

PATENT SPECIFICATION

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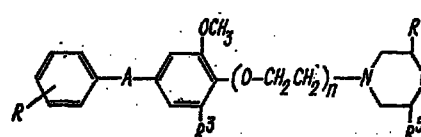
(54) MORPHOLINE DERIVATIVES, THE PREPARATION THEREOF AND COMPOSITIONS CONTAINING THEM

(71) We, CARLO ERBA S.P.A., an Italian Body Corporate of Via Carlo Imbonati 24, Milan, Italy, 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 certain ethers having anti-tussive (anti-cough) activity, to a process for their preparation and to pharmaceutical compositions containing them.

During the last ten years (after the development of more accurate testing processes) many anti-tussive compounds have been synthesized in an attempt to obtain products devoid of the troublesome side effects, especially habituation and influence on the respiratory rhythm, found with natural alkaloids. These drawbacks are present, however, even in compounds derived from natural alkaloids, e.g. the metadone derivatives. Some synthetic anti-tussive compounds are basic esters, which are, however, readily enzymically hydrolysed in the upper part of the intestinal tract, and are thus inactivated. In fact, a number of β - cyano- β,β - diphenyl - propionic acid basic esters, which had proved effective in pharmacological tests by the intravenous route, were found to be ineffective in subsequent clinical tests by the oral route. We have now found that certain aromatic ethers with basic side chains have anti-tussive activity and are not hydrolysed by intestinal enzymes.

The ethers of the invention have the general formula (I)



wherein R is a halogen or hydrogen atom, a trifluoromethyl group, a lower alkyl or alkoxy group, or a substituted or unsubstituted amino group; A is a carbonyl group or a group of formula $-C(R^1)(R^2)-$, wherein R^1 is a hydrogen atom or a lower alkyl, hydroxymethyl or hydroxy group, and R^2 is a hydrogen atom or a lower alkyl group; n is an integer of 1 to 3; R^3 is a hydrogen or halogen atom or a lower alkyl or alkoxy group; and each of R^4 and R^5 , which may be the same or different, is a hydrogen atom or a lower alkyl group. Pharmaceutically acceptable acid addition salts thereof also form part of the invention.

The terms "lower alkyl" and "lower alkoxy", as used herein, refer to those groups having 1 to 4 carbon atoms; the groups can be branched or straight chain.

When R is a substituted amino group, it is suitably a mono- or di-alkylamino group, preferably a dimethylamino group. Other suitable meanings of R are a fluorine, chlorine or bromine atom or methyl group. R is preferably in the 4-position but can, if desired, be in the 2- or 3-position.

R^1 and R^2 are suitably both hydrogen atoms or both ethyl groups or alternatively R^1 is a

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hydroxy group and R^2 is a hydrogen atom or a butyl group.

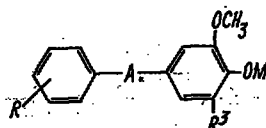
- 5 Preferably, R^3 is a hydrogen atom or a methoxy group, but it can, if desired, be a bromine atom or a methyl group, while R^4 and/or R^5 are suitably methyl groups.

The reduction of the keto group of the benzophenone ethers to an alcoholic group gives products with lower anti-tussive activity, whereas catalytic reduction of the keto group to a methylene group results in products with a high anti-tussive activity and lower toxicity.

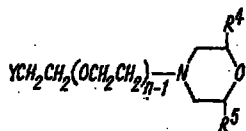
10 Examples of suitable acid addition salts are those with inorganic acids (e.g. hydrochloric, phosphoric and sulphuric acid) and organic acids [e.g. citric acid and *o*-(*p*'-hydroxy-benzoyl)-benzoic acid].

The invention also provides a process for preparing the ethers, the process comprising

- 20 (a) reacting a compound of general formula (II)

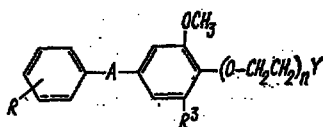


- 25 wherein M is an alkali metal atom, and A, R and R^3 are as defined above, with a compound of general formula (III)

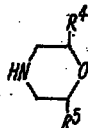


wherein Y is a halogen atom, and n, R^4 and R^5 are as defined above; or

- 30 (b) reacting a compound of general formula (IV)



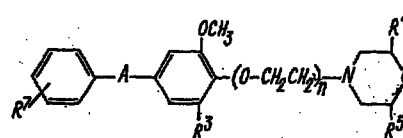
wherein Y is a halogen atom, and n, A, R and R^3 are as defined above, with a compound of general formula (V)



wherein R^4 and R^5 are as defined above; or

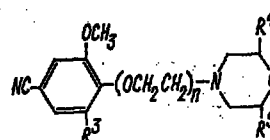
- 40 (c) reducing a compound of general formula (I) wherein A is a carbonyl group, and n, R^3 , R^4 and R^5 are as defined above, to give a compound of general formula (I) wherein A is a group of formula $-C(R^1)(R^2)-$, wherein R^1 is a hydroxy group and R^2 is a hydrogen atom, or wherein both R^1 and R^2 are hydrogen atoms; or

- 45 (d) reducing a compound of general formula (VI)

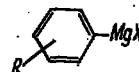


wherein R^7 is a nitro group, and n, A, R^3 , R^4 and R^5 are as defined above, to give a compound of general formula (I) wherein R is an unsubstituted amino group, and then converting in a manner known *per se* the reduction product to a compound of general formula (I) wherein R is a substituted amino group;

(e) reacting a compound of general formula (VII)

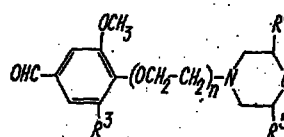


wherein n, R^3 , R^4 and R^5 are as defined above, with a compound of general formula (VIII)



wherein X is a halogen atom and R is as defined above to give a Grignard adduct which is then hydrolysed to give a compound of general formula (I) wherein A is a carbonyl group; or

(f) reacting a compound of general formula (IX)



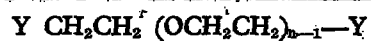
wherein n, R^3 , R^4 and R^5 are as defined above, with a compound of general formula (VIII) to give a Grignard adduct which is then hydrolysed to give a compound of general formula (I) wherein A is $-CHOH-$; or

(g) oxidizing a compound of general formula (I) wherein A is a group of formula $-C(R^1)(R^2)-$, wherein R^1 is a hydroxy group and R^2 is a hydrogen atom, and n, R^3 , R^4 and R^5 are as defined above, to give a compound of general formula (I) wherein A is a carbonyl group;

and, if desired, converting the product of (a) to (g) into a pharmaceutically acceptable acid addition salt by reaction with the appropriate acid.

The expression "in a manner known *per se*", as used herein, refers to those methods in use or described in the literature.

The compound of general formula (IV) can be prepared by reacting a compound of general formula (II) with a compound of general formula (X)



wherein each Y, which may be the same or different, is a halogen atom, and n is as defined above.

5 The ethers were evaluated for anti-tussive activity by determining the lowest dose show-

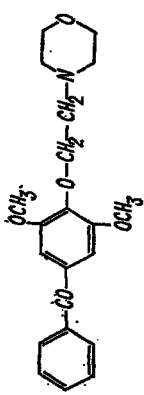
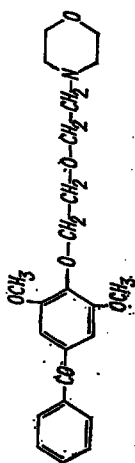
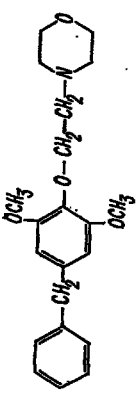
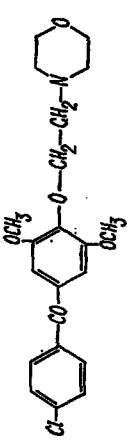
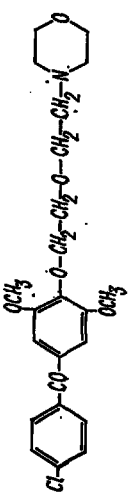
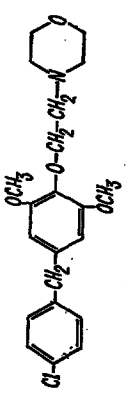
ing total cough inhibition in cats by Domenjoz's method (Arch. Exper. Path. und Pharmacol., 1952., 215, 1924). Solutions of the ethers in distilled water were administered by the intraduodenal route through a previously inserted cannula. The doses reported in the Table refer to the hydrochlorides.

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TABLE

Compound	Toxicity in mouse (mg/kg) by the oral route	Dose (mg/kg by intra-duodenal route) showing total cough inhibition	Duration in minutes of total inhibition
	338	20	40'
	610	35	45'
	550	50	65'
	552	30	
	500	35	60'
	500	50	60'

The ethers are tasteless, which is a particularly advantageous feature from the therapeutic viewpoint.

The invention also provides pharmaceutical compositions comprising a compound of general formula (I) or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

The compositions are preferably in a form suitable for oral administration, for example tablets, capsules, powder packets, liquid solutions, suspensions or elixirs.

The invention is illustrated by the following Examples.

15 EXAMPLE 1

2 G. of 50% sodium hydride in oil, suspended in dimethylformamide (300 ml.), is treated quickly with 3,5-dimethoxy-4-hydroxybenzophenone (10.32 g.) in dimethylformamide (50 ml.), and then heated at 120—130°C for 4 hrs. to give a yellow suspension of the sodium salt of the hydroxybenzophenone. After cooling, β -morpholinoethyl chloride (9 g.) was added and the mixture heated at 120—130°C. for two hours. A precipitate of sodium chloride was filtered off and the solvent was evaporated *in vacuo*. The residue was distilled to give 3,5 - dimethoxy - 4 - (β - morpholinoethoxy)benzophenone, b.p. 230/0.8 mm, the hydrochloride of which was obtained by known methods and melted at 146—148°C. (after crystallisation from tetrahydrofuran/99% ethanol/petroleum ether). The following compounds could be obtained in a similar way: 3,5 - dimethoxy - 2' - methyl - 4 - (β - morpholinoethoxy)benzophenone hydrochloride (m.p. 176—8°C.); 3,5 - dimethoxy - 4' - methyl - 4 - (β - morpholinoethoxy)benzophenone hydrochloride (m.p. 151—3°C.); 3 - methoxy - 5 - methyl - 4 - (β - morpholinoethoxy)benzophenone hydrochloride (m.p. 191—2°C.); and 3 - methoxy - 5 - bromo - 4 - (β - morpholinoethoxy)benzophenone hydrochloride (m.p. 201—3°C.).

EXAMPLE 2

Sodium methoxide (1.2 g.) in dimethylformamide (150 ml.) was treated with 3,5-dimethoxy - 4' - chloro - 4 - hydroxy - benzophenone (6 g.) in dimethylformamide (50 ml.), and was heated for 2 hr. at 120°C., treated with β -morpholinoethyl chloride (3.4 g.), heated for 1 hr. at 140°C., evaporated to dryness, and treated with water to give a solid material. The mixture was filtered, washed and crystallized from cyclohexane to give 3,5 - dimethoxy - 4' - chloro - 4 - (β - morpholinoethoxy) - benzophenone (6.5 g.), m.p. 91—92°C., which was reacted with gaseous hydrogen chloride in alcohol to give, after crystallization from isopropanol, the hydrochloride, m.p. 187—9°C.

The following substances could be prepared in a similar way: 3,5 - dimethoxy - 4' -

fluoro - 4 - (β - morpholinoethoxy)benzophenone hydrochloride (m.p. 163—5°C.); 3,5-dimethoxy - 4' - bromo - 4 - (β - morpholinoethoxy)benzophenone hydrochloride (m.p. 195—7°C.); 3,5 - dimethoxy - 2' - chloro - 4 - (β - morpholinoethoxy)benzophenone hydrochloride; (212—4°C.); 3,5 - dimethoxy - 4 - (β - morpholinoethoxy) - 3' - trifluoromethylbenzophenone (m.p. 105—7°C.).

EXAMPLE 3

3,5 - Dimethoxy - 4 - [β - (β' - chloroethoxy) - ethoxy] - benzophenone (7 g., 215°/0.2 mm; from 3,5 - dimethoxy - 4 - hydroxybenzophenone, sodium salt, and β,β' -dichlorodiethylether in dimethylformamide) in anhydrous ethanol (25 ml.) was treated with morpholine (7 ml.), heated in a Carius apparatus at 120°C. for 8 hr. and then evaporated to dryness. The residue was distributed between water and ether; the ethereal layer was washed with 1% sodium hydroxide. The solvent was removed on a steam bath to give 3,5-dimethoxy - 4 - [β - (β' - morpholinoethoxy)ethoxy]benzophenone, which could be reacted in known manner, to give, after crystallisation from isopropanol the hydrochloride, m.p. 75°C.

EXAMPLE 4

3,5 - Dimethoxy - 4 - [β - [β' - (β'' - chloroethoxy)ethoxy]ethoxy]benzophenone (8.17 g.; b.p. 190—200°C./0.01 mm. from 3,5 - dimethoxy - 4 - hydroxybenzophenone and β - chloro - β' - chloroethoxyethyl - ether), in ethanol (25 ml.) containing morpholine (7 g.), was heated in a Carius tube at 100°C. for two hours, evaporated to dryness and, after dilution with water, extracted with diethylether. The mixture was washed with 0.5% sodium hydroxide, and the residue, after concentration, was distilled under high vacuum to give, as a yellowish oil, 3,5 - dimethoxy - 4 - [β - [β' - (β'' - morpholinoethoxy)ethoxy]ethoxy] - benzophenone, b.p. 235—240°C./0.01 mm.

By a similar process 3,5 - dimethoxy - 4' - chloro - 4 - [β - [β' - (β'' - morpholinoethoxy) - ethoxy] - ethoxy] - benzophenone (b.p. 245—250°C./0.01mm) could be obtained.

EXAMPLE 5

3,5 - Dimethoxy - 4' - dimethylamino - 4 - hydroxybenzophenone (3 g.) in dimethylformamide (30 ml.) was added to 0.5 g. of 50% sodium hydride in oil, suspended in dimethylformamide (200 ml.), and was heated for 2 hr. at 100°C. to give an orange-yellow solution of the sodium salt of the hydroxybenzophenone. β - Morpholinoethyl chloride (2.2 g.) was added, and then the mixture was heated at 140°C. The inorganic salts were filtered off, the mixture was then concentrated *in vacuo*, and then the residue was dissolved in ether and washed repeatedly with 0.5% sodium hydroxide. Removal of the ether gave 3,5-

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dimethoxy - 4' - dimethylamino - 4 - (β -morpholinoethoxy) - benzophenone dihydrochloride (m.p. 254—6°C.).

- 5 The same compound can be obtained by reducing and then methylating 3,5 - dimethoxy - 4 - (β - morpholinoethoxy) - 4' - nitrobenzophenone.

EXAMPLE 6

- 10 3,5 - Dimethoxy - 4 - [β - (β' - chloroethoxy)ethoxy] - benzophenone (3.65 g.) and 2 - methylmorpholine (2.3 g.) in ethanol (10 ml.) were heated for 8 hrs. in a Carius tube at 120°C. Working-up by known methods gave 3,5 - dimethoxy - 4 - [β - (β' - (2-methylmorpholino)ethoxy)ethoxy] - benzophenone, from which the hydrochloride, m.p. 136—7°C., could be obtained after crystallisation from benzene/petroleum ether.

EXAMPLE 7

- 20 3,5 - Dimethoxy - 4 - hydroxy - diphenylmethane (5.5 g.) in dimethyl-formamide (25 ml.) was added to sodium methoxide (1.25 g.) in dimethyl-formamide (100 ml.) and was kept for 0.5 hr. at 80°C., and then β -morpholinoethyl/chloride (3.4 g.) was added. The mixture was heated for 2 hr. at 100°C. The inorganic salts were filtered off, the solution concentrated *in vacuo* and the residue dissolved in ether and washed with water. The solvent was evaporated and the residue reacted by known methods to give, after crystallisation from ethyl acetate/petroleum ether, 3,5 - dimethoxy - 4 - (β - morpholinoethoxy)-diphenylmethane hydrochloride, m.p. 112—4°C.

- 35 By a similar process, 3,5 - dimethoxy - 4 - (β - morpholinoethoxy) - 4' - chloro - diphenylmethane hydrochloride, m.p. 152—4°C., could be obtained.

EXAMPLE 8

- 40 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy)benzophenone (5.5 g.) in ethanol (100 ml.) was hydrogenated under 2—3 atmospheres pressure in the presence of palladium on charcoal (2 g.) and *N*-hydrochloric acid (15.1 ml.). After filtration and concentration, crystallization of the residue from benzene/petroleum ether gave 3,5 - dimethoxy - 4 - (β - morpholinoethoxy)benzhydrol, hydrochloride, m.p. 121—123°C.

EXAMPLE 9

- 55 4' - Chloro - 3,5 - dimethoxy - 4 - [β - (β' - chloroethoxy)ethoxy] - benzophenone (10 g.) and morpholine (6.5 g.) in absolute ethanol (30 ml.) were heated in a Carius tube at 125°C. for 12 hours. After cooling, the mixture was evaporated to dryness on a steam bath and distributed between 10% hydrochloric acid and ether. The aqueous phase was then basified with concentrated sodium hydroxide and extracted with ether. Evaporation of the solvent gave 4' - chloro - 3,5 - dimethoxy - 4 - [β - (β' - morpholinoethoxy)-

ethoxy] - benzophenone, which was reacted in methanol solution with phosphoric acid to give, after crystallisation from methanol/ether, the phosphate, m.p. 79—80°C.

The following compounds can be prepared in a similar way: 4' - chloro - 3,5 - dimethoxy - 4 - [β - (β' - (2'' - methylmorpholino)ethoxy)ethoxy] - benzophenone and 4' - chloro - 3,5 - dimethoxy - 4 - [β - (β' - (2'',6'' - dimethylmorpholino)ethoxy)ethoxy] - benzophenone.

EXAMPLE 10

4' - Chloro - 3,5 - dimethoxy - 4 - (β -chloroethoxy) - benzophenone (5.5 g.) and 2-methylmorpholine (4.7 g.) in alcoholic solution were heated at 110°C. to give 4' - chloro-3,5-dimethoxy - 4 - [β - (2'' - methylmorpholino)ethoxy] - benzophenone, which could be reacted to give, after crystallisation from benzene/benzene, the hydrochloride, m.p. 75—6°C. By a similar process, 4' - chloro - 3,5 - dimethoxy - 4 - [β - (2'',6'' - dimethylmorpholino)ethoxy] - benzophenone hydrochloride (m.p. 182—4°C.) could be obtained.

EXAMPLE 11

A suspension of the sodium salt of 3-phenyl-3 - (3' - methoxy - 4' - hydroxyphenyl)-pentane (from 1 g. of 50% sodium hydride in oil and 5.4 g. of the phenol), was heated with β -morpholinoethyl chloride (3.5 g.) at 130°C. After normal working-up, the residual oil was reacted by known methods to give, after crystallisation from benzene/petroleum ether, 3 - phenyl - 3 - [3' methoxy - 4' - (β - morpholinoethoxy) - phenyl] - pentane hydrochloride, m.p. 158—180°C.

EXAMPLE 12

A solution of a Grignard reagent prepared from magnesium (1.5 g.) and *p*-chlorobromobenzene (11.4 g.) in tetrahydrofuran (100 ml) was treated with 3,5 - dimethoxy - 4 - (β -morpholino - ethoxy) - benzonitrile (5.9 g.) and refluxed for 14 hours, cooled, treated with 5% hydrochloric acid and refluxed for another hour. After extraction with ether (extract discarded) the solution was treated with ammonium hydroxide to give a brown precipitate which was crystallized from cyclohexane to give 3,5 - dimethoxy - 4' - chloro - 4 - (β - morpholinoethoxy) - benzophenone, m.p. 91—92°.

EXAMPLE 13

3,5 - Dimethoxy - 4 - (β - morpholinoethoxy)-benzaldehyde (11.6 g.) was added to a Grignard reagent, prepared from magnesium (3 g.) and *p*-chlorobromobenzene (23 g.), and the mixture was refluxed for 4 hours, chilled and treated with aqueous ammonium chloride. The organic phase was concentrated and the residual oil (3,5-dimethoxy - 4 - (β -morpholinoethoxy) - 4' - chloro - benzhydrol) added to 4.5 g of chromium trioxide in pyridine. After 15 hours at room temperature a few

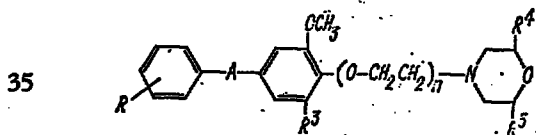
drops of isopropanol were added and the mixture diluted with ice to give a solid which was crystallized from cyclohexane to yield 3,5-dimethoxy - 4' - chloro - 4 - (β - morpholinoethoxy) - benzophenone, m.p. 91—92°C.

Examples of other compounds of the invention are

- 3,5 - dimethoxy - 4 - [β - (2 - methylmorpholino)ethoxy] - benzophenone.
- 10 3,5 - dimethoxy - 3' - trifluoromethyl - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.
- 3,5 - dimethoxy - 4' - amino - 4 - (β - morpholinoethoxy) - benzophenone.
- 15 3,5 - dimethoxy - 4' - amino - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.
- 3,5 - dimethoxy - 2' - methyl - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.
- 20 3 - methoxy - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.
- 3 - methoxy - 4 - [β - (β' - (2'' - methylmorpholino)ethoxy)ethoxy] - benzophenone.
- 3 - methoxy - 4 - (β - morpholinoethoxy) - diphenylamine.
- 25 3 - methoxy - 4 - [β - (β' - morpholinoethoxy)ethoxy] - diphenylmethane.
- 3,5 - dimethoxy - 4 - (β - morpholinoethoxy) - α - butylbenzhydrol.
- 3 - phenyl - 3 - [3',5' - dimethoxy - 4' - (β - morpholinoethoxy) - phenyl]pentane.
- 30 3,5 - dimethoxy - 4' - chloro - 4 - [β - (2' - methylmorpholino) - ethoxy]benzophenone.

WHAT WE CLAIM IS:—

1. An ether of general formula (I)



wherein R is a halogen or hydrogen atom, a trifluoromethyl group, a lower alkyl or alkoxy group, or a substituted or unsubstituted amino group; A is a carbonyl group or a group of formula $-C(R^1)(R^2)-$ wherein R^1 is a hydrogen atom or a lower alkyl, hydroxymethyl or hydroxy group, and R^2 is a hydrogen atom or a lower alkyl group; n is an integer of 1 to 3; R^3 is a hydrogen or halogen atom or a lower alkyl or alkoxy group; and each of R^4 and R^5 , which may be the same or different, is a hydrogen atom or a lower alkyl group; or a pharmaceutically acceptable acid addition salt thereof.

- 50 2. An ether according to claim 1, wherein R is a chlorine atom or a dimethylamino group.
3. An ether according to claim 1 or 2, wherein R is in the 4-position.
- 55 4. An ether according to any one of the preceding claims, wherein R^1 and R^2 are both hydrogen atoms, or are both ethyl groups, or R^2 is a hydrogen atom and R^1 is a hydroxy group.

5. An ether according to any one of the preceding claims, wherein R^3 is a methoxy group.

6. An ether according to any one of the preceding claims, wherein one or both of R^4 and R^5 are methyl groups.

7. An ether according to any one of the preceding claims, in the form of the hydrochloride salt.

8. An ether according to claim 1 wherein R is other than a trifluoromethyl group.

9. 3,5 - Dimethoxy - 4 - [β - (morpholino)ethoxy]benzophenone.

10. 3,5 - Dimethoxy - 4 - [β - (2 - methylmorpholino)ethoxy]benzophenone.

11. 3,5 - Dimethoxy - 4 - [β - [β' - (2'' - methylmorpholino)ethoxy] - ethoxy] - benzophenone.

12. 3,5 - Dimethoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

13. 3,5 - Dimethoxy - 4 - [β - [β' - (β'' - morpholinoethoxy) - ethoxy] - ethoxy] - benzophenone.

14. 3,5 - Dimethoxy - 3' - trifluoromethyl - 4 - (β - morpholinoethoxy) - benzophenone.

15. 3,5 - Dimethoxy - 3' - trifluoromethyl - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

16. 3,5 - Dimethoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - 4' - chlorobenzophenone.

17. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - 4' - chlorobenzophenone.

18. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - 2' - chlorobenzophenone.

19. 3,5 - Dimethoxy - 4' - amino - 4 - (β - morpholinoethoxy) - benzophenone.

20. 3,5 - Dimethoxy - 4' - amino - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.

21. 3,5 - Dimethoxy - 2' - methyl - 4 - (β - morpholinoethoxy) - benzophenone.

22. 3,5 - Dimethoxy - 2' - methyl - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

23. 3 - Methoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

24. 3 - Methoxy - 4 - [β - [β' - (2'' - methylmorpholino) - ethoxy]ethoxy] - benzophenone.

25. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - diphenylmethane.

26. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - benzhydrol.

27. 3 - Methoxy - 4 - (β - morpholinoethoxy) - diphenylmethane.

28. 3 - Methoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - diphenylmethane.

29. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - α - butylbenzhydrol.

30. 3 - Phenyl - 3 - [3',5' - dimethoxy - 4' - (β - morpholinoethoxy) - phenyl]pentane.

31. 3,5 - Dimethoxy - 4' - chloro - 4 - [β - (β' - (2'' - methylmorpholino) - ethoxy]ethoxy] - benzophenone.

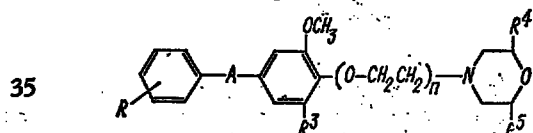
drops of isopropanol were added and the mixture diluted with ice to give a solid which was crystallized from cyclohexane to yield 3,5-dimethoxy - 4' - chloro - 4 - (β - morpholinoethoxy) - benzophenone, m.p. 91—92°C.

Examples of other compounds of the invention are

- 3,5 - dimethoxy - 4 - [β - (2 - methylmorpholinoethoxy)] - benzophenone.
- 10 3,5 - dimethoxy - 3' - trifluoromethyl - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.
- 3,5 - dimethoxy - 4' - amino - 4 - (β - morpholinoethoxy) - benzophenone.
- 15 3,5 - dimethoxy - 4' - amino - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.
- 3,5 - dimethoxy - 2' - methyl - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.
- 20 3 - methoxy - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.
- 3 - methoxy - 4 - [β - (β' - (2'' - methylmorpholinoethoxy)ethoxy] - benzophenone.
- 3 - methoxy - 4 - (β - morpholinoethoxy) - diphenylamine.
- 25 3 - methoxy - 4 - [β - (β' - morpholinoethoxy)ethoxy] - diphenylmethane.
- 3,5 - dimethoxy - 4 - (β - morpholinoethoxy) - α - butylbenzhydrol.
- 3 - phenyl - 3 - [3',5' - dimethoxy - 4' - (β - morpholinoethoxy) - phenyl]pentane.
- 30 3,5 - dimethoxy - 4' - chloro - 4 - [β - (2' - methylmorpholino) - ethoxy]benzophenone.

WHAT WE CLAIM IS:—

1. An ether of general formula (I)



wherein R is a halogen or hydrogen atom, a trifluoromethyl group, a lower alkyl or alkoxy group, or a substituted or unsubstituted amino group; A is a carbonyl group or a group of formula $-C(R^1)(R^2)-$ wherein R^1 is a hydrogen atom or a lower alkyl, hydroxymethyl or hydroxy group, and R^2 is a hydrogen atom or a lower alkyl group; n is an integer of 1 to 3; R^3 is a hydrogen or halogen atom or a lower alkyl or alkoxy group; and each of R^4 and R^5 , which may be the same or different, is a hydrogen atom or a lower alkyl group; or a pharmaceutically acceptable acid addition salt thereof.

2. An ether according to claim 1, wherein R is a chlorine atom or a dimethylamino group.
3. An ether according to claim 1 or 2, wherein R is in the 4-position.
- 55 4. An ether according to any one of the preceding claims, wherein R^1 and R^2 are both hydrogen atoms, or are both ethyl groups, or R^2 is a hydrogen atom and R^1 is a hydroxy group.

5. An ether according to any one of the preceding claims, wherein R^3 is a methoxy group.

6. An ether according to any one of the preceding claims, wherein one or both of R^4 and R^5 are methyl groups.

7. An ether according to any one of the preceding claims, in the form of the hydrochloride salt.

8. An ether according to claim 1 wherein R is other than a trifluoromethyl group.

9. 3,5 - Dimethoxy - 4 - [β - (morpholino)ethoxy]benzophenone.

10. 3,5 - Dimethoxy - 4 - [β - (2 - methylmorpholino)ethoxy] - benzophenone.

11. 3,5 - Dimethoxy - 4 - [β - [β' - (2'' - methylmorpholino)ethoxy] - ethoxy] - benzophenone.

12. 3,5 - Dimethoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

13. 3,5 - Dimethoxy - 4 - [β - [β' - (β'' - morpholinoethoxy) - ethoxy] - ethoxy] - benzophenone.

14. 3,5 - Dimethoxy - 3' - trifluoromethyl - 4 - (β - morpholinoethoxy) - benzophenone.

15. 3,5 - Dimethoxy - 3' - trifluoromethyl - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

16. 3,5 - Dimethoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - 4' - chlorobenzophenone.

17. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - 4' - chlorobenzophenone.

18. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - 2' - chlorobenzophenone.

19. 3,5 - Dimethoxy - 4' - amino - 4 - (β - morpholinoethoxy) - benzophenone.

20. 3,5 - Dimethoxy - 4' - amino - 4 - [β - (β' - morpholinoethoxy)ethoxy] - benzophenone.

21. 3,5 - Dimethoxy - 2' - methyl - 4 - (β - morpholinoethoxy) - benzophenone.

22. 3,5 - Dimethoxy - 2' - methyl - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

23. 3 - Methoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - benzophenone.

24. 3 - Methoxy - 4 - [β - [β' - (2'' - methylmorpholino) - ethoxy] - ethoxy] - benzophenone.

25. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - diphenylmethane.

26. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - benzhydrol.

27. 3 - Methoxy - 4 - (β - morpholinoethoxy) - diphenylmethane.

28. 3 - Methoxy - 4 - [β - (β' - morpholinoethoxy) - ethoxy] - diphenylmethane.

29. 3,5 - Dimethoxy - 4 - (β - morpholinoethoxy) - α - butylbenzhydrol.

30. 3 - Phenyl - 3 - [3',5' - dimethoxy - 4' - (β - morpholinoethoxy) - phenyl]pentane.

31. 3,5 - Dimethoxy - 4' - chloro - 4 - [β - (β' - (2'' - methylmorpholino) - ethoxy] - ethoxy] - benzophenone.



32. 3,5 - Dimethoxy - 4' - chloro - 4 - { β - [β' - (2'',6'' - dimethylmorpholino)-ethoxy]-ethoxy} - benzophenone.

33. 3,5 - Dimethoxy - 4' - chloro - 4 - [β - (2' - methylmorpholino)ethoxy] - benzophenone.

34. 3,5 - Dimethoxy - 4' - chloro - 4 - [β - (2'',6'' - dimethylmorpholino) - ethoxy] - benzophenone.

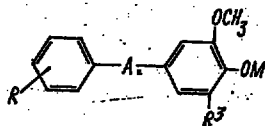
35. 3,5 - Dimethoxy - 4' - chloro - 4 - { β - [β' - (β'' - morpholinoethoxy)-ethoxy]-ethoxy} - benzophenone.

36. 3,5 - Dimethoxy - 4 - (β -morpholinoethoxy) - 4' - chlorodiphenylmethane.

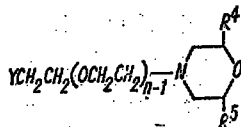
37. An ether according to claim 1, substantially as described herein.

38. A process for preparing an ether according to any one of the preceding claims, the process comprising

(a) reacting a compound of general formula (II)

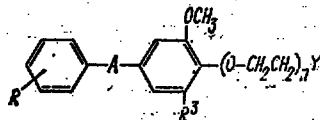


wherein M is an alkali metal atom, and A, R and R³ are as defined in claim 1, with a compound of general formula (III)

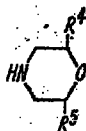


wherein Y is a halogen atom, and n, R⁴ and R⁵ are as defined in claim 1; or

(b) reacting a compound of general formula (IV)



wherein Y is a halogen atom, and n, A, R and R³ are as defined in claim 1, with a compound of general formula (V)



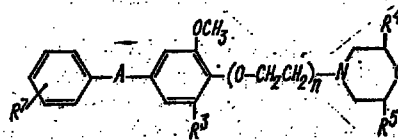
wherein R⁴ and R⁵ are as defined in claim 1; or

(c) reducing a compound of the general formula (I)

wherein A is a carbonyl group, and n, R, R³, R⁴ and R⁵ are as defined in claim 1, to give a compound of general formula (I) wherein A is a group of formula $-C(R^1)(R^2)-$, wherein

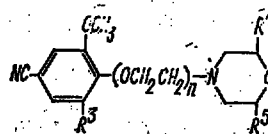
R¹ is a hydroxy group and R² is a hydrogen atom, or wherein both R¹ and R² are hydrogen atoms; or

(d) reducing a compound of general formula (VI)

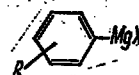


wherein R¹ is a nitro group, and n, A, R³, R⁴ and R⁵, are as defined in claim 1, to give a compound of general formula (I) wherein R is an unsubstituted amino group, and then converting in a manner known *per se* the reduction product to a compound of general formula (I) wherein R is a substituted amino group; or

(e) reacting a compound of general formula (VIII)

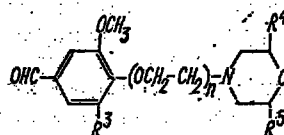


wherein n, R³, R⁴ and R⁵ are as defined in claim 1, with a compound of general formula (VIII)



wherein X is a halogen atom and R is as defined in claim 1 to give a Grignard adduct which is then hydrolysed to give a compound of general formula (I) wherein A is a carbonyl group; or

(f) reacting a compound of general formula (IX)



wherein n, R³, R⁴ and R⁵ are as defined in claim 1, with a compound of general formula (VIII) to give a Grignard adduct which is then hydrolysed to give a compound of general formula (I) wherein A is $-CHOH-$; or

(g) oxidizing a compound of general formula (I) wherein A is a group of formula $-C(R^1)(R^2)-$, wherein R¹ is a hydroxy group and R² is a hydrogen atom, and n, R, R³, R⁴ and R⁵ are as defined in claim 1, to give a compound of general formula (I) wherein A is a carbonyl group; and, if desired, converting the product of (a) to (g) into a pharma-

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ceutically acceptable acid addition salt by reaction with the appropriate acid.

39. A process according to claim 38, wherein the compound of general formula (IV) is prepared by reacting a compound of general formula (II) with a compound of general formula (X)



10 wherein each Y, which may be same or different, is a halogen atom, and n is as defined in claim 1.

40. A process according to claim 38 or 39, wherein Y is a chlorine atom.

15 41. A process according to claim 38 wherein (a) M is a sodium atom.

42. A process according to claim 38, wherein in (d) the reduction product is methylated to give a compound of general formula (I) wherein R is a dimethylamino group.

43. A process according to claim 38, substantially as described in any one of the Examples. 20

44. An ether, as defined in claim 1, prepared by a process according to any one of claims 38 to 43. 25

45. A pharmaceutical composition comprising an ether according to any one of claims 1 to 37 and 44, and a pharmaceutically acceptable carrier or diluent.

46. A composition according to claim 45 substantially as described herein. 30

47. A pharmaceutical composition comprising an ether according to any one of claims 8 to 12, 14 to 25 and 27 to 29, and a pharmaceutically acceptable carrier or diluent. 35

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