

PATENT SPECIFICATION

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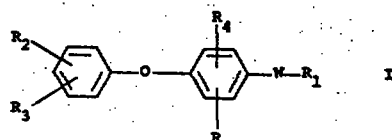


(54) DIPHENYL ETHERS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, CH-4002 Basle, Switzerland, a Swiss Body Corporate, 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:—

This invention relates to phenoxyphenyl derivatives.

More particularly, the invention relates to compounds of formula I,



in which

W signifies $>C=O$ or $>CHOH$,

R and R₁, which may be same or different, each signifies hydrogen, alkyl of 1 to 4 carbon atoms, fluorine or chlorine,

R₂ signifies branched alkyl of 3 to 5 carbon atoms, and

R₃ and R₄, which may be the same or different, each signifies hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, fluorine or chlorine.

The compound 4 - phenoxy - pivalophenone has been previously disclosed in the literature by D. S. Tarbell *et al.*, J.A.C.S. 65, 2169—74 (1943). The compound α - tert. - butyl-*p* - phenoxy - benzyl alcohol has been also previously described by B. W. Farnum *et al.*, Proc. N. Dak. Acad. Sci. 20, 78—81 (1966). The compound 4 - phenoxyphenyl isopropyl ketone has been described by Buu Hoi *et al.*, J.C.S. 1954, 1034—38. In addition, the compound 4' - methoxy - 4 - phenoxyisovalerophenone has been described by Petit and Buu-Hoi, J. Org. Chem. 26, 3834 (1961). Furthermore, the compound 4 - phenoxyphenyl isopentyl ketone has been described by Tomita

and Watanabe, J. Pharm. Soc. Japan 71, 1198—1203 (1951). To our knowledge, no pharmacological activity has heretofore been associated with any of these compounds.

The present invention is based on the discovery that the compounds of formula I possess pharmacological activity. In particular, they are indicated for use as hypolipidemic agents, in particular, hypolipoproteinemia agents as indicated, for example, by lowering cholesterol and triglyceride blood serum levels in tests on a group of white rats which are given typically 30—250 milligrams per kilogram of body weight *per diem* of the compound orally, for 6 days, followed by extraction, with isopropanol, of serum or plasma after anaesthetizing the rats with sodium hexobarbital, and then noting the cholesterol and triglyceride contents as compared to those of a control group. The cholesterol and triglyceride contents are determined by the methods of Lofland, Anal. Biochem, 9, 393, (1964) and G. Kessler and H. Lederer, Technicon Symposium, Mediad Inc., New York, pages 345—347, (1965), respectively.

As stated, the compounds of formula I are therefore indicated for use as hypolipidemic agents and, in particular, as hypolipoproteinemia agents. An indicated suitable daily dosage is from 200 to 3,000 mg, suitably administered in divided dosages of from 50 to 1,500 mg two to four times daily, or in retard form.

According to the present invention, there is provided a pharmaceutical composition comprising a compound of formula I, stated above, in association with a pharmaceutically acceptable diluent or carrier.

The invention also provides a process for the production of such pharmaceutical compositions, which comprises working up a compound of formula I, stated above, in a state of purity sufficient for pharmaceutical acceptability, with a pharmaceutically acceptable diluent or carrier.

In the compositions of the invention, preferably the quantity of the compound of formula I in relation to the quantity of the composition as a whole is such that a unit dosage of the composition contains from 50 to 1,500 mg of the compound of formula I.

As used herein, the term "unit dosage" refers both to solid and liquid dosage forms and means generally that quantity of the composition in the final dosage form in question (i.e. the compositions as administered), which is appropriate for administration of the required dosage of active ingredient.

The compositions of the invention may already be in the final form ready for administration, for example, in the form of integral solid dosage forms, such as tablets and capsules. Alternatively, the compositions may be in liquid dosage forms, such as syrups, elixirs, suspensions and solutions or in the form of a liquid suitable for parenteral use, such as a solution, suspension, dispersion or emulsion, e.g. a sterile injectable liquid such as an aqueous suspension or solution. In the case of integral, solid dosage forms, the term "unit dosage" simply means the weight of one such form and this, of course, may vary depending, for example, on the form in question. Liquid final dosage forms contain the active ingredient in such a concentration that a "unit dosage" of the liquid form, e.g. a teaspoonful, contains the required dosage of active ingredient. Again, the concentration may vary within fairly wide limits.

Although it is, as indicated, difficult to generalise, integral solid final dosage forms may suitably have a total weight of from 60 mg to 2,000 mg, preferably from 100 to 1,000 mg, while liquid final dosage forms may suitably contain from 0.5 to 90%, preferably from 3 to 50%, by weight of the active ingredient.

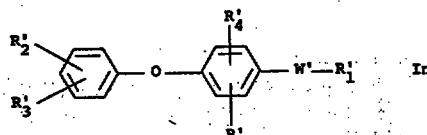
The compositions of the invention may also be in a form requiring further working up to obtain the final dosage form. They may thus, for example, be in the form of dispersible powders, granules or liquid concentrates. In this case, an appropriate quantity of the composition, for example a teaspoonful, is generally dissolved or dispersed in or diluted with an appropriate quantity of water, for example, a glass thereof, to obtain a "unit dosage" of the final dosage form. The concentration of active ingredient in that "unit dosage" will then suitably fall within the preferred concentrations given above for the liquid final dosage form of the compositions of the invention.

The compositions of the invention may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more conventional adjuvants, such as sweetening agents, flavouring agents,

colouring agents and preserving agents, in order to provide an elegant and palatable preparation. Tablets may contain the active ingredient in admixture with conventional pharmaceutical excipients, e.g. inert diluents such as calcium phosphate, calcium sulphate dihydrate, lactose and talc, granulating and disintegrating agents, e.g. starch and alginic acid, binding agents, e.g. starch, gelatin, polyvinyl pyrrolidone and acacia, and lubricating agents, e.g. magnesium stearate, stearic acid and talc. The tablets may be uncoated or coated by known techniques to delay disintegration and adsorption in the gastro-intestinal tracts and thereby provide a sustained action over a longer period. Similarly, suspensions, syrups and elixirs may contain the active ingredient in admixture with any of the conventional excipients utilized for the preparation of such compositions, e.g. suspending agents (methylcellulose, tragacanth and sodium alginate), wetting agents (lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan monooleate) and preservatives (ethyl p-hydroxybenzoate). Capsules may contain the active ingredient alone or admixed with an inert liquid or solid diluent, e.g. calcium carbonate, calcium phosphate, kaolin, peanut oil, sesame oil and corn oil.

The preferred compounds of formula I are those in which R_1 , R_2 , R_3 and R_4 are hydrogen, and those in which R_1 is tert-butyl, the most preferred compound being 4-phenoxypivalophenone.

The invention further provides the novel compounds of formula In,



in which R' , R'_1 , R'_2 , R'_3 , R'_4 and W' have the same significance as R , R_1 , R_2 , R_3 , R_4 and W defined above, provided that

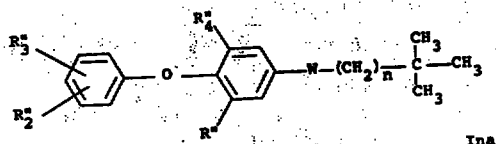
(i) when R' , R'_2 , R'_3 and R'_4 each signifies hydrogen, then R'_1 signifies other than $-C(CH_3)_3$,

(ii) when R'_1 , R'_2 , R'_3 and R'_4 each signifies hydrogen and W' signifies $>C=O$, then R'_1 signifies other than $-CH(CH_3)_2$ or $-(CH_2)_2CH(CH_3)_2$, and

(iii) when one of R'_1 and R'_3 signifies CH_2O- in the 4-position and the other signifies hydrogen, R' and R'_4 each signifies hydrogen and W' signifies $>C=O$, then R'_1 signifies other than $-CH_2CH(CH_3)_2$.

The preferred compounds of formula In are those in which R' , R'_2 , R'_3 and R'_4 are hydrogen and in those in which R'_1 is tert-butyl.

Further representative compounds of formula In are those of formula Ina,



Ina

in which

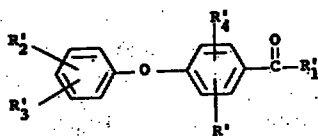
W is as defined above,

n signifies 0 or 1,

5 R'' and R''_4 , which may be the same or different, each signifies hydrogen, chlorine or alkyl of 1 to 4 carbon atoms, and

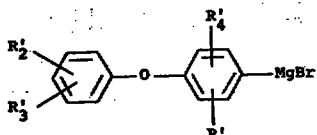
10 R''_2 and R''_3 , which may be the same or different, each signifies hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, fluorine or chlorine, provided that at least one of R'' , R''_2 , R''_3 , and R''_4 signifies other than hydrogen.

15 The invention also provides processes for the production of compounds of formula In, characterised by a) producing a compound of formula Inb,



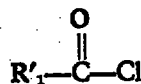
Inb

20 in which R' , R'_1 , R'_2 , R'_3 , and R'_4 are as defined above, by hydrolysing the product of the reaction between a compound of formula II,



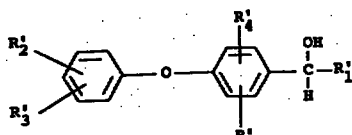
II

25 in which R' , R'_2 , R'_3 , and R'_4 are as defined above, and a compound of formula III,



III

in which R'_1 is as defined above, or (b) producing a compound of formula Inc,



Inc

30 in which R' , R'_1 , R'_2 , R'_3 , and R'_4 are as defined above, by reducing the carbonyl group of a compound of formula Inb, stated above, in the presence of an inert organic solvent.

35 In process a) the hydrolysis may be effected under alkaline, neutral or acid conditions, preferably mild acidic conditions, suitably using hydrochloric or sulphuric acid, preferably hydrochloric acid. The hydrolysis

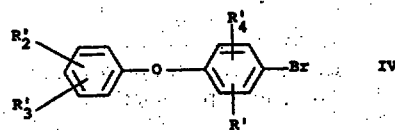
may be carried out conveniently at a temperature of from -40 to $+100^\circ\text{C}$, or higher where desirable, preferably at a temperature of from $+10$ to $+30^\circ\text{C}$.

The product employed as starting material in process a) may be produced by reacting compounds II and III under Grignard conditions, e.g. at a temperature of from 0 to 100°C , in the presence of an inert organic solvent of conventional type, including cyclic or acyclic ethers, such as diethyl ether and tetrahydrofuran.

Process b) may be effected in known manner, suitably at a temperature of from 0° to 100°C , and conveniently employing a reducing agent of known type, such as sodium borohydride, lithium aluminium hydride or diborane, preferably sodium borohydride. Suitable inert organic solvents include ethanol, isopropanol, diethyl ether and tetrahydrofuran.

The resulting compounds of formula I may be isolated and purified by conventional techniques.

The compounds of formula II, employed as starting materials in the preparation of the compounds of formula Inb, may be prepared by reacting a compound of formula IV,



IV

in which R' , R'_2 , R'_3 , R'_4 are as defined above, with magnesium.

The reaction may be carried out in a manner conventional for the preparation of a Grignard reagent from the corresponding bromo compound.

The resulting compounds of formula II may be isolated and purified by conventional techniques, but are suitably used directly to produce compounds Inb, without isolation.

The compounds of formulae III and IV are either known or may be produced in conventional manner from available materials.

The known compounds of formula I may also be prepared by the methods given above for the production of the compounds of formula In.

The following Examples illustrate the invention.

EXAMPLE 1.

Tablets

Tablets suitable for oral administration which contain the following ingredients may be prepared by conventional tableting techniques. Such tablets are indicated for use in treating lipidemia, particularly hypolipoproteinemia, at a dosage of one tablet two to four times a day.

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	<u>Ingredient</u>	<u>Weight (m.g.)</u>	<u>Dry Filled Capsules</u>	
			<u>Ingredients</u>	<u>Weight (mg)</u>
5	Compound of formula I, e.g. 4-phenoxy-pivalophenone	50	Compound of formula I, e.g. 4-phenoxy-pivalophenone	100
	Tragacanth	10	Inert solid diluent	25
	Lactose	197.5	(starch, lactose, kaolin)	200
	Corn Starch	25		
	Talcum	15		
	Magnesium stearate	2.5		

EXAMPLE 2.

- 10 Capsules suitable for oral administration which contain the following ingredients are prepared in conventional manner. Such capsules are indicated for use in treating lipidemia, particularly hypolipoproteinemia, at a dosage of one capsule 2 to 4 four times per day.

	<u>Liquid Filled Capsules</u>	<u>Weight (mg)</u>
20	Compound of formula I, e.g. 4-phenoxy-pivalophenone	100
	Peanut or sesame oil	120

EXAMPLE 3.
Sterile Suspension for Injection and Oral Liquid Suspension

The following pharmaceutical compositions are formulated with the indicated amount of active agent using conventional techniques. The injectable suspension and the oral liquid suspension represent formulations indicated for use as unit doses in the treatment of lipidemia, particularly hypolipoproteinemia. The injectable suspension is indicated as suitable for administration once or twice a day whereas the oral liquid suspension is indicated as suitable for administration 2 to 4 times per day.

<u>Ingredients</u>	<u>Weight (mg)</u>	
	<u>sterile injectable suspension</u>	<u>oral liquid suspension</u>
Compound of formula I, e.g. 4-phenoxy-pivalophenone	200	100
Sodium carboxymethyl- cellulose U.S.P.	1.25	12.5
Methylcellulose	0.4	—
Poly vinylpyrrolidone	5	—
Lecithin	3	—
Benzyl alcohol	0.01	—
Magnesium aluminium silicate	—	47.5
Flavour	—	q.s.
Colour	—	q.s.
Methyl paraben U.S.P.	—	4.5
Propyl paraben U.S.P.	—	1.0
Polysorbate 80 (e.g. Tween 80) U.S.P. (Reg. Trade Mark)	—	5
Sorbitol solution 70% U.S.P.	—	2,500
Buffer agent to adjust pH for desired stability	q.s.	q.s.
Water	for injection, q.s. to 1 ml.	q.s. to 5 ml

EXAMPLE 4.

4-Phenoxy-pivalophenone [process a)]

To a flask containing 33.6 g of magnesium and crystals of iodine, is added 50—70 ml of a solution of 300 g of (*p*-bromophenyl)phenyl ether in 500 ml of tetrahydrofuran. The remainder of the solution is added as needed to maintain a gentle reflux and the resulting mixture heated to reflux for 30 minutes. The resulting mixture is then added to a solution of trimethylacetyl chloride in 500 ml of tetrahydrofuran at a rate to maintain 40—50°C. The resulting mixture is then stirred at ambient temperature for one hour and then 200 ml of 2N hydrochloric acid is added. The organic layer is washed twice with one litre of 2N sodium carbonate solution, dried and evaporated *in vacuo* to a liquid weighing about 290 g. This liquid is distilled under reduced pressure to obtain 4 - phenoxy - pivalophenone, b.p. 136—139°C at 0.1 mm/Hg. This product may also be named 2,2 - dimethyl-4' - phenoxy - propiophenone.

EXAMPLE 5 [process a)]

In manner analogous to Example 4, but employing appropriate starting materials in approximately equivalent amounts, the following compounds are obtained:

- A) 4 - (*m* - chlorophenoxy) - pivalophenone,
- B) 4 - (*p* - methoxyphenoxy) - 3,5 - dichloropivalophenone, m.p. 63—65°C,
- C) 4 - (*p* - methoxyphenoxy) - 3 - chloropivalophenone, m.p. 59—60°C,
- D) 4 - (*p* - methoxyphenoxy) - pivalophenone, m.p. 78—81°C,
- E) 4 - phenoxy - 3 - methyl - pivalophenone,
- F) 4 - (*p* - methylphenoxy) - pivalophenone,
- G) 4 - (3' - chloro - 4' - methoxyphenoxy) - 3,5 - dichloropivalophenone, m.p. 76—79°C,
- H) 4 - (3',5' - di - *t* - butylphenoxy) - pivalophenone, m.p. 70—85°C,
- I) 4 - (*p* - chlorophenoxy) - pivalophenone, m.p. 60—62°C,
- J) 4 - phenoxy - 3,5 - dichloro - pivalophenone,
- K) 4 - (*p* - fluorophenoxy) - pivalophenone,
- L) 4 - phenoxyphenyl isopropyl ketone, b.p. 130—135°C at 0.2 mm/Hg,
- M) 4 - phenoxyphenyl isopentyl ketone,
- N) 4' - methoxy - 4 - phenoxyisovalerophenone, and
- O) 4 - phenoxyphenyl neopentyl ketone, m.p. 32—34°C.

EXAMPLE 6.

α - tert. - Butyl - *p* - phenoxy - benzyl alcohol [process b)]

To a solution of 25.4 g of 4 - phenoxy-pivalophenone in 250 ml of isopropanol is added 5.0 g of sodium borohydride. The re-

sulting mixture is stirred at ambient temperature for 2 hours, evaporated *in vacuo* and the residue extracted with water and with ether. The organic phase is evaporated *in vacuo* to a clear oil which crystallizes on standing to yield *α* - tert. - butyl - *p* - phenoxy - benzyl alcohol, m.p. 79—80°C.

EXAMPLE 7 [process b)]

In manner analogous to Example 6, but employing appropriate starting materials in approximately equivalent amounts, the following compounds are obtained:

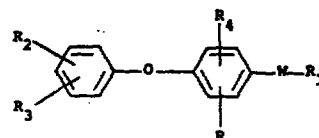
- A) *α* - isopropyl - *p* - phenoxy - benzyl alcohol,
- B) *α* - tert. - butyl - *p* - (*p* - methoxyphenoxy) benzyl alcohol, m.p. 44°—46°C,
- C) *α* - tert. - butyl - *p* - (*m* - chlorophenoxy) benzyl alcohol,
- D) *α* - tert. - butyl - *p* - phenoxy - *m,m* - dichloro - benzyl alcohol,
- E) *α* - tert. - butyl - *p* - (*p* - chlorophenoxy) benzyl alcohol, m.p. 64°—67°C,
- F) *α* - tert. - butyl - *p* - (3',5' - di - tert. - butylphenoxy) benzyl alcohol, m.p. 104°—106°C,
- G) *α* - tert. - butyl - *p* - (*p* - methylphenoxy) benzyl alcohol, m.p. 58°—61°C,
- H) *α* - tert. - butyl - *p* - (*p* - fluorophenoxy) benzyl alcohol, m.p. 55°—59°C,
- I) *α* - tert. - butyl - *m,m* - dichloro - *p* - (*p* - methoxyphenoxy) benzyl alcohol,
- J) *α* - tert. - butyl - *m* - chloro - *p* - (*p* - methoxyphenoxy) benzyl alcohol,
- K) *α* - tert. - butyl - *m* - methyl - *p* - phenoxy - benzyl alcohol,
- L) *α* - tert. - butyl - *m,m* - dichloro - *p* - (*m* - chloro - *p* - methoxyphenoxy) benzyl alcohol,
- M) *α* - isopentyl - *p* - phenoxy - benzyl alcohol,
- N) *α* - isobutyl - *p* - (*p* - methoxyphenoxy) benzyl alcohol, and
- O) *α* - 2,2 - dimethylpropyl - *p* - phenoxy - benzyl alcohol.

EXAMPLE 8.

The compositions in Examples 1, 2 and 3 may be reformulated using, in place of 4-phenoxy - pivalophenone, any one of the compounds of Examples 5, 6 and 7.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of formula I,



in which

W signifies >C=O or >CHOH,



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EXAMPLE 4.

4-Phenoxy-pivalophenone [process a)]

To a flask containing 33.6 g of magnesium and crystals of iodine, is added 50—70 ml of a solution of 300 g of (*p*-bromophenyl)phenyl ether in 500 ml of tetrahydrofuran. The remainder of the solution is added as needed to maintain a gentle reflux and the resulting mixture heated to reflux for 30 minutes. The resulting mixture is then added to a solution of trimethylacetyl chloride in 500 ml of tetrahydrofuran at a rate to maintain 40—50°C. The resulting mixture is then stirred at ambient temperature for one hour and then 200 ml of 2N hydrochloric acid is added. The organic layer is washed twice with one litre of 2N sodium carbonate solution, dried and evaporated *in vacuo* to a liquid weighing about 290 g. This liquid is distilled under reduced pressure to obtain 4 - phenoxy - pivalophenone, b.p. 136—139°C at 0.1 mm/Hg. This product may also be named 2,2 - dimethyl-4' - phenoxy - propiophenone.

EXAMPLE 5 [process a)]

In manner analogous to Example 4, but employing appropriate starting materials in approximately equivalent amounts, the following compounds are obtained:

- A) 4 - (*m* - chlorophenoxy) - pivalophenone,
- B) 4 - (*p* - methoxyphenoxy) - 3,5 - dichloropivalophenone, m.p. 63—65°C,
- C) 4 - (*p* - methoxyphenoxy) - 3 - chloropivalophenone, m.p. 59—60°C,
- D) 4 - (*p* - methoxyphenoxy) - pivalophenone, m.p. 78—81°C,
- E) 4 - phenoxy - 3 - methyl - pivalophenone,
- F) 4 - (*p* - methylphenoxy) - pivalophenone,
- G) 4 - (3' - chloro - 4' - methoxyphenoxy) - 3,5 - dichloropivalophenone, m.p. 76—79°C,
- H) 4 - (3',5' - di - *t* - butylphenoxy) - pivalophenone, m.p. 70—85°C,
- I) 4 - (*p* - chlorophenoxy) - pivalophenone, m.p. 60—62°C,
- J) 4 - phenoxy - 3,5 - dichloro - pivalophenone,
- K) 4 - (*p* - fluorophenoxy) - pivalophenone,
- L) 4 - phenoxyphenyl isopropyl ketone, b.p. 130—135°C at 0.2 mm/Hg,
- M) 4 - phenoxyphenyl isopentyl ketone,
- N) 4' - methoxy - 4 - phenoxyisovalerophenone, and
- O) 4 - phenoxyphenyl neopentyl ketone, m.p. 32—34°C.

EXAMPLE 6.

α - tert. - Butyl - *p* - phenoxy - benzyl alcohol [process b)]

To a solution of 25.4 g of 4 - phenoxy-pivalophenone in 250 ml of isopropanol is added 5.0 g of sodium borohydride. The re-

sulting mixture is stirred at ambient temperature for 2 hours, evaporated *in vacuo* and the residue extracted with water and with ether. The organic phase is evaporated *in vacuo* to a clear oil which crystallizes on standing to yield α - tert. - butyl - *p* - phenoxy - benzyl alcohol, m.p. 79—80°C.

EXAMPLE 7 [process b)]

In manner analogous to Example 6, but employing appropriate starting materials in approximately equivalent amounts, the following compounds are obtained:

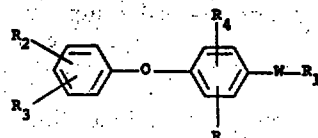
- A) α - isopropyl - *p* - phenoxy - benzyl alcohol,
- B) α - tert. - butyl - *p* - (*p* - methoxyphenoxy) benzyl alcohol, m.p. 44°—46°C,
- C) α - tert. - butyl - *p* - (*m* - chlorophenoxy) benzyl alcohol,
- D) α - tert. - butyl - *p* - phenoxy - *m,m* - dichloro - benzyl alcohol,
- E) α - tert. - butyl - *p* - (*p* - chlorophenoxy) benzyl alcohol, m.p. 64°—67°C,
- F) α - tert. - butyl - *p* - (3',5' - di - tert-butylphenoxy) benzyl alcohol, m.p. 104°—106°C,
- G) α - tert. - butyl - *p* - (*p* - methylphenoxy) benzyl alcohol, m.p. 58°—61°C,
- H) α - tert. - butyl - *p* - (*p* - fluorophenoxy) benzyl alcohol, m.p. 55°—59°C,
- I) α - tert. - butyl - *m,m* - dichloro - *p* - (*p* - methoxyphenoxy) benzyl alcohol,
- J) α - tert. - butyl - *m* - chloro - *p* - (*p* - methoxyphenoxy) benzyl alcohol,
- K) α - tert. - butyl - *m* - methyl - *p* - phenoxy - benzyl alcohol,
- L) α - tert. - butyl - *m,m* - dichloro - *p* - (*m* - chloro - *p* - methoxyphenoxy) benzyl alcohol,
- M) α - isopentyl - *p* - phenoxy - benzyl alcohol,
- N) α - isobutyl - *p* - (*p* - methoxyphenoxy) benzyl alcohol, and
- O) α - 2,2 - dimethylpropyl - *p* - phenoxy - benzyl alcohol.

EXAMPLE 8.

The compositions in Examples 1, 2 and 3 may be reformulated using, in place of 4-phenoxy - pivalophenone, any one of the compounds of Examples 5, 6 and 7.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of formula I,



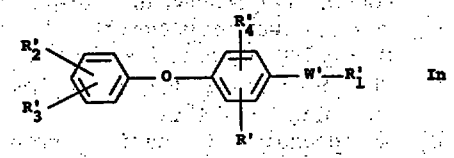
in which
W signifies >C=O or >CHOH,

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- R and R₁, which may be the same or different, each signifies hydrogen, alkyl of 1 to 4 carbon atoms, fluorine or chlorine,
- 5 R₁ signifies branched alkyl of 3 to 5 carbon atoms, and
- 10 R₂ and R₃, which may be the same or different, each signifies hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, fluorine or chlorine, in association with a pharmaceutically acceptable diluent or carrier.
- 15 2. A pharmaceutical composition according to Claim 1, in which the quantity of the compound of formula I in relation to the quantity of the composition as a whole is such that a unit dosage of the composition contains from 50 to 1,500 mg of the compound of formula I.
- 20 3. A pharmaceutical composition according to Claim 1 or 2, in which, in the compound of formula I, R, R₂, R₃ and R₄ each signifies hydrogen.
- 25 4. A pharmaceutical composition according to Claim 1, 2 or 3, in which, in the compound of formula I, R₁ signifies *t*-butyl.
- 30 5. A pharmaceutical composition according to any one of Claims 1 to 4, in which the compound of formula I is 4-phenoxy-pivalophenone.
- 35 6. A pharmaceutical composition according to any one of the preceding claims, in the form of an integral solid final dosage form containing from 50 to 1,500 mg of the compound of formula I per unit dosage.
- 40 7. A pharmaceutical composition according to Claim 6, in which the integral solid final dosage form is a tablet.
- 45 8. A pharmaceutical composition according to Claim 6, in which the integral solid final dosage form is a capsule.
- 50 9. A pharmaceutical composition according to any one of Claims 6 to 8, in which the integral solid final dosage form has a total weight of from 60 to 2,000 mg.
- 55 10. A pharmaceutical composition according to any one of Claims 6 to 8, in which the integral solid final dosage form has a total weight of from 100 to 1,000 mg.
- 60 11. A pharmaceutical composition according to any one of Claims 1 to 5, in the form of a liquid final dosage form, in which the concentration of the compound of formula I is such that a unit dosage of the liquid final dosage form contains from 50 to 1,500 mg of the compound of formula I.
- 65 12. A pharmaceutical composition according to Claim 11, in which the liquid final dosage form is an oral dosage form.
13. A pharmaceutical composition according to Claim 12, in which the oral dosage form is an elixir, syrup, suspension or solution.
14. A pharmaceutical composition according to Claims 6 to 10, 12 or 13, comprising one or more of a sweetening agent, a flavouring agent, a colouring agent and a preserving agent.

15. A pharmaceutical composition according to claim 11, in the form of a sterile injectable solution or suspension.
16. A pharmaceutical composition according to any one of Claims 11 to 15, in which the liquid final dosage form contains from 0.5 to 90% by weight of the compound of formula I.
17. A pharmaceutical composition according to any one of Claims 11 to 16, in which the liquid final dosage form contains from 3 to 50% by weight of the compound of formula I.
18. A pharmaceutical composition according to any one of Claims 1 to 5, in the form of granules, a dispersible powder or a liquid concentrate.
19. A pharmaceutical composition comprising a compound of formula I, stated in Claim 1, in association with a pharmaceutically acceptable diluent or carrier, substantially as herein described with reference to any one of Examples 1 to 3 and 8.
20. A process for the production of a pharmaceutical composition which comprises working up a compound of formula I, stated in Claim 1, in a state of purity sufficient for pharmaceutical acceptability, with a pharmaceutically acceptable diluent or carrier.
21. A pharmaceutical composition whenever produced by a process according to Claim 20.
22. A process for the production of a compound of formula In,



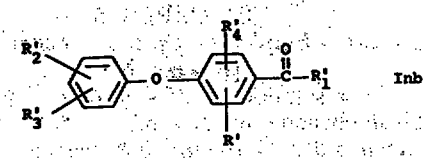
in which R', R'₁, R'₂, R'₃, R'₄ and W' have the same significance as R, R₁, R₂, R₃, R₄ and W defined in Claim 1, provided that

(i) when R', R'₂, R'₃ and R'₄ each signifies hydrogen, then R'₁ signifies other than -C(CH₃)₃,

(ii) when R', R'₂, R'₃ and R'₄ each signifies hydrogen and W' signifies >C=O, then R'₁ signifies other than -CH(CH₃)₂ or -(CH₂)₂CH(CH₃)₂ and

(iii) when one of R'₂ and R'₃ signifies CH₃O- in the 4-position and the other signifies hydrogen, R' and R'₄ each signifies hydrogen and W' signifies >C=O, then R'₁ signifies other than -CH₂CH(CH₃)₂, characterised by

(a) producing a compound of formula Inb,





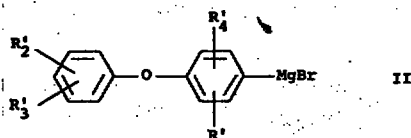
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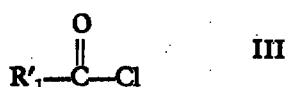
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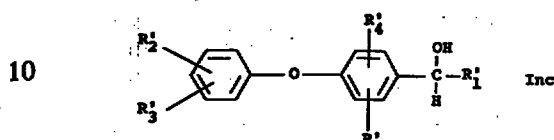
in which R' , R'_2 , R'_3 and R'_4 are as defined above, by hydrolysing the product of the reaction between a compound of formula II,



- 5 in which R' , R'_2 , R'_3 and R'_4 are as defined above, and a compound of formula III,



in which R'_1 is as defined above, or
b) producing a compound of formula Inc,



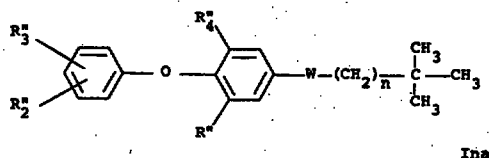
in which R' , R'_1 , R'_2 , R'_3 and R'_4 are as defined above, by reducing the carbonyl group of the compound of formula Inb, stated above, in the presence of an inert organic solvent.

- 15 23. A process for the production of a compound of formula In, stated in Claim 22, substantially as herein described with reference to Examples 5 A) to K) and Example 7.

- 20 24. A compound of formula In, stated in Claim 22, whenever produced by a process according to Claim 22, whenever produced by a process according to Claim 22 or Claim 23.

- 25 25. A compound of formula In, stated in Claim 22.

26. A compound of formula Ina,



in which

- 30 W is as defined in Claim 1,
n signifies 0 or 1,

R'' and R''_4 which may be the same or different, each signifies hydrogen, chlorine or alkyl of 1 to 4 carbon atoms, and

R''_2 and R''_3 which may be the same or different, each signifies hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, fluorine or chlorine, provided that at least one of R'' , R''_2 , R''_3 and R''_4 signifies other than hydrogen.

27. A compound of formula In, stated in Claim 22, in which R' , R'_2 , R'_3 and R'_4 each signifies hydrogen.

28. A compound of formula In, stated in Claim 22, in which R'_1 signifies *t*-butyl.

29. 4 - (*m* - Chlorophenoxy) - pivalophenone.

30. 4 - (*p* - Methoxyphenoxy) - 3,5 - dichloropivalophenone.

31. 4 - (*p* - Methoxyphenoxy) - 3 - chloropivalophenone.

32. 4 - (*p* - Methoxyphenoxy) - pivalophenone.

33. 4 - phenoxy - 3 - methyl - pivalophenone.

34. 4 - (*p* - Methylphenoxy) - pivalophenone.

35. 4 - (3' - Chloro - 4' - methoxyphenoxy) - 3,5 - dichloropivalophenone.

36. 4 - (3',5' - di - *t* - Butylphenoxy) - pivalophenone.

37. 4 - (*p* - Chlorophenoxy) - pivalophenone.

38. 4 - Phenoxy - 3,5 - dichloro - pivalophenone.

39. 4 - (*p* - Fluorophenoxy) - pivalophenone.

40. 4 - Phenoxyphenyl neopentyl ketone.

41. α - Isopropyl - *p* - phenoxy - benzyl alcohol.

42. α - tert. - Butyl - *p* - (*p* - methoxyphenoxy) benzyl alcohol.

43. α - tert. - Butyl - *p* - (*m* - chlorophenoxy) benzyl alcohol.

44. α - tert. - Butyl - *p* - phenoxy - *m,m*-dichloro - benzyl alcohol.

45. α - tert. - Butyl - *p* - (*p* - chlorophenoxy) benzyl alcohol.

46. α - tert. - Butyl - *p* - (3',5' - di - tert. - butylphenoxy) benzyl alcohol.

47. α - tert. - Butyl - *p* - (*p* - methylphenoxy) benzyl alcohol.

48. α - tert. - Butyl - *p* - (*p* - fluorophenoxy) benzyl alcohol.

49. α - tert. - Butyl - *m,m* - dichloro - *p* - (*p* - methoxyphenoxy) benzyl alcohol.

50. α - tert. - Butyl - *m* - chloro - *p* - (*p* - methoxyphenoxy) benzyl alcohol.

51. α - tert. - Butyl - *m* - methyl - *p* - phenoxy - benzyl alcohol.

52. α - tert. - Butyl - *m,m* - dichloro - *p* - (*m* - chloro - *p* - methoxyphenoxy) benzyl alcohol.

53. α - isopentyl - *p* - phenoxy - benzyl alcohol.

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54. α - isobutyl - *p* - (*p* - methoxyphen-
oxy) benzyl alcohol.

55. α - 2,2 - dimethylpropyl - *p* - phenoxy-
benzyl alcohol.

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