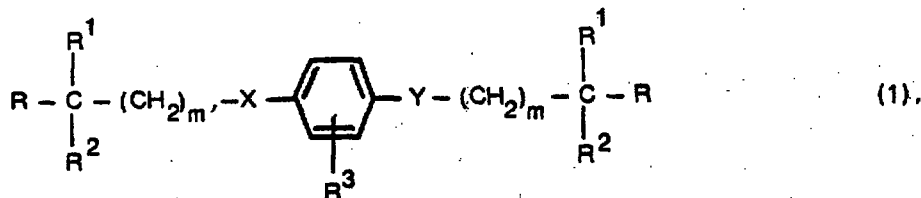
worin Q und Q' austretende Gruppen sind und m, m' und R⁶ der in Anspruch 1 angegebenen Definition entsprechen, mit einer Verbindung der folgenden Formel



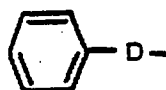
worin R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen, umgesetzt wird und als resultierende Produkt isoliert wird.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung einer der folgenden Formeln 1 bis 5:

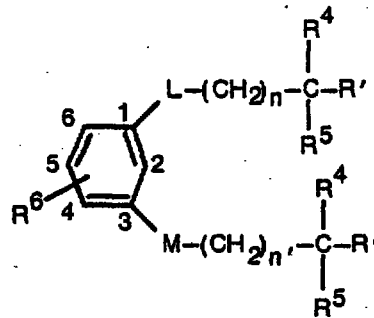


worin X und Y gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; m und m' gleich oder verschieden sind und ganze Zahlen im Bereich von 2 bis 5 bedeuten; R CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischen Amins oder ein Ammoniumkation bedeutet; jedes von R¹ und R², die gleich oder verschieden sind, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen bedeutet, oder R¹ zusammen mit dem R² am selben Kohlenstoffatom —(CH₂)₃₋₅— bedeutet; und R³ ein Wasserstoff- oder Halogenatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, Methoxy, Phenyl, Trifluormethyl, 2,5-Dichlor, 2,5-Dimethyl, 2,3,5-Trimethyl, Carboxyl-Acyl mit 1 bis 6 Kohlenstoffatomen, alpha-Hydroxyalkyl mit 1 bis 6 Kohlenstoffatomen, 2-Chlorphenyl, 4-Chlorphenyl, 2,4-Dichlorphenyl, 4-Methoxyphenyl, 2-Tolyl, 4-Tolyl oder



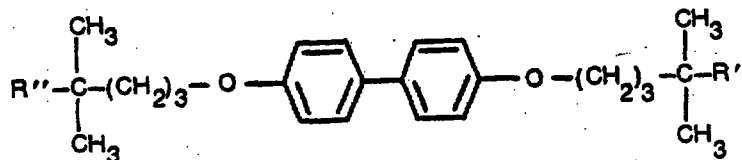
bedeutet; worin D O, CO, S, SO, SO₂, CH₂ oder CHOH bedeutet; mit der Maßgabe, daß R³ kein Wasserstoffatom ist, wenn alle der folgenden Bedingungen erfüllt sind, nämlich wenn X und Y beide Sauerstoffatome sind, m und m' beide 2 bedeuten; R¹ und R² beide CH₃ bedeuten und R CO₂H ist;



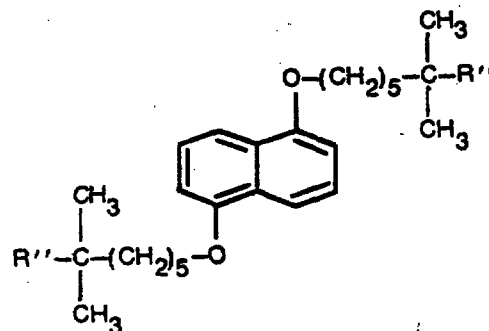


(2)

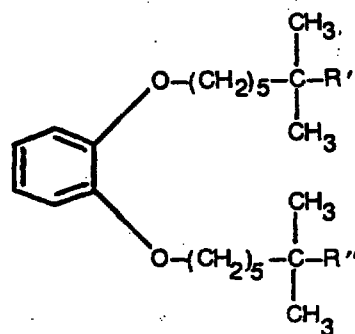
worin L und M gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; n und n' gleich oder verschieden sind und ganze Zahlen im Bereich von 2 bis 5 bedeuten; jedes von R⁴ und R⁵, die gleich oder verschieden sind, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen bedeutet; jedes R' CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischenamins oder ein Ammoniumkation bedeutet; und R⁶ ein Wasserstoffatom, 4-Formyl, 2-Nitro, 2-Methyl, 5-Methyl, 4-Benzoyl oder 4-Chlor bedeutet:



(3)

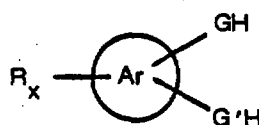


(4)



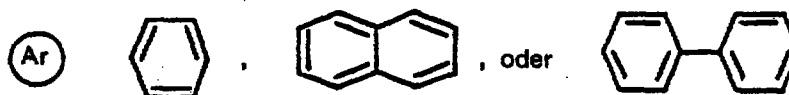
(5)

worin, in Formel 3, 4 oder 5, jedes R'' CH₂OH, CHO oder CO₂A bedeutet, worin A ein Wasserstoffatom, ein Alkylradikal mit 1 bis 6 Kohlenstoffatomen, ein Alkali- oder Erdalkalimetallkation, das Kation eines organischenamins oder ein Ammoniumkation bedeutet; oder, wenn R, R' oder R'' in irgendeiner dieser Verbindungen COOH bedeutet, ein pharmazeutisch akzeptables Salz dieser Verbindung; welches Verfahren gekennzeichnet ist durch die Umsetzung einer Verbindung der folgenden allgemeinen Formel

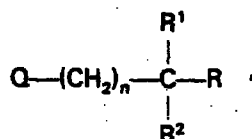


worin



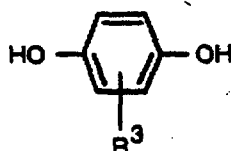


bedeutet; G und G' gleich oder verschieden sind und Sauerstoff oder Schwefel bedeuten; und R_x irgendeinen der Substituenten R³ und R⁶, wie oben definiert, bedeutet, mit einer Verbindung der folgenden allgemeinen Formel:

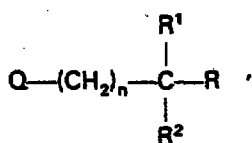


worin Q eine austretende Gruppe bedeutet und n, R, R¹ und R² der oben angegebenen Definition entsprechen; und entweder Isolierung des resultierenden Produkts, oder, wenn eines von G und G' Schwefel bedeutet, Oxidation des gekuppelten Produkts und Isolierung des oxidierten Produkts.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel

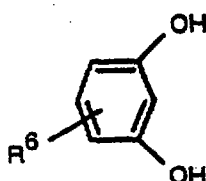


worin R³ der in Anspruch 1 angegebenen Definition entspricht, mit einer Verbindung der Formel

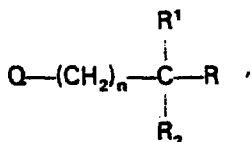


worin Q, n, R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen, umgesetzt wird und das resultierende Produkt isoliert wird.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel

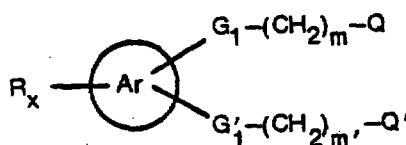


worin R⁶ der in Anspruch 1 angegebenen Bedeutung entspricht, mit einer Verbindung der Formel



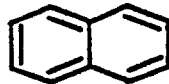
worin Q, n, R, R¹ und R² der in Anspruch 1 angegebenen Bedeutung entsprechen, umgesetzt wird und das resultierende Produkt isoliert wird.

4. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches Verfahren dadurch gekennzeichnet ist, daß eine Verbindung der folgenden allgemeinen Formel

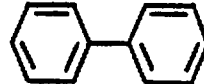


worin

5

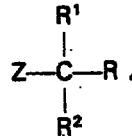


, oder



bedeutet; G und G₁' gleich oder verschieden sind und Sauerstoff, Schwefel, Sulfon oder Sulfoxid bedeuten; R_x irgendeinen der Substituenten R³ und R⁶, wie in Anspruch 1 definiert, bedeutet; Q und Q' gleich oder verschieden sind und austretende Gruppen sind; und m und m' der in Anspruch 1 angegebenen Bedeutung entsprechen; mit einer Verbindung der folgenden Formel

10



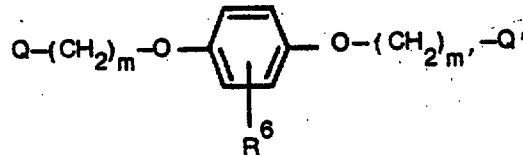
15

worin Z ein Alkalimetall bedeutet und R, R¹ und R² der in Anspruch 1 angegebenen Bedeutung entsprechen; umgesetzt wird und das resultierende Produkt isoliert wird.

20

5. Verfahren nach Anspruch 4, welches Verfahren dadurch gekennzeichnet ist, daß eine Verbindung der Formel

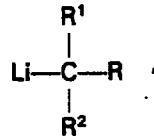
25



30

worin Q und Q' austretende Gruppen sind und m, m' und R⁶ der in Anspruch 1 angegebenen Definition entsprechen; mit einer Verbindung der Formel

35

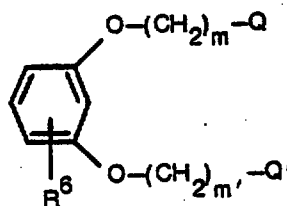


40

worin R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen, umgesetzt wird und das resultierende Produkt isoliert wird.

6. Verfahren nach Anspruch 4, welches Verfahren dadurch gekennzeichnet ist, daß eine Verbindung der Formel

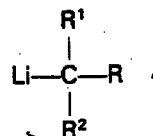
45



50

worin Q und Q' austretende Gruppen sind und m, m' und R⁶ der in Anspruch 1 angegebenen Definition entsprechen, mit einer Verbindung der Formel

55

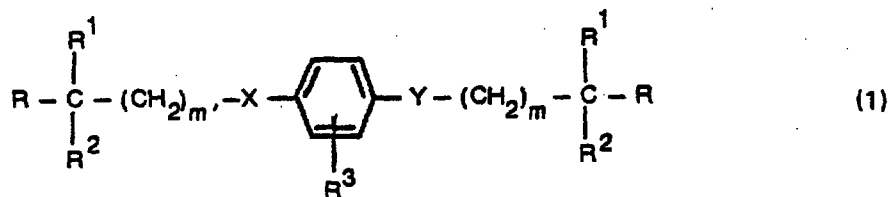


60

worin R, R¹ und R² der in Anspruch 1 angegebenen Definition entsprechen, umgesetzt wird und das resultierende Produkt isoliert wird.

65

1. Composé ayant l'une des formules 1 à 5:



dans lesquelles:

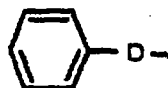
X et Y sont identiques ou différents et représentent oxygène, soufre, sulfone ou sulfoxyde;

m et m' sont égaux ou différents et représentent des entiers dans la gamme de 2 à 5;

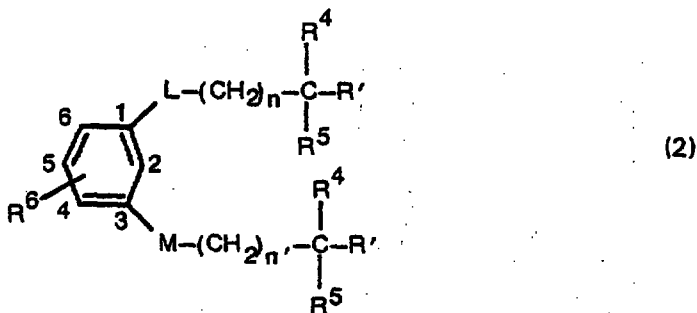
chaque R représente CH_2OH , CHO ou CO_2A dans lesquels A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium;

R^1 et R^2 sont identiques ou différents et représentent chacun un radical alkyle possédant de 1 à 6 atomes de carbone, ou R^1 lorsqu'il est pris en même temps que R^2 partageant le même atome de carbone représente $-(\text{CH}_2)_{3-5}-$; et,

R^3 est un hydrogène ou un atome d'halogène, un radical alkyle possédant de 1 à 6 atomes de carbone, méthoxy, phényle, trifluorométhyle, 2,5-dichloro, 2,5-diméthyle, 2,3,5-triméthyle, un acyle carboxylique ayant 1 à 6 atomes de carbone, alpha-hydroxyalkyle ayant 1 à 6 atomes de carbone, 2-chlorophényle, 4-chlorophényle, 2,4-dichlorophényle, 4-méthoxyphényle, 2-tolyle, 4-tolyle ou



dans lequel D représente O, CO, S, SO, SO_2 , CH_2 ou CHOH ; pourvu que R^3 ne soit pas un atome d'hydrogène lorsque toutes les autres conditions sont satisfaites, à savoir lorsque X et Y sont simultanément des atomes d'hydrogène, m et m' sont égaux à 2, R^1 et R^2 sont simultanément CH_3 , et R est CO_2H :



dans laquelle:

L et M sont identiques ou différents, et représentent oxygène, soufre, sulfone ou sulfoxyde;

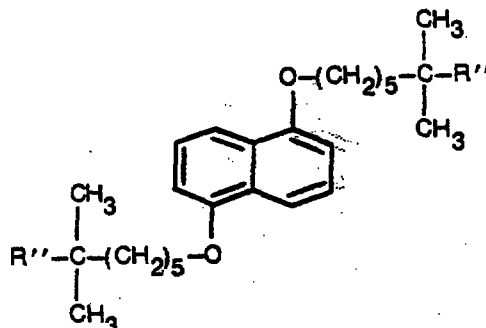
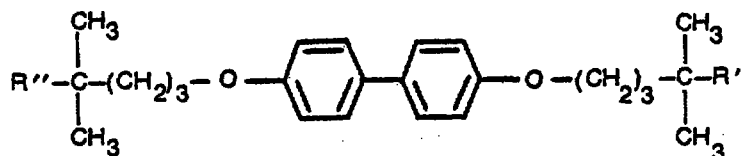
n et n' sont égaux ou différents et représentent des entiers dans la gamme de 2 à 5;

R^4 et R^5 qui peuvent être identiques ou différents, représentent chacun un radical alkyle possédant de 1 à 6 atomes de carbone;

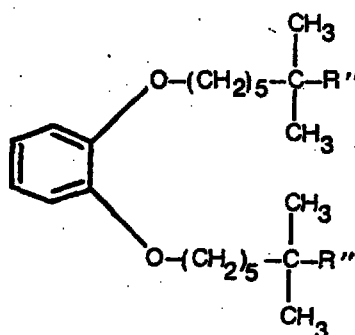
les R' représentent chacun CH_2OH , CHO ou CO_2A dans lequel A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium; et,

R^6 est un atome d'hydrogène, 4-formyle, 2-nitro, 2-méthyle, 5-méthyle, 4-benzoyl ou 4-chloro:





(4)



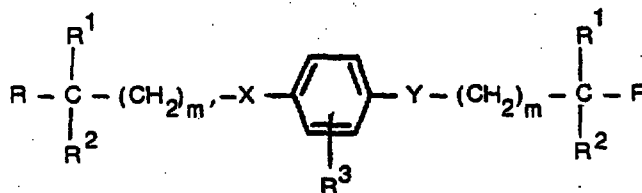
(5)

dans lequel, dans les formules 3, 4 ou 5:

les R'' représentent chacun CH₂OH, CHO ou CH₂A dans lequel A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium;

— ou lorsque R, R' ou R'' représente COOH dans l'un quelconque de ces composés, un sel pharmaceutiquement acceptable de ce composé.

2. Composé tel que revendiqué dans la revendication 1, qui a la formule:



(1)

dans laquelle:

X et Y sont identiques ou différents et représentent oxygène, soufre, sulfone ou sulfoxyde;

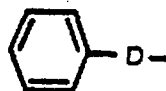
m et m' sont égaux ou différents et représentent des entiers dans la gamme de 2 à 5;

les R représentent chacun CH₂OH, CHO ou CO₂A dans lequel A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium;

R¹ et R² sont les mêmes ou différents, représentent chacun un radical alkyle possédant de 1 à 6 atomes de carbone, ou R¹ pris en même temps que le R² qui partage le même atome de carbone représente —(CH₂)₃₋₅—; et,

R³ est un hydrogène ou un atome d'halogène, un radical alkyle possédant de 1 à 6 atomes de carbone, méthoxy, phényle, trifluorométhyle, 2,5-dichloro, 2,5-diméthyle, 2,3,5-triméthyle, acyle carboxylique ayant 1 à 6 atomes de carbone, un alpha-hydroxyalkyle ayant 1 à 6 atomes de carbone, 2-chlorophényle, 4-chlorophényle, 2,4-dichlorophényle, 4-méthoxyphényle, 2-tolyle, 4-tolyle ou

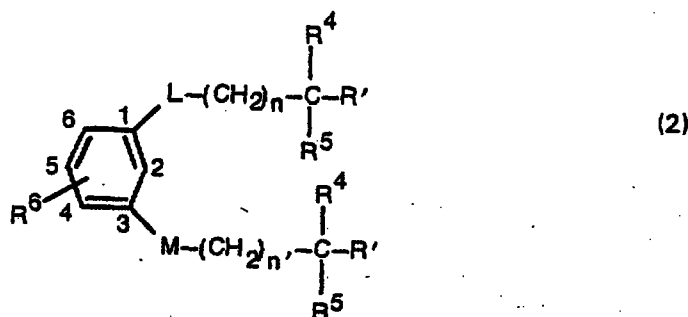




dans lequel D représente O, CO, S, SO, SO₂, CH₂ ou CHOH; pourvu que R³ ne soit pas un atome d'hydrogène lorsque toutes les autres conditions suivantes sont satisfaites, à savoir lorsque X et Y représentent simultanément un oxygène, m et m' représentent tous les deux 2, R¹ et R² représentent tous les deux CH₃, et R représente CO₂H;

— ou lorsque R représente COOH, un sel pharmaceutiquement acceptable du composé.

3. Composé tel que revendiqué dans la revendication 1, qui possède la formule



dans laquelle:

L et M sont identiques ou différents et représentent oxygène, soufre, sulfone ou sulfoxyde;

n et n' sont les mêmes différents et représentent des entiers dans la gamme de 2 à 5;

R⁴ et R⁵ qui sont les mêmes ou différents, représentent chacun un radical alkyle possédant de 1 à 6 atomes de carbone;

chacun des R' représente CH₂OH, CHO ou CO₂A dans lequel A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation de métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium;

R⁶ représente un atome d'hydrogène, 4-formyle, 2-nitro, 2-méthyle, 5-méthyle, 4-benzoyle ou 4-chloro;

— ou lorsque R' représente COOH, un sel pharmaceutiquement acceptable de ce composé.

4. Composé tel que revendiqué dans la revendication 1 et qui est choisi dans le groupe consistant

par:

- 5,5'-[(2-fluoro-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[(2-acétyl-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[(2-méthyl-1,3-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- Acide 5,5'-[(2'-chloro[1,1'-biphényl]-2,5-diyl)bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[(2'-méthyl[1,1'-biphényl]-2,5-diyl)bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[(2-trifluorométhyl-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoïque];
- 5,5'-[(2(1-oxopropyl)-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[(2(1-oxobutyl)-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[(2-benzoyl-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[2,5-diméthyl-1,4-phénylènebis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- Acide 5,5'-[(2-phénylthio)-1,4-phénylène]bis(oxy)]bis[2,2-diméthylpentanoïque];
- 5,5'-[(2-méthoxy-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[(2-méthyl-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- 5,5'-[(2-bromo-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoate] de diméthyle;
- Acide 5,5'-[(1,1'-biphényl)-2,5-diyl]bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[1,4-phénylènebis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[(2,5-dichloro-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[(2-chloro-1,4-phénylène)bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[1,3-phénylènebis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[2-(hydroxyéthyl)-1,4-phénylènebis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[2-(benzyl)-1,4-phénylène]bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[2-(hydroxyphénylméthyl)-1,4-phénylènebis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[(2-hydroxyméthyl)-1,4-phénylènebis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[2-(1-hydroxybutyl)-1,4-phénylène]bis(oxy)]bis[2,2-diméthylpentanoïque];
- Acide 5,5'-[2(phénylsulfinyl)-1,4-phénylène]bis(oxy)]bis[2,2-diméthylpentanoïque]; et,
- Acide 5,5'-[2-(1-hydroxypropyl)-1,4-phénylènebis(oxy)]bis[2,2-diméthylpentanoïque].



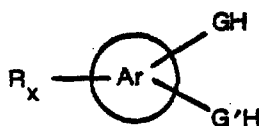
5. Composé tel que revendiqué dans la revendication 1, qui est l'acide 6,6'-[1,4-phénylènebis(oxy)]bis[2,2-diméthylhexanoïque]; l'acide 6,6'-[1,3-phénylènebis(oxy)]bis[2,2-diméthylhexanoïque]; ou le 6,6'-[1,4-phénylènebis(oxy)]bis[2,2-diméthyl-1-hexanol].

6. Composé tel que revendiqué dans la revendication 1, qui est l'acide 4,4'-[(2-chloro-1,4-phénylène)bis(oxy)]bis[2,2-diméthylbutanoïque]; ou l'acide 4,4'-[1,3-phénylènebis(oxy)]bis[2,2-diméthylbutanoïque].

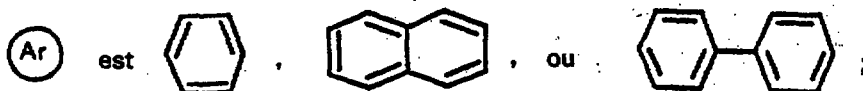
7. Composé tel que revendiqué dans la revendication 1, qui est l'acide 7,7'-[1,2-phénylènebis(oxy)]bis[2,2-diméthylheptanoïque].

8. Composé tel que revendiqué dans la revendication 1, qui est l'acide 5-[[4-[(4-carboxy-4-méthylpentyl)oxy]phényl]thio]-2,2-diméthylpentanoïque; ou, l'acide 5-[[4-[(4-carboxy-4-méthylpentyl)oxy]phényl]sulfinyl]-2,2-diméthylpentanoïque.

9. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, procédé consistant à faire réagir un composé de la formule générale suivante:

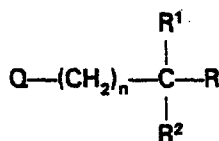


dans laquelle:



G et G' étant identiques ou différents et représentant chacun oxygène ou soufre;

R_x représente un quelconque des substituants R³ et R⁶ tels que définis dans la revendication 1; avec un composé de la formule générale suivante:



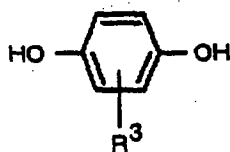
dans laquelle:

Q est un groupe partant; et,

n, R¹ et R² sont tels que définis dans la revendication 1;

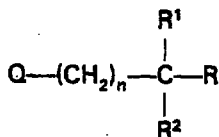
et soit à isoler le produit résultant ou, lorsque G et G' représentent l'un et l'autre un soufre, à oxyder le produit couplé et à isoler le produit oxydé.

10. Procédé suivant la revendication 9, consistant à faire réagir un composé de la formule:



dans laquelle:

R³ est tel que défini dans la revendication 1, avec un composé de formule:



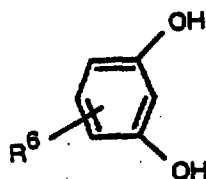
dans laquelle:

Q est un groupe partant; et,

n, R, R¹ et R² sont tels que définis dans la revendication 1, et à isoler le produit qui en résulte.

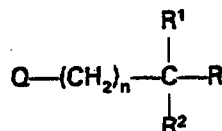


11. Procédé suivant la revendication 9, qui consiste à faire réagir un composé de la formule:



10 dans laquelle:

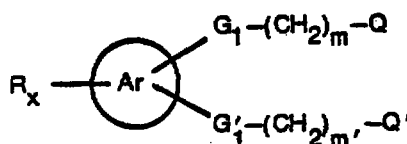
R^6 est tel que défini dans la revendication 1, avec un composé de la formule:



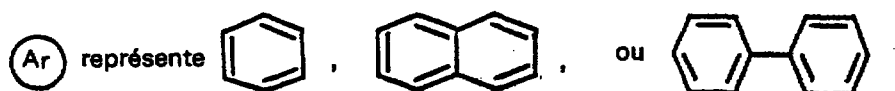
20 dans laquelle:

Q est un groupe partant; et, n, R, R^1 et R^2 sont tels que définis dans la revendication 1, et à isoler le produit qui en résulte.

12. Procédé de préparation d'un composé tel que revendiqué dans la revendication 1, procédé consistant à faire réagir un composé de formule générale suivante:



35 dans laquelle:



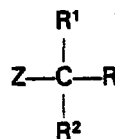
G_1 et G'_1 qui sont identiques ou différents, représentent chacun un oxygène, soufre, sulfone ou sulfoxyde;

R_x représente l'un quelconque des substituants R^3 et R^6 tels que définis dans la revendication 1;

Q et Q' sont identiques ou différents et représentent des groupes partants;

m et m' sont tels que définis dans la revendication 1;

avec un composé de formule générale suivante:



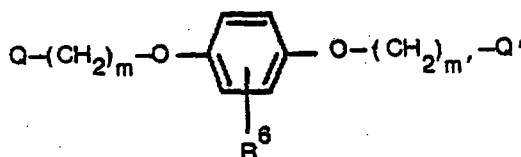
50 dans laquelle:

R, R^1 et R^2 sont tels que définis dans la revendication 1; et,

Z est un métal alcalin,

55 et à isoler le produit qui en résulte.

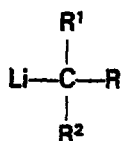
13. Procédé suivant la revendication 12, consistant à faire réagir un produit de la formule:



65 dans laquelle:



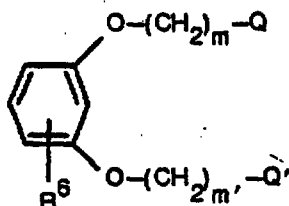
Q et Q' sont des groupes partant; et
m, m' et R⁶ sont tels que définis dans la revendication 1,
avec un composé de la formule suivante:



dans laquelle:

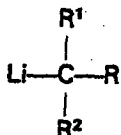
R, R¹ et R² sont tels que définis dans la revendication 1,
et à isoler le produit qui en résulte.

14. Procédé suivant la revendication 12, consistant à faire réagir un composé de la formule:



dans laquelle:

Q et Q' sont des groupes partant; et,
m, m' et R⁶ sont tels que définis dans la revendication 1,
avec un composé de la formule suivante:

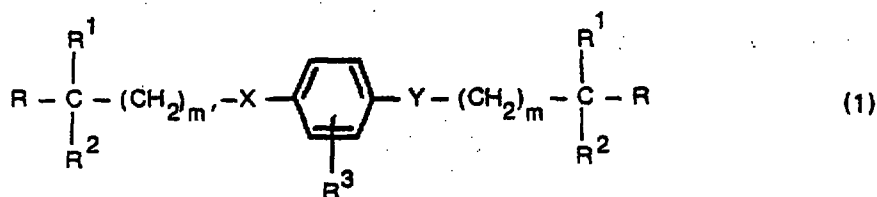


dans laquelle:

R, R¹ et R² sont tels que définis dans la revendication 1,
et à isoler le produit qui en résulte.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé ayant l'une des formules suivantes 1 à 5:



dans lesquelles:

X et Y sont identiques ou différents et représentent oxygène, soufre, sulfone ou sulfoxyde;

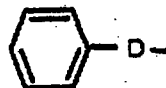
m et m' sont égaux ou différents et représentent des entiers dans la gamme de 2 à 5;

chaque R représente CH₂OH, CHO ou CO₂A dans lesquels A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium;

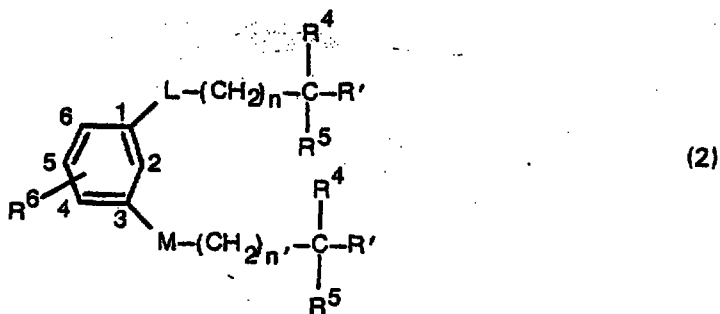
R¹ et R² sont identiques ou différents et représentent chacun un radical alkyle possédant de 1 à 6 atomes de carbone, ou R¹ lorsqu'il est pris en même temps que R² partageant le même atome de carbone représente —(CH₂)₃₋₅—; et,

R³ est un hydrogène ou un atome d'halogène, un radical alkyle possédant de 1 à 6 atomes de carbone, méthoxy, phényle, trifluorométhyle, 2,5-dichloro, 2,5-diméthyle, 2,3,5-triméthyle, un acyle carboxylique ayant 1 à 6 atomes de carbone, alpha-hydroxyalkyle ayant 1 à 6 atomes de carbone, 2-chlorophényle, 4-chlorophényle, 2,4-dichlorophényle, 4-méthoxyphényle, 2-tolyle, 4-tolyle ou



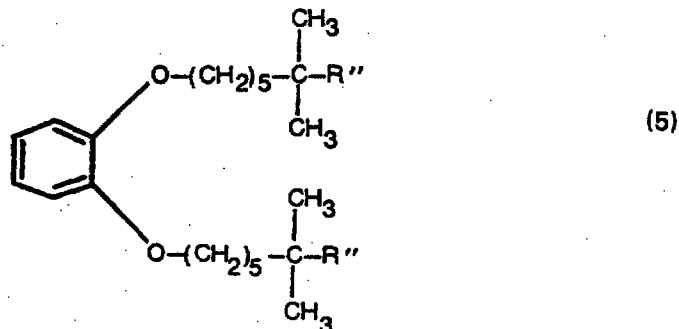
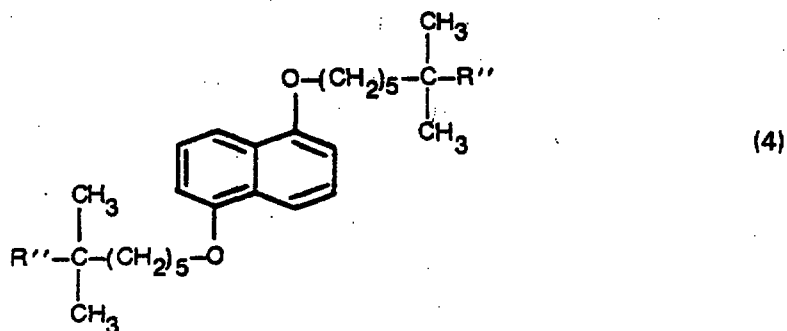
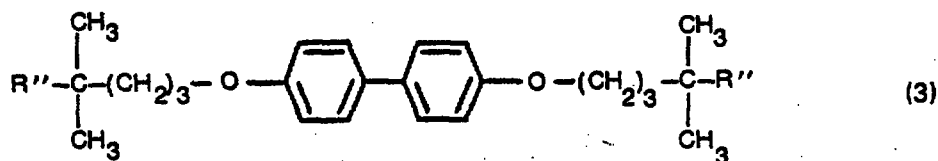


- 5 dans lequel D représente O, CO, S, SO, SO₂, CH₂ ou CHOH; pourvu que R³ ne soit pas un atome d'hydrogène lorsque toutes les autres conditions sont satisfaites, à savoir lorsque X et Y sont simultanément des atomes d'hydrogène, m et m' sont égaux à 2, R¹ et R² sont simultanément CH₃, et R est CO₂H:



dans laquelle:

- 25 L et M sont identiques ou différents, et représentent oxygène, soufre, sulfone ou sulfoxyde;
 n et n' sont égaux ou différents et représentent des entiers dans la gamme de 2 à 5;
 R⁴ et R⁵ qui peuvent être identiques ou différents, représentent chacun un radical alkyle possédant de 1 à 6 atomes de carbone;
 les R' représentent chacun CH₂OH, CHO ou CO₂A dans lequel A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium; et,
 30 R⁶ est un atome d'hydrogène, 4-formyle, 2-nitro, 2-méthyle, 5-méthyle, 4-benzoyl ou 4-chloro:

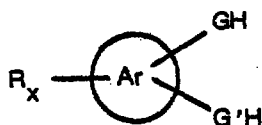


65 dans lequel, dans les formules 3, 4 ou 5:

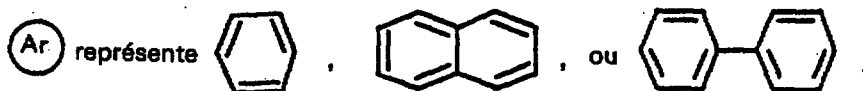


les R'' représentent chacun CH₂OH, CHO ou CH₂A dans lequel A est un atome d'hydrogène, un radical alkyle possédant de 1 à 6 atomes de carbone, un cation d'un métal alcalin ou alcalinoterreux, un cation amine organique ou un cation ammonium;

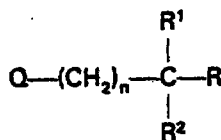
— ou lorsque R, R' ou R'' représente COOH dans l'un quelconque de ces composés, un sel pharmaceutiquement acceptable de ce composé:
procédé consistant à faire réagir un composé de formule générale suivante:



dans laquelle:



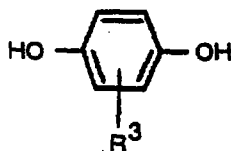
G et G' identiques ou différents représentent oxygène ou soufre; et,
R_x représente l'un quelconque des substituant R³ et R⁶ tels que définis ci-dessus,
avec un composé de la formule générale suivante:



dans laquelle:

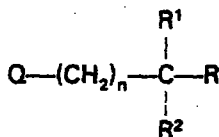
Q est un groupe partant; et,
n, R¹ et R² sont tels que définis ci-dessus,
et soit à isoler le produit qui en résulte, soit, lorsque G et G' représentent l'un et l'autre un soufre, à oxyder le produit couplé et à isoler le produit oxydé.

2. Procédé suivant la revendication 1, qui consiste à faire réagir un composé de la formule:



dans laquelle:

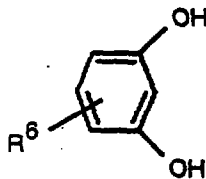
R³ est tel que défini dans la revendication 1,
avec un composé de la formule:



dans laquelle:

Q, n, R, R¹ et R² sont tels que définis dans la revendication 1, et à isoler le produit qui en résulte.

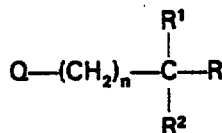
3. Procédé suivant la revendication 1, qui consiste à faire réagir un composé de la formule:



dans laquelle:

R⁶ est tel que défini dans la revendication 1,
avec un composé de la formule:

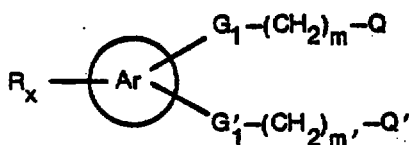




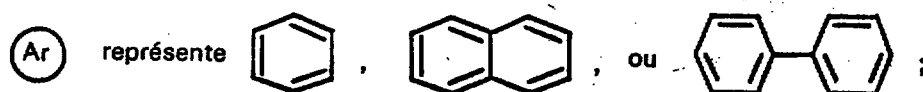
dans laquelle:

Q, n, R, R¹ et R² sont définis dans la revendication 1, et à isoler le produit qui en résulte.

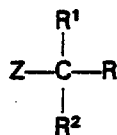
4. Procédé de préparation d'un composé tel que défini dans la revendication 1, procédé consistant à faire réagir un composé de formule générale suivante:



dans laquelle:



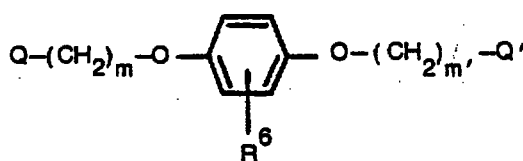
G et G₁' sont identiques ou différents, représentent oxygène, soufre, sulfone ou sulfoxyde; R_x représente l'un quelconque des substituants R³ et R⁶ tels que définis dans la revendication 1; Q et Q' sont identiques ou différents et sont des groupes partants; m et m' sont tels que définis dans la revendication 1, avec un composé de formule suivante:



dans laquelle:

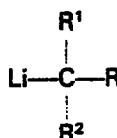
Z est un métal alcalin; et, R, R¹ et R² sont tels que définis dans la revendication 1, et à isoler le produit qui en résulte.

5. Procédé suivant la revendication 4, consistant à faire réagir un composé de la formule générale suivante:



dans laquelle:

Q et Q' sont des groupes partants; et m, m' et R⁶ sont tels que définis dans la revendication 1, avec un composé de la formule:

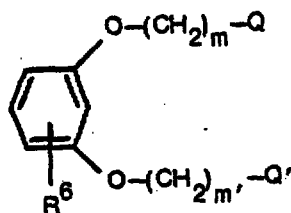


dans laquelle:

R, R¹ et R² sont tels que définis dans la revendication 1, et à isoler le produit qui en résulte.

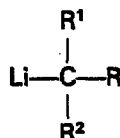


6. Procédé suivant la revendication 4, consistant à faire réagir un composé de la formule:



dans laquelle:

Q et Q' sont des groupes partant; et,
m, m' et R⁶ sont tels que définis dans la revendication 1,
avec un composé de la formule:



dans laquelle:

R, R¹ et R² sont tels que définis dans la revendication 1,
et à isoler le produit qui en résulte.

