

L038,185



PATENT SPECIFICATION

L038,185

NO DRAWINGS

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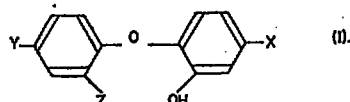
COMPLETE SPECIFICATION

New Diphenyl Ethers and processes for their production, and Pharmaceutical Compositions containing them

We J. R. GEIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns processes for the production of new substituted diphenyl ethers which have valuable biological properties.

Up to the present, halogen-substituted o-hydroxydiphenyl ethers (o-phenoxy phenols) corresponding to the general formula I



wherein X and Y independently of each other represent chlorine or bromine, and Z represents hydrogen, chlorine or bromine, have not been known. It has now been found that these compounds have antimicrobial properties of surprising intensity and variety while, at the same time, their toxicity is relatively slight. Because of these properties as well as their stability, their substantially colourlessness and absence of irritation to the skin and mucous membranes, they can be used as antimicrobial active substances for the most various purposes, for example, for the protection of organic materials and objects from microorganisms, particularly from attack by bacteria, and also as disinfectant additives in soaps and washing agents as well as in ointments for the skin and other preparations for personal hygiene. Their use, as active ingredients, is particularly valuable for the healing of diseased conditions of the skin, the intestinal system and urinal tract of warm blooded animals as can be seen from their excellent activity against the pathogenic fungi and bacteria given below, their elimination

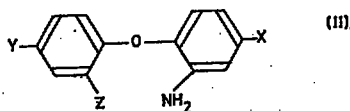
[Price 4s. 6d.]

tion from the body in substantially unchanged, active form and their relatively slight toxicity.

The compounds of general formula I have an excellent growth-inhibiting action, for example, on the following gram positive and gram negative bacteria as well as on pathogenic fungi: *Staphylococcus aureus* Smith, *Staphylococcus lactis*, *Bacillus pumilus*, *Bacillus subtilis*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium butyricum*, *Clostridium welchii*, *Clostridium tetani*, *Klebsiella pneumoniae*, *Alcaligenes faecalis*, *Salmonella pullorum*, *Salmonella typhi*, *Salmonella paratyphi A* and *B*, *Salmonella typhi* murium, *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Brucella abortus*, *Proteus mirabilis*, *Achromobacter spec.*, *Serratia marcescens*, *Pasteurella pseudotuberculosis*; *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans* var. *sabourandi*, *Trichophyton schönleini*, *Trichophyton quinckeanum*, *Microsporon canis*, *Microsporon gypseum*, *Blastomyces dermatidis*, *Sporotrichum schenckii*, *Epidermophyton floccosum*.

The compounds of the general formula I can be used, for example, as active ingredients for disinfectants for the hands, cosmetics, ointments for wounds, eye ointments and other agents for external use, as well as active ingredients for internal use. Examples of the latter are tablets for the disinfection for the mouth and throat as well as tablets and sugar coated tablets (dragées) for the disinfection of the intestinal system and urinal tract.

To produce the compounds of general formula I, a substituted o-aminodiphenyl ether of the general formula II



Corynebacterium

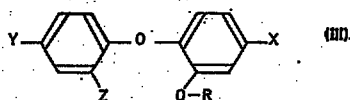
sabourandi

of



wherein X, Y and Z have the meanings given above, is converted into a diazonium salt, preferably into the sulphate, and this is boiled down with water or with an aqueous acid, in particular sulphuric acid. The diazotisation and boiling down are performed by methods known per se. For example, the sulphate prepared by means of nitrosyl sulphuric acid or by means of sodium nitrite in sulphuric acid is used as diazonium salt and it is boiled down in about 50—80% sulphuric acid at the boiling temperature thereof, or in the presence of a higher boiling inert organic solvent such as, e.g. o-dichlorobenzene, which takes up the reaction product, until the evolution of nitrogen ceases.

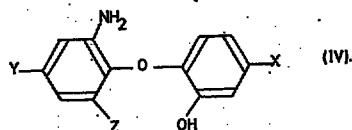
Another process for the production of compounds of the general formula I is characterised by dealkylating an o-alkoxy-diphenyl ether corresponding to the general formula III



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wherein R is a low alkyl radical, particularly the methyl radical and X, Y and Z have the meanings given above. The dealkylation can be performed by the methods known for the cleavage of aryl-alkyl ethers, e.g. by treatment with aluminium chloride in an inert solvent, e.g. in benzene at the boiling temperature thereof, also by heating with concentrated aqueous hydrobromic acid, with hydrogen bromide in glacial acetic acid or a mixture of hydrobromic acid and acetic acid.

Compounds of the general formula I are obtained by a third process by producing, in the known manner, from a compound of the general formula IV

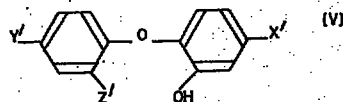


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wherein X, Y and Z have the meanings given above, a diazonium salt and converting the latter into the corresponding compound containing hydrogen instead of the original amino group. This modification can be effected with the usual agents, e.g. by boiling in a low alkanol, particularly ethanol, or in dilute hypophosphoric acid, until the evolution of nitrogen ceases.

45

Finally, compounds of the general formula I are also obtained by producing from a compound of the general formula V



wherein one or two of the symbols X', Y' and Z' represent the amino group and the remaining symbol(s) have the meaning(s) given for X, Y or Z above, a diazonium salt and converting the latter into the corresponding compound containing chlorine or bromine instead of the original amino groups X', Y' or Z'. This modification is performed by the known Sandmeyer or Gatterman reaction methods by treating the diazonium salt, in particular the chloride or bromide, in aqueous medium with cuprous chloride or cuprous bromide, or with the corresponding halogen hydracids in the presence of copper powder, until the evolution of nitrogen ceases.

Starting materials of the general formula II are obtained, for example like the known 2-amino-4,4'-dichlorodiphenyl ether, from the corresponding halogen-substituted 2-nitrodiphenyl ethers by reduction, e.g. by means of stannous chloride and hydrochloric acid, zinc dust and acetic acid, or iron and hydrochloric acid, or by catalytic hydrogenation. Some of the substituted 2-nitro-diphenyl ethers are known and can be produced by reaction of 2,5-dihalogeno-1-nitrobenzenes with alkali metal salts of 4-halogeno- or 2,4-dihalogenophenols.

Halogen substituted o-alkoxydiphenyl ethers of the general formula III are obtained, for example, by reacting alkali metal salts of 2-alkoxy-4-halogen phenols, in particular 4-chloro- or 4-bromo- guaiacol, with 4-halogen-1-nitrobenzenes, 3,4-dihalogen-1-nitrobenzenes, 2,5-dihalogen-1-nitrobenzenes or 2,3,5-trihalogen-1-nitrobenzenes to form 2-alkoxy-4-halogen-4'-nitro-diphenyl ethers, 2-alkoxy-4,2'-dihalogen-4-nitrodiphenyl ethers, 2-alkoxy-4,4'-dihalogen-2'-nitrodiphenyl ethers or 2-alkoxy-2,4,4'-trihalogen-6'-nitrodiphenyl ethers respectively, and converting these in the usual way by catalytic hydrogenation or by reduction with stannous chloride and hydrochloric acid, zinc dust and acetic acid or iron and hydrochloric acid, into the corresponding amino compounds. Amino compounds having an amino group in the 4'-position and, if desired, also those having an amino group in the 2'-position are converted into the corresponding diazonium chlorides in order to replace this group by chlorine or bromine, and these chlorides are treated according to Sandmeyer with cuprous chloride or cuprous bromide. On the other hand, amino compounds having the amino group in the 6'-position and, if desired, also those having an amino group in 2'-position, i.e. compounds which already contain the halogen



atom Y in the 4'-position, are converted into the corresponding diazonium salts, in particular into the sulphates, and these are warmed with ethanol whereby a hydrogen atom takes the place of the intermediary diazonium group.

Starting materials of the general formula IV and V for the third and fourth production processes are obtained, for example, if the 2-alkoxy diphenyl ethers substituted by halogen and a nitro group which are formed as intermediate products in the above reaction scheme are dealkylated analogously to the second production process and then reduced to the corresponding amino compounds having a free hydroxyl group. The starting materials of the general formula IV containing two amino groups can be obtained in an analogous manner, e.g., by reacting the sodium salt of 4-nitroguaiacol with 4-halogen-1-nitrobenzenes, 3,4-dihalogen-1-nitrobenzenes or 2,5-dihalogen-1-nitrobenzenes, or by reacting the sodium salt of 4-chloro- or 4-bromo-guaiacol with 4-halogen-1,3-dinitrobenzenes, dealkylating the 2-methoxy-4,4'-dinitrodiphenyl ethers, 2-methoxy-2'-halogen-4,4'-dinitrodiphenyl ethers, 2-methoxy-4'-halogen-4,2'-dinitrodiphenyl ethers or 2-methoxy-4-halogen-2',4'-dinitrodiphenyl ethers and hydrogenating or reducing these.

The following examples further illustrate the invention. The temperatures are given in degrees Centigrade.

EXAMPLE 1

200 g of 100% nitrosyl sulphuric acid are dissolved in 1560 g of concentrated sulphuric acid and 381 g of 2-amino-4,4'-dichlorodiphenyl ether are added within about 2 hours while stirring well at 40—45°. The mixture is stirred for another 3 hours at room temperature. 450 ml of water are then poured in while cooling with ice water whereupon the temperature rises to 70°. 800 ml of o-dichlorobenzene are added and then the mixture is boiled in an oil bath 200° (final inner temperature 165°) until no more diazo compound can be traced. The upper organic phase is then removed while still hot, 1000 ml of water and 125 ml of 30% sodium hydroxide solution are added and the o-dichlorobenzene is distilled off with steam. The aqueous residue of this steam distillation contains the 2-hydroxy-4,4'-dichlorodiphenyl ether dissolved therein as the sodium salt as well as, as precipitate, 3,6-dichlorodibenzofuran which is formed as side product. After cooling, the aqueous residue is filtered off and washed. The filtrates are poured into 150 ml of concentrated hydrochloric acid and the precipitate formed, after it has solidified, is filtered off, washed neutral and dried. The crude 2-hydroxy-4,4'-dichlorodiphenyl ether obtained is purified by distillation in vacuo and the distillate is recrystallised from petroleum ether. B.P. 201—206°/12—13 Torr; M.P. 78—79° (white crystals).

If instead of the 381 g of 2-amino-4,4'-di-

chlorodiphenyl ether, equimolar amounts of:

- a') 2-amino-4,2',4'-trichlorodiphenyl ether,
- b') 2-amino-4-chloro-4'-bromodiphenyl ether,
- c') 2-amino-4-bromo-4'-chlorodiphenyl ether,
- d') 2-amino-4,4'-dibromodiphenyl ether or
- e') 2-amino-4,2',4'-tribromodiphenyl ether

are used and the procedure described in the example is followed, then the following substituted diphenyl ethers are obtained:

- a) 2-hydroxy-4,2',4'-dichlorodiphenyl ether, M.P. 60—61°,
- b) 2-hydroxy-4-chloro-4'-bromodiphenyl ether, M.P. 79—80°,
- c) 2-hydroxy-4-bromo-4'-chlorodiphenyl ether, B.P. 214—215°/13 Torr,
- d) 2-hydroxy-4,4'-dibromodiphenyl ether, M.P. 53—54°, or
- e) 2-hydroxy-4,2',4'-tribromodiphenyl ether, B.P. 170—173°/0.06 Torr.

EXAMPLE 2

a) 67.5 g of finely milled 2-hydroxy-2'-amino-4,4'-dichloro-diphenyl ether are added while stirring well to a mixture of 65 ml of concentrated hydrochloric acid and 175 ml of water. At 0—50, 55 g of a 33% sodium nitrate solution are introduced under the surface of the liquid and the diazo suspension formed is stirred in 2500 ml of ethyl alcohol and 7 g of copper powder for another 15 hours. When no more diazo compound can be traced, the mixture is filtered. The alcohol is distilled off from the filtrate, the residue is taken up in ether, the aqueous phase is separated, the ethereal phase is washed neutral and concentrated. The crude product which remains is distilled under water jet vacuum and the distillate, which passes over at 197°—204°/12 Torr and solidifies on cooling, is recrystallised from petroleum ether. The 2-hydroxy-4,4'-dichlorodiphenyl ether obtained melts at 78—79°.

The starting material, 2-hydroxy-2'-amino-4,4'-dichlorodiphenyl ether is prepared in the following manner:

b) 223 g of 50.3% potassium hydroxide solution are added dropwise within about 4 hours to the melt of 317 g of 2-methoxy-4-chlorophenol (-chloro-guaiacol) and 384 g of 2,5-dichloro-1-nitrobenzene. The addition is made while stirring well at 115—120°, and water and slight amounts of organic substances are distilled off through a sloping condenser. The temperature is then kept at 145—150° for 12 hours. After cooling, the reaction mixture is poured into a mixture of 3000 ml of water and 140 ml of 30% sodium hydroxide solution, the reaction product is taken up on ether, the ether solution is washed neutral and concentrated, finally, in vacuo. 2-Methoxy-2'-nitro-4,4'-dichlorodiphenyl ether remains as an oil and is further reacted in this state.

c) 400 g of iron powder, 1000 ml of water and 20 ml of 80% acetic acid are boiled for 15



Formula



Trichlorodiphenyl

4

dichlorodiphenyl



(4-chloro-guaiacol)



minutes while stirring well. The crude 2-methoxy-2'-nitro-4,4'-dichlorodiphenyl ether is then added within about 2 hours through a heated dropping funnel and the reduction is completed by refluxing the reaction mixture for 12 hours. The mass is made alkaline with sodium carbonate. 1000 ml of chlorobenzene are added and it is again boiled. The hot mixture is filtered through animal charcoal to remove iron slurry, the filtrate is made acid to congo paper with hydrochloric acid and the chlorobenzene is distilled off with steam. The residue is neutralised with sodium hydroxide solution and, after it has solidified, the 2-methoxy-2'-amino-4,4'-dichlorodiphenyl ether is milled with water, again filtered off, washed neutral and dried. This crude product, which melts at 73—76°, is used without further purification in the next step of the reaction.

d) 426 g of finely milled 2-methoxy-2'-amino-4,4'-dichloro-diphenyl ether are added to a mixture of 1500 ml of hydrobromic acid (48%) and 500 ml of acetic acid and the whole is boiled for 48 hours. After cooling, the reaction mixture is buffered with sodium hydroxide solution until it just turns congo paper violet, and then it is made neutral to congo paper with sodium acetate. The mixture is filtered, the residue is washed neutral and dissolved in 250 ml of 30% sodium hydroxide solution and 2000 ml of water, the solution is filtered and the reaction product is precipitated by the addition of hydrochloric acid until the reaction is congo violet, filtered off, washed neutral and dried. After recrystallisation from ligroin with the addition of animal charcoal, the 2-hydroxy-2'-amino-4,4'-dichlorodiphenyl ether melts at 126—128°.

EXAMPLE 3

a) 243 g of aluminium chloride are added to a solution of 187.5 g of 2-methoxy-4,2',4'-trichlorodiphenyl ether in 800 ml of benzene and the reaction mixture is boiled for 30 minutes while stirring. After cooling, it is poured into a mixture of ice and hydrochloric acid, the benzene phase is separated and thoroughly shaken with water and sodium hydroxide solution. The mimosa alkaline aqueous phase is separated, the last traces of benzene are removed by bubbling steam through, then filtered and acidified with hydrochloric acid. The 2-hydroxy-4,2',4'-trichlorodiphenyl ether which precipitates is at first smeary but it solidifies after some time. It is filtered off, washed and dried. After recrystallisation from petroleum ether it melts at 60—61°.

2-Hydroxy-4,4'-dichlorodiphenyl ether (M.P. 78—79°) (compare example 1) is obtained in an analogous manner from 2-methoxy-4,4'-dichlorodiphenyl ether.

The starting materials, 2-methoxy-4,2',4'-trichlorodiphenyl ether, and 2-methoxy-4,4'-

dichlorodiphenyl ether, are prepared in the following manner:

b) In a three-necked flask fitted with a stirrer and sloping condenser, 475 g of 4-chloro-2-methoxyphenol (4-chloroguaiacol) and 578 g of 3,4-dichloro-1-nitrobenzene are melted in 400 ml of diethylene glycol dimethyl ether and, at about 120°, 342 g of 49.6% potassium hydroxide solution are added dropwise within about 4 hours. The inner temperature is then kept at 140—150° for 12 hours whereupon water and slight amounts of organic substances are distilled off, some even at the beginning of the dropwise addition of the potassium hydroxide solution. The reaction mixture is poured into a mixture of water and sodium hydroxide solution, the precipitate is filtered off, dried and recrystallised from benzene. The 2-methoxy-4,2'-dichloro-4'-nitrodiphenyl ether obtained melts at 159—161°.

c) 623 g of 2-methoxy-4,2'-dichloro-4'-nitrodiphenyl ether in 400 ml of dioxan are catalytically hydrogenated in the presence of 250 g of Raney nickel at room temperature and normal pressure. After the calculated amount of hydrogen has been taken up, the Raney nickel is filtered off and the 2-methoxy-4,2'-dichloro-4'-aminodiphenyl ether is precipitated with water, filtered off, washed and dried. M.P. 100—102°.

d) 204 g of well milled 2-methoxy-4,2'-dichloro-4'-aminodiphenyl ether are added at room temperature while stirring well to a mixture of 254 ml of concentrated hydrochloric acid and 1600 ml of water. The suspension obtained is cooled to 0—5° and at this temperature, 225 g of 33% sodium nitrite solution are added under the surface of the liquid. The mixture is stirred for 12 hours at 0—5°.

A solution of 86 g of sodium sulphite and 60 g of sodium hydroxide in 640 ml of water are poured at 80° into a solution of 400 g of crystallised copper sulphate and 466 g of sodium chloride in 1280 ml of water. The cuprous chloride formed is allowed to settle, the water on top of it is poured off and the precipitate is purified by decanting three times with water.

The residue is dissolved in 640 ml of concentrated hydrochloric acid, heated to 65—70° and the diazo suspension obtained according to the first paragraph of c) is added while stirring. After cooling, the aqueous phase is poured off, the resinous organic phase is taken up in ether, the ether solution is extracted with sodium hydroxide solution, washed neutral, dried over sodium sulphate and concentrated. The residue is distilled under water jet vacuum. The 2-methoxy-4,2',4'-trichlorodiphenyl ether obtained boils at 210—217°.

If, instead of 2-methoxy-4,2'-dichloro-4'-aminodiphenyl ether, the 2-methoxy-4,4'-dichloro-2'-aminodiphenyl ether produced according to example 2 steps a) and b) is diazotised in the same way and the diazo sus-

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100

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115

120

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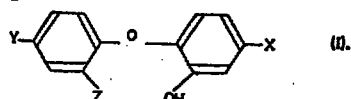
Product It

pension formed is stirred with 10,000 ml of boiling ethyl alcohol and 28 g of copper powder until no more diazo compound can be traced (about 10 minutes), then after filtration and removal of excess alcohol, 2-methoxy-4,4'-dichlorodiphenyl ether is obtained. B.P.¹² 197—203°.

e) If, in step b), instead of 4-chloro-2-methoxyphenol, 4-bromo-2-methoxyphenol is used and otherwise the procedure given in steps a)—d) is followed, then 2-hydroxy-4-bromo-2',4'-dichlorodiphenyl ether is obtained as end product—it boils at 223—229° under 12 Torr.

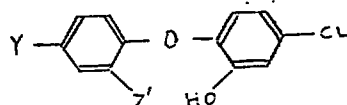
WHAT WE CLAIM IS:—

1. Compounds of the formula I



wherein X and Y independently of each other represent chlorine or bromine, and Z represents hydrogen, chlorine or bromine.

2. Compounds of the formula

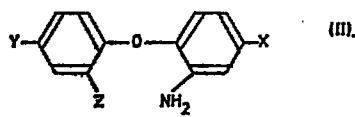


wherein Y represents chlorine or bromine and Z' represents hydrogen or chlorine.

3. 2 - Hydroxy - 4,4' - dichloro - diphenyl-ether.
4. 2 - Hydroxy - 4,2',4' - trichloro-diphenyl-ether.
5. 2 - Hydroxy - 4,4' - dibromo - diphenyl-ether.
6. 2 - Hydroxy - 4,2',4' - tribromo - diphenyl ether.

7. Compounds of the formula I defined in claim 1, substantially as herein described with reference to and as illustrated in any of the foregoing examples.

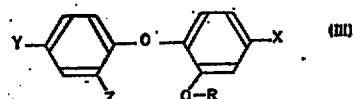
8. A process for the production of a compound of the general formula I as defined in claim 1 which comprises converting into a diazonium salt, a compound of the general formula II



wherein X, Y and Z have the meanings given above into a diazonium salt and boiling this diazonium salt in water, an aqueous acid or 50—80% sulphuric acid or in a higher boiling

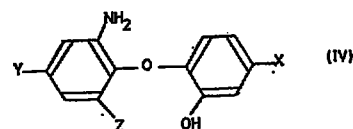
inert organic solvent, in which the diazonium salt is soluble until the evolution of nitrogen ceases.

9. A process for the production of a compound of the general formula I as defined in claim 1, which comprises dealkylating by methods known for the cleavage of aryl-alkyl ethers an o-alkoxydiphenyl ether of the general formula III—



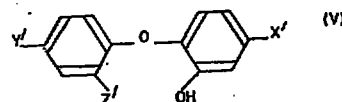
wherein R is low alkyl, and X, Y and Z have the meanings given in claim 1.

10. Modifications of the process according to claim 8 characterised by converting into a diazonium salt a compound of the general formula IV



wherein X, Y and Z have the meanings given in claim 1 and boiling this diazonium salt in a low alkanol or dilute hypophosphoric acid until the evolution of nitrogen ceases.

11. Modification of the process according to claim 8 characterised by converting into a diazonium salt a compound of the general formula V



wherein one or two of the symbols X', Y' and Z' represent the amino group and the remainder has/have the meaning(s) given in claim 1 for X, Y or Z, and converting this diazonium salt in the known way in aqueous medium with cuprous chloride or cuprous bromide until the evolution of nitrogen ceases.

12. A process as claimed in any of claims 8 to 11 substantially as herein described with reference to and as illustrated in any of the foregoing examples.

13. A pharmaceutical composition comprising as active agent a compound of the formula I defined in claim 1, together with a pharmaceutical carrier.

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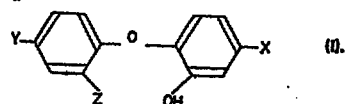
Product It

pension formed is stirred with 10,000 ml of boiling ethyl alcohol and 28 g of copper powder until no more diazo compound can be traced (about 10 minutes), then after filtration and removal of excess alcohol, 2-methoxy-4,4'-dichlorodiphenyl ether is obtained. B.P.₁₂ 197—203°.

e) If, in step b), instead of 4-chloro-2-methoxyphenol, 4-bromo-2-methoxyphenol is used and otherwise the procedure given in steps a)—d) is followed, then 2-hydroxy-4-bromo-2',4'-dichlorodiphenyl ether is obtained as end product—it boils at 223—229° under 12 Torr.

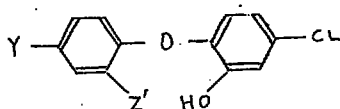
WHAT WE CLAIM IS:—

1. Compounds of the formula I



wherein X and Y independently of each other represent chlorine or bromine, and Z represents hydrogen, chlorine or bromine.

2. Compounds of the formula



wherein Y represents chlorine or bromine and Z' represents hydrogen or chlorine.

3. 2-Hydroxy-4,4'-dichloro-diphenyl ether.

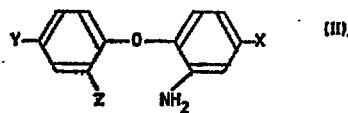
4. 2-Hydroxy-4,2',4'-trichloro-diphenyl ether.

5. 2-Hydroxy-4,4'-dibromo-diphenyl ether.

6. 2-Hydroxy-4,2',4'-tribromo-diphenyl ether.

7. Compounds of the formula I defined in claim 1, substantially as herein described with reference to and as illustrated in any of the foregoing examples.

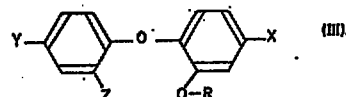
8. A process for the production of a compound of the general formula I as defined in claim 1 which comprises converting into a diazonium salt, a compound of the general formula II



wherein X, Y and Z have the meanings given above into a diazonium salt and boiling this diazonium salt in water, an aqueous acid or 50—80% sulphuric acid or in a higher boiling

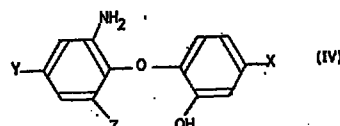
inert organic solvent, in which the diazonium salt is soluble until the evolution of nitrogen ceases.

9. A process for the production of a compound of the general formula I as defined in claim 1, which comprises dealkylating by methods known for the cleavage of aryl-alkyl ethers an o-alkoxydiphenyl ether of the general formula III



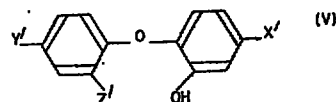
wherein R is low alkyl, and X, Y and Z have the meanings given in claim 1.

10. Modifications of the process according to claim 8 characterised by converting into a diazonium salt a compound of the general formula IV



wherein X, Y and Z have the meanings given in claim 1 and boiling this diazonium salt in a low alkanol or dilute hypophosphoric acid until the evolution of nitrogen ceases.

11. Modification of the process according to claim 8 characterised by converting into a diazonium salt a compound of the general formula V



wherein one or two of the symbols X', Y' and Z' represent the amino group and the remainder has/have the meaning(s) given in claim 1 for X, Y or Z, and converting this diazonium salt in the known way in aqueous medium with cuprous chloride or cuprous bromide until the evolution of nitrogen ceases.

12. A process as claimed in any of claims 8 to 11 substantially as herein described with reference to and as illustrated in any of the foregoing examples.

13. A pharmaceutical composition comprising as active agent a compound of the formula I defined in claim 1, together with a pharmaceutical carrier.

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