PATENT SPECIFICATION

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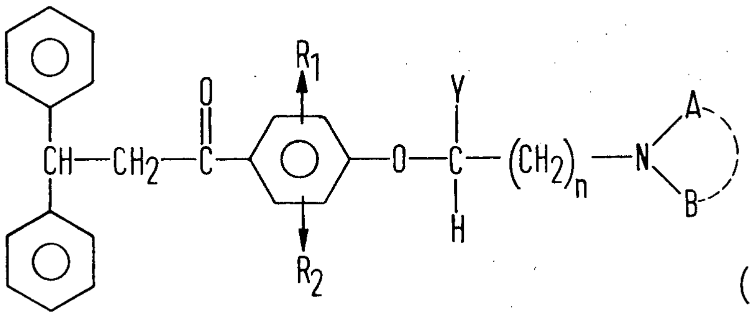
(54) BENZOYLETHERS

(71) We, NATTERMANN & CIE GmbH, a Company organised under the laws of the Federal Republic of Germany, of Nattermannallee 1, 5000 Köln 30, Federal Republic of Germany, 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 novel benzoylethers and their preparation.

Benzoylethers according to one aspect of the invention have the general formula:



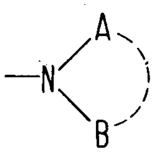
(I)

wherein

Y represents hydrogen or an alkyl group;

A represents hydrogen, or a branched or straight chain alkyl group having 1 to 8 carbon atoms, or an arylalkyl group wherein the alkyl group is branched or straight chain and contains 1 to 8 carbon atoms, and

B represents hydrogen, or a branched or straight chain alkyl group having 1 to 8 carbon atoms, or an arylalkyl group wherein the alkyl group is branched or straight chain and contains from 1 to 8 carbon atoms, or the

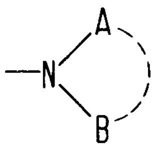


group represents a heterocyclic ring which may be a 5- or 6-membered ring and which may contain an additional hetero atom such as nitrogen, oxygen or sulphur;

n is an integer of from 1 to 4; and

R$_1$ and R$_2$ represent the same groups and each is a branched or straight chain alkyl group having from 1 to 4 carbon atoms.

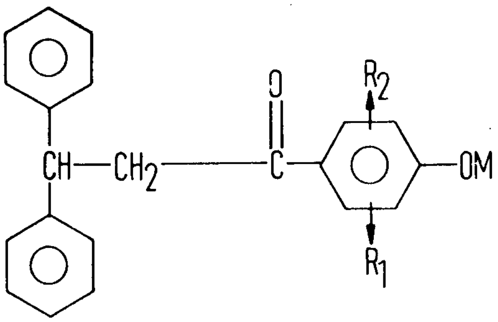
In the case of compounds of formula I wherein the



group represents a heterocyclic 5- or 6-membered ring, such heterocyclic group may be, for example, pyrrolidino, piperidino, piperazino, morpholino, 1-pyrazolyl, 1-imidazolyl or 3-thiazolyl. These groups may also be substituted with an alkyl, aryl, and/or an alkoxy group.

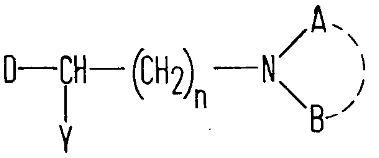
The invention also includes acid addition salts and quaternary ammonium salts of the compounds of formula I. Certain compounds of the invention have been found to have pharmacodynamic properties.

According to another aspect of the invention a process for preparing benzoylethers of formula I comprises reacting an alkali metal salt of a phenol, the salt having the general formula:



(II)

wherein M is an alkali metal atom and R_1 and R_2 have the same meanings as in formula I, with a compound having the general formula

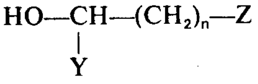


(III)

wherein Y, A, B and *n* have the same meanings as in formula I and D represents a halogen atom, preferably chlorine.

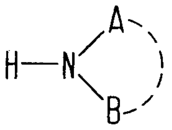
The alkali metal salt of the phenol of formula II may be prepared by reacting, in the presence of a solvent such as acetone, methyl ethyl ketone, toluene or benzene, a phenol of formula V below with an alkali metal basic compound such as sodium amide, sodium hydride or sodium carbonate or the corresponding potassium compounds.

The amino alkylhalides of formula (III) are preferably prepared by condensing a hydroxyalkyl halide having the general formula

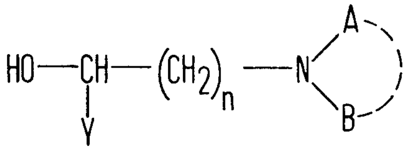


$$HO{-}\underset{\displaystyle Y}{\underset{|}{CH}}{-}(CH_2)_n{-}Z$$

wherein Y and *n* have the same meanings as in formula I and Z represents a halogen, with an amine having the general formula



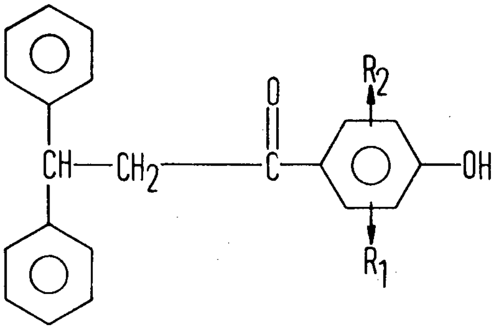
wherein A and B have the same meanings as in formula I, in a suitable solvent, preferably dioxane, to form a compound having the general formula



(IV)

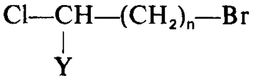
The compound of formula IV may then be halogenated with an inorganic acid halide, such as thionyl chloride, boron trifluoride, phosphorus oxychloride or phosphorus pentachloride in a suitable solvent, such as chloroform, ether, toluene or benzene, and thus transformed into an amino alkylhalide of formula III.

According to a further aspect of the invention a process for preparing benzoylethers of formula I comprises (a) reacting a phenol having the general formula:



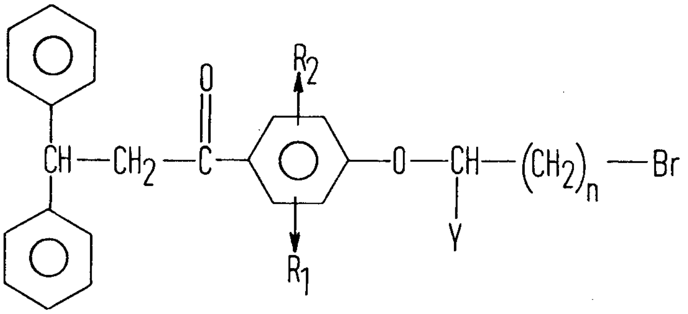
(V)

wherein R_1 and R_2 have the same meanings as in formula I with a chloro- and bromo-substituted alkane having the general formula:



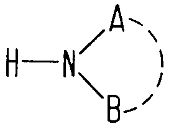
$$\underset{\substack{|\\ Y}}{Cl\text{—}CH}\text{—}(CH_2)_n\text{—}Br \qquad \text{(VI)}$$

wherein Y and *n* have the same meanings as in formula I in an alkaline medium to produce a bromoalkoxybenzoyl derivative having the general formula:



(VII)

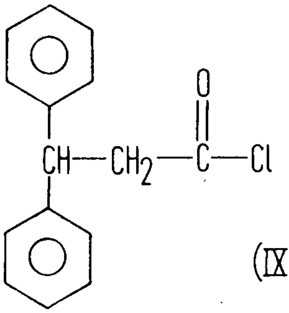
wherein R_1, R_2, Y and *n* have the same meanings as in formula I, and (b) reacting the bromoalkoxybenzoyl derivative with an amine having the general formula



wherein A and B have the same meanings as in formula I.

The first step (a) of this process may be conducted in a solvent, preferably acetone, and in the presence of a base such as potassium carbonate. The second step (b) may be carried out in a suitable solvent such as dioxane, acetone or methyl ethyl ketone, and preferably in the presence of a base such as potassium carbonate.

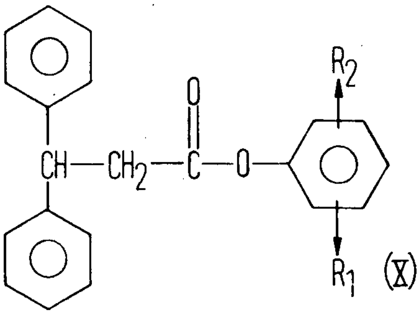
The phenols of formula V may be prepared by acylating dialkylphenols with 3,3-diphenylpropionic acid chloride having the formula:



(IX)

The acylation may take place in a suitable solvent such as chlorobenzene, nitrobenzene or dichloroethane and in the presence of a Lewis acid, preferably aluminium chloride $AlCl_3$, by means of the "Friedel-Crafts" reaction as disclosed by P. H. Gore in *Chem. Reviews 55,* (1955) and E. Berliner in *Org. Reactions 5,* 229—89 (1949).

Alternatively, the dialkylphenols may be reacted with 3,3-diphenylpropionic acid chloride of the above formula IX in a solvent such as chloroform or tetrahydrofuran in the presence of a base such as a tertiary amine, preferably triethylamine, to form an ester having the general formula:



(X)

wherein R_1 and R_2 have the same meanings as in formula I.

These esters may subsequently be rearranged according to "FRIES" as disclosed by A. H. Blatt, *Org. Reactions* I, 342 (1942), in a suitable solvent, preferably chloroform, in the presence of aluminium chloride, to form the acylated phenols of formula V.

The pharmaceutically acceptable acid addition and quaternary ammonium salts of the benzoylethers of formula I may be prepared from those benzoylethers, the quaternisation introducing a further substituent on the nitrogen atom of formula I. This substituent may be an alkyl group with from 1 to 6 carbon atoms or an aralkyl group optionally substituted by halogen, nitro, alkoxy or alkyl. Acid addition salts include, for example, oxalates, fumarates, dichloroacetates and chlorides, Quaternary ammonium salts include, for example, halides such as iodides, bromides or chlorides, tosylates and alkylsulphates such as methylsulphates.

The acid addition salts may be prepared by reacting the benzoylethers of formula I with a suitable acid, e.g. oxalic, fumaric, dichloroacetic or hydrochloric acid.

The quaternary ammonium salts may be prepared by reacting the benzoylethers of formula I with (a) alkylhalides such as ethylchloride, ethylbromide or methyliodide, (b) dialkylsulphates such as dimethylsulphate or diethylsulphate, (c) alkyl or arylalkyl tosylates, or (d) aryl-alkylhalides such as benzyl chloride or dichlorobenzyl chloride. This reaction may be carried out in a suitable solvent, such as methanol, ethanol or acetone.

The following compounds may be prepared by means of these processes:

4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (hydrochloride: herein after "BC 58")

4 - [2 - piperidino - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - diisopropylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (hydrochloride: herein after "BC 79")

4 - [2 - morpholino - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - dimethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (hydrochloride: hereinafter "BC 77")

4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - diisopropyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - diethylamino) - ethoxy] - 3,6 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - dibenzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - pyrrolidino - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - diethylamino) - ethoxy] - 2,6 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - dimethylamino) - propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - dimethylamino) - 1 - methyl - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N - isopropylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - dibutylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [3 - (4′ - methyl - piperazino) - propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [3 - (N,N - diethylamino) - propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N - ethyl - N - butylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [3 - piperidino - propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [3 - (N,N - dibutylamino) - propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [4 - (N,N - diethylamino) - butoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone

4 - [2 - (N,N - diethyl - N - methylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - iodide (hereinafter "BC 96")

4 - [2 - (N,N - diethyl - N - methylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - methosulphate (hereinafter "BC 96α")

4 - [2 - (N,N - diethyl - N - propylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - bromide

4 - [2 - (N,N,N - triethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - ethosulphate

4 - [2 - (N,N - diethyl - N - 4′ - chlorobenzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - chloride

4 - [N,N - diethyl - N - benzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - chloride (hereinafter BC 96 c).

The compounds of the present invention have useful pharmacodynamic properties. The main activity is a relaxing effect on the smooth muscle tissue of mammals. Accordingly, musculotropespasmolytic effects as well as vasodilatory effect in the coronary area and in the periphery area of mammals were observed. The advantages in comparison with known antispasmodic substances lie, particularly, in a longer lasting effect and in an improved pharmacodynamic activity at lower dosage levels.

The quaternary ammonium salts of the benzoylethers of the present invention are particularly characterized by the fact that they have a good effect when applied orally.

Pharmacodynamic Effect

1. Acute Toxicity

	LD$_{50}$ mouse	(mg/kg)	LD$_{50}$rat	(mg/kg)
	i.v.	p.o.	i.v.	p.o.
BC 58	60	1,900	54	
BC 96		4,316.50		
BC 96 a	7.93	1,284.97		
BC 96 c	10—12	2,000 approx.		
Papaverine	44	343+	18+	325+

2. Spasmolytic Effect

2.1 MAGNUS intestine of the guinea pig (against $BaCl_2$-spasmus)

Examples:

BC 58	ED_{50}: 4.4×10^{-8} g/ml bath
BC 77	ED_{50}: 7.9×10^{-7} g/ml bath
BC 79	ED_{50}: 2.8×10^{-7} g/ml bath
Papaverine	ED_{50}: 7.9×10^{-7} g/ml bath

2.2 Spasmolysis in situ of a guinea pig modified according to BROCK (against $BaCl_2$ spasmus)

BC 58	At 5.6 mg/kg i.v.	55% inhibition
	At 10.0 mg/kg i.v.	67% inhibition
	At 17.8 mg/kg i.v.	88% inhibition
Papaverine	At 5.6 mg/kg i.v.	5% inhibition
	At 10.0 mg/kg i.v.	8% inhibition
	At 17.8 mg/kg i.v.	57% inhibition

+according to KOMLOS and PETOCZ, 20 Arzneimittel-Forschung 1338 (1970)

3. Increase in perfusion

3.1 LANGENDORFF heart of the guinea pig

Examples:

BC 58	ED_{50}++:	approx. 2.2 μg
BC 77	ED_{50}:	approx. 6.6 μg
BC 79	ED_{50}:	approx. 2.3 μg
Papaverine	ED_{50}:	approx. 6.0 μg

3.2 Increase in peripheral vasodilation (A. femoralis) in the case of the narcotized dog (with planimetric evaluation taking into account the duration of the effect).

BC 58	At 3.16 mg/kg i.v.	approx. 400 ml×min
	At 5.6 mg/kg i.v.	approx. 800 ml×min
	At 10.0 mg/kg i.v.	approx. 2,200 ml×min
Papaverine	At 3.16 mg/kg i.v.	approx. 100 ml×min
	At 5.6 mg/kg i.v.	approx. 250 ml×min
	At 10.0 mg/kg i.v.	approx. 180 ml×min

The pronounced difference results, in particular from the longer duration of the effect of BC 58.

3.3 Increase in coronary vasodilation (Bretschneider catheter) in the case of a narcotized dog (with planimetric evaluation taking into account the duration of the effect).

BC 58	At 3.16 mg/kg i.v.	approx. 350 ml×min
	At 5.6 mg/kg i.v.	approx. 680 ml×min
Papaverine	At 3.16 mg/kg i.v.	approx. 50 ml×min
	At 5.6 mg/kg i.v.	approx. 75 ml×min

4. Effect on blood pressure and heart frequency

Decrease of the arterial blood pressure (systolic)

BC 58	At 3.16 mg/kg i.v.	approx. 30 mm Hg
	At 5.6 mg/kg i.v.	approx. 30 mm Hg
	At 10.0 mg/kg i.v.	approx 40 mm Hg

++ a 50% increase in flow

Papaverine	At 3.16 mg/kg i.v.	approx. 25 mm Hg
	At 5.6 mg/kg i.v.	approx. 35 mm Hg
	At 10.0 mg/kg i.v.	approx. 40 mm Hg

Change of the heart frequency

BC 58	At 3.16 mg/kg i.v.	approx. −10 pulses/min
	At 5.6 mg/kg i.v.	approx. −12 pulses/min
	At 10.0 mg/kg i.v.	approx. −24 pulses/min
Papaverine	At 3.16 mg/kg i.v.	approx. +46 pulses/min
	At 5.6 mg/kg i.v.	approx. +49 pulses/min
	At 10.0 mg/kg i.v.	approx. +33 pulses/min

The administration of the compounds of the present invention is effected in the usual way, preferably orally or intravenously.

Generally, in the case of oral administration it has been found to be advantageous to administer quantities of from about 0.1 to 10 mg per kg, preferably from about 0.5 to 5 mg per kg body-weight per day of BC 58, and from 0.01 to 5 mg per kg, preferably from 0.1 to 1 mg per kg body-weight per day of the quaternary ammonium compounds, for obtaining effective results. In the case of intravenous administration the dosage of BC 58 amounts to from about 0.005 to 0.5 mg per kg, preferably from 0.02 to 0.2 mg per kg body-weight per day, and the dosage of the quaternary ammonium compounds amount to from 0.001 to 0.1 mg per kg, preferably from 0.002 to 0.02 mg per kg body-weight per day.

In spite of this it may be necessary to deviate from the amounts stated, depending on the body-weight and the condition of the subject and its individual reaction to the pharmaceutical composition as well as on the route of administration. In some cases it might suffice to use less than the above-mentioned minimum dosage level, whereas in others the upper limit stated might have to be exceeded. If greater amounts are necessary, it might be recommendable to administer several single doses e.g. 2 to 4 during the day.

For therapeutical application the compounds of the present invention can be incorporated into pharmaceutical preparations such as tablets, capsules, pills, coated tablets, granules, suspensions and solutions together with inert, non-toxic pharmaceutically suitable solid or liquid carriers, or diluents. the therapeutically effective compound should be present in a concentration of from about 1.0 to 90 percent by weight, i.e. in amounts sufficient for reaching the range of dosage stated.

The pharmaceutical preparations may be produced e.g. by blending the active components with liquid or solid carriers, or diluents, optionally with addition of emulsifying agents and/or dispersing agents. If water is used as solvent, it may be advantageous to use an organic co-solvent.

The following carriers and adjuvants are stated by way of example: Water, non-toxic organic solvents as glycols, vegetable oil, alcohols; solid carriers, e.g. natural stone powders (e.g. kaolins, talcum), synthetic powders (e.g. silicates), sugar (e.g. lactose and dextrose); emulsifying agents, e.g. anionic and non-ionic emulsifiers (e.g. polyoxyethylene fatty acid esters, alkyl and aryl sulphonates), dispersing agents (e.g. lignin, starch, polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, stearic acid, talcum).

The present invention is further illustrated by the following Examples.

Example 1

46.37 grams (a 10% excess) of 3,3 - diphenylpropionic acid chloride in 120 ml tetrahydrofuran are placed into a 500 ml round-bottom flask which is equipped with a mechanical agitator. 18.30 grams of 2,6 - dimethylphenol with 16.7 grams triethylamine in 150 ml tetrahydrofuran are added, dropwise, to this solution while stirring. The mixture is stirred for 12 hours at room temperature. The precipitated triethylamine-hydrochloride is sucked off and the tetrahydrofuran is evaporated *in vacuo*. The residue is taken up in ether and washed three times with water. The solvent is dried with sodium sulphate and then evaporated *in vacuo*. There remain 45.0 grams of 3,3-diphenylpropionic acid-2,6-dimethylphenyl ester [91.2% yield]. 45.0 grams of this ester are dissolved in a 500 ml flask in 200 ml nitrobenzene. 18.20 grams of aluminium chloride are added and the substance is stirred, excluding any humidity, with a KPG agitator. The mixture is heated to 100°C and the components are left to react at this temperature for 1 day.

The nitrobenzene is distilled off *in vacuo*, the residue is taken up with ether and crushed ice is added. Subsequently, the ether phase is washed well with water, dried with sodium sulphate and the ether is evaporated except for a small amount. 32 grams [71.3%] 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone crystallize out. 10 grams of this compound are dissolved in 80 ml dry acetone for the etherification and 25 grams of water-free potash (100% excess) are added. 12.25 grams (200% excess) of 2 - diethylaminoethylchloride, dissolved in 150 ml acetone, are added dropwise, with the exclusion of humidity, to this solution. The solution is boiled under reflux for 1 day. The potash is filtered off, the acetone evaporated *in vacuo* and the residue taken up in ether. The ether solution is washed in water and dried with sodium sulphate. The hydrochloride salt is precipitated with ethereal hydrochloric acid. After recrystallization from a methanol/ether solution, 9.55 grams [67.8%] of 4 - [2 - (N,N - diethylamino- - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride (melting point 95—97°C) and 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone fumarate (melting point 226°C [decomposition]) are obtained.

Example 2

16.70 grams (0.16 mol) of triethylamine are added to 18.30 grams (0.15 mol) of 2,6 - dimethylphenol, which is dissolved in 100 ml dry tetrahydrofuran, and 40.37 grams 3,3 - diphenylpropionic acid chloride, dissolved in 150 ml dry tetrahydrofuran, are added, dropwise, at room temperature while stirring. The components have reacted after 20 hours at room temperature.

After having sucked off the triethylaminehydrochloride, the tetrahydrofuran is evaporated *in vacuo* and the residue taken up with ether. The ethereal solution is washed several times with water and dried with sodium sulphate.

After evaporating the ether *in vacuo*, 46.9 grams [94.7%] of β,β - diphenylpropionic acid - 2,6 - dimethylphenyl ester are obtained.

46.90 grams (0.14 mol) of the ester are dissolved in 200 ml chlorobenzene and, subsequently, 18.5 grams (0.139 mol) of aluminium chloride are added. The mixture is stirred for 2 days at approximately 100°C. Chlorobenzene is distilled off *in vacuo*, crushed ice is added to the residue and subsequently ether and then it is washed several times with water.

After drying the ether phase, the ether is evaporated *in vacuo*. The remaining solid product is washed several times with petroleum ether. 32.80 grams [70%] of 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone are obtained.

15.0 grams of the obtained phenol are mixed in 100 ml dry acetone with 14 grams of water-free potassium carbonate. While stirring well, 7.5 grams of 2 - chloroethylmorpholine, dissolved in 100 ml dry acetone, are added dropwise. After boiling under reflux for 2 days, the residue is filtered off, acetone is evaporated *in vacuo* and the residue is taken up in ether, washed with water and dried with sodium sulphate. The free base is precipitated with ethereal hydrochloric acid as a hydrochloride. After recrystallization from hot methanol, 15 grams of 4 - [2 - morpholino - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride (melting point of 211—216°C) are obtained.

Example 3

50.0 grams (0.41 mol) of 2,6 - dimethylphenol and 40.9 grams (0.34 mol) of aluminium chloride are mixed together in 700 ml of chlorobenzene. At room temperature and while stirring with a KPG agitator, 101 grams (0.415 mol) of 3,3 - diphenylpropionic acid chloride, dissolved in 300 ml chlorobenzene, are added dropwise. The reaction mixture is kept at 100°C for 8 hours. The chlorobenzene is distilled off *in vacuo*, the residue is taken up in ether and ice is added. The ethereal phase is washed out with water. After drying the ethereal phase with sodium sulphate, the solvent is evaporated *in vacuo*. The slimy residue is mixed with petroleum ether. There remain red crystals which are recrystallized from acetone/petroleum ether or ether/petroleum ether.

79 grams [58.5%] 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone (melting point of 137°C) are obtained.

30 grams of the propiophenone derivative are dissolved in 200 ml dry acetone and 75 grams water-free potash are added. While stirring with a KPG agitator, 36.75 grams 2 - diethylaminoethylchloride, dissolved in 250 ml dry acetone, are added to the solution, dropwise. After boiling under reflux for 10 hours, the phenol reacts. The solution is filtered off and the filtrate is concentrated *in vacuo*. The residue is taken up in ether and the solution is washed several times with water.

After drying with sodium sulphate, the free base is precipitated with ethereal hydrochloric acid as the hydrochloride. After recrystallization from methanol/ether, 25.4 grams [65%] of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride (melting point range 95—97°C) are obtained.

Example 4

53.0 grams of 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 300 mls of dry toluene. 38.4 grams (100% excess) of 1 - diethylamino - propylchloride, dissolved in 100 mls of toluene, are added to this solution dropwise. At that time, 13.8 grams sodium amide, 50% in toluene suspension, are added dropwise with stirring. This mixture is boiled for two days under reflux. The precipitate is filtered and the toluene is evaporated *in vacuo*. The residue is taken up in ether and washed several times with water. After drying with sodium sulphate, the hydrochloride is precipitated with ethereal hydrochloric acid and it is filtered over active carbon and recrystallized from acetone/ether. 4 - [3 - (N,N - diethylamino) - propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride (melting point 179°C) is obtained.

Example 5

48.8 grams (0.2 mol) of 2 - bromoethanol are dissolved in 200 mls of dioxane and 51.6 grams (0.2 mol) of dibutylamine, dissolved in 100 mls of dioxane, are added dropwise to form a discoloured solution. The reaction medium is boiled under reflux for two days. The dioxane is distilled off *in vacuo*, the residue is taken up with water, a layer of ether is then added and the mixture is washed with a sodium carbonate solution. The free base (2 - dibutylaminoethanol) will, subsequently, be in the ethereal phase. After drying with sodium sulphate, the ether is evaporated *in vacuo*. The free base is distilled using a high vacuum.

15.3 grams of 2 - dibutylaminoethanol, together with 6.5 mls of thionylchloride, are dissolved in 200 mls of distilled chloroform for the chlorination of the amino alcohol. The mixture is boiled under reflux for three days, and subsequently, the solvent is evaporated *in vacuo*. The residue is washed with ether. 2 - dibutylaminoethylchloride hydrochloride precipitates as a white substance.

21.8 grams of 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 150 mls of water-free acetone and 18 grams of water-free potash are added. 12.6 grams of dibutylaminoethylchloride, dissolved in 100 mls of acetone, are added dropwise. The mixture is boiled under reflux for two days.

After the solution has cooled, it is filtered and the filtrate is narrowed down. The residue is taken up in ether and washed with water. After drying with sodium sulphate, the hydrochloride is precipitated by adding ethereal hydrochloric acid. After recrystallization from acetone/methanol/ether, 4 - [2 - (N,N - dibutylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride is obtained in the form of white crystals having a melting point range of 162—164°C.

Example 6

50 grams (0.15 mol) of 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3), dissolved in 200 mls of acetone, are added, with stirring, to a reaction mixture consisting of 29 grams (0.184 mol) of 1 - bromo - 3 - chloropropane in 300 mls of acetone and 42 grams (0.304 mol) of water-free potash. The preparation is boiled under reflux for one day and the precipitate is sucked off. The acetone is evaporated, the residue taken up with ether and a little acetone and, subsequently, washed with water. The ethereal phase is dried over sodium sulphate. The solvent is evaporated *in vacuo*. The residue is crystallized from acetone/petroleum ether. 52.5 grams [85.5%] of 4 - (3 - bromopropoxy) - 3,5 - dimethyl - β,β - diphenylpropiophenone are obtained.

25.0 grams (0.0617 mol) of the etherified propiophenone are mixed with 150 mls of dioxane and, while stirring, 5.17 grams (0.0617 mol) of N - methylpiperazine in 50 mls of dioxane are added dropwise. The solution is boiled for four days at reflux. The dioxane is evaporated *in vacuo*. The residue contains the hydrochloride which, for purification, is transformed into the free base by treatment with sodium carbonate in water. The base is extracted with ether and the hydrochloride is again precipitated by adding ethereal hydrochloric acid. It is recrystallized from methanol and 14.7 grams [44.2%] of 4 - [3 - (4′ - methyl - piperazino) -

propoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride, having a melting point range of 243—248°C, are obtained.

Example 7

25.0 grams of 2 - bromoethanol are dissolved in 100 mls of dioxane. 20.2 grams of N - ethyl - N - butylamine are added dropwise and the mixture is boiled under reflux for two days. The dioxane is distilled off, and the residue is mixed with ether. A solid product forms which, for the purpose of further reaction, is transformed into the free base.

16.0 grams of 2 - (N - ethyl - N - butylamino) ethanol are obtained. This product is dissolved in distilled chloroform and, with stirring, 14.4 grams (8.9 mls) of thionylchloride are slowly added dropwise. Then, the reaction mixture is boiled under reflux for eight hours. The solution is evaporated to dryness and the residue is treated several times with ether and sucked off. 17.0 grams of 2 - (N - ethyl - N - butylamino)ethylchloride hydrochloride are obtained.

28.1 grams of 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved with 200 mls of acetone and 13 grams of water-free potash are added. With vigorous stirring, 14 grams of 2 - (N - ethyl - N - butylamino)ethylchloride, dissolved in 100 mls of acetone, are added dropwise. After cooling, the precipitate is sucked off and the acetone is evaporated *in vacuo*. The residue is taken up with ether and washed with water. After drying with sodium sulphate, ethereal hydrochloric acid is added, thus precipitating the hydrochloride. After recrystallization from methanol/ether, 4 - [2 - (N - ethyl - N - butylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone hydrochloride, having a melting point range of between 164 and 166°C, is obtained.

Example 8

5.0 grams (0.15 mol) of 4 - hydroxy - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 300 mls of acetone and added dropwise to 31.5 grams (0.184 mol) of 1 - bromo - 4 - chlorobutane which was prepared in 200 mls of acetone with 42 grams (0.304 mol) of potassium carbonate. The reaction is completed after three days of reflux.

The precipitate is sucked off, the acetone drawn off and the residue taken up in ether. The precipitate is then washed with water and dried with sodium sulphate. The ether is evaporated *in vacuo*. 62.6 grams of 4 - (4 - chlorobutoxy) - 3,5 - dimethyl - β,β - diphenylpropiophenone are obtained.

62.6 grams (0.149 mol) of the above propiophenone are dissolved in 300 mls of dioxane. While stirring, 10.85 grams (0.149 mol) of diethylamine, dissolved in 200 mls of dioxane, are added dropwise. The mixture is refluxed for three days. After the reaction, the precipitate is sucked off and the acetone evaporated *in vacuo*. The residue is taken up in ether and washed with water. After drying with sodium sulphate, the hydrochloride of the base is precipitated by adding ethereal hydrochloric acid. Several recrystallizations with methanol/ether are effected.

4 - [4 - (N,N - diethylamino) - butoxy] - β,β - diphenylpropiophenone hydrochloride, having a melting point of from 168 to 169°C, is obtained.

Example 9

50.0 grams of 2,6 - dissopropylphenol and 37.4 grams of aluminium chloride are mixed in 650 mls of chlorobenzene. While stirring with a KPG agitator, 75.35 grams of 3,3 - diphenylpropionic acid chloride, dissolved in 300 mls of chlorobenzene are added dropwise at room temperature. After the solution is kept for 6 hours at 100°C, the chlorobenzene is distilled off *in vacuo*. The residue, taken up in ether, is washed several times with water. The ethereal phase is dried with sodium sulphate and the solvent evaporated *in vacuo*. 70 grams of 4 - hydroxy - 3,5 - diisopropyl - β,β - diphenylpropiophenone are obtained.

15.0 grams (0.0388 mol) of the propiophenone derivative are dissolved in 100 mls of dry acetone and 21.5 grams (0.1552 mol) of water-free potash are added. While stirring, 13.4 grams (0.0785 mol) of 2 - diethylaminoethylchloride, dissolved in 75 mls of acetone, are added dropwise. After stirring for 12 hours at room temperature, the mixture is filtered and the acetone evaporated *in vacuo*. The residue is taken up in ether, washed several times with water, and dried with sodium sulphate. Subsequently, the hydrochloride is precipitated with ethereal hydrochloric acid. The solid substance is recrystallized with methanol/ether. 35.9 grams [49.5%] of 4 - [(N,N - diethylamino) - ethoxy] - 3,5 - diisopropyl - β,β -

diphenylpropiophenone hydrochloride (having a melting point range of 179 to 182°C) are obtained.

Example 10

12.0 grams (0.098 mol) of 3,5 - dimethylphenol and 13.2 grams (0.098 mol) of aluminium chloride are mixed with 50 mls of chlorobenzene. 24.2 grams (0.098 mol) of 3,3 - diphenylpropionic acid chloride, dissolved in 50 mls of chlorobenzene, are added dropwise. The preparation is reacted at 100°C. After evaporation of the chlorobenzene *in vacuo*, the residue is taken up in ether and washed several times with water. The ethereal phase is dried with sodium sulphate and evaporated *in vacuo*. 15.2 grams [46.2%] of 4 - hydroxy - 2,6 - dimethyl - β,β - diphenylpropiophenone are obtained.

20.0 grams (0.0605 mol) of the propiophenone derivative are dissolved in 100 mls dry acetone and 33.4 grams (0.242 mol) of potassium carbonate (water-free) are then added. While stirring, 12.9 grams (0.095 mol) of 2 - diethylamioethylchloride, dissolved in 100 mls of acetone, are added dropwise. The reaction is effected at room temperature. The precipitate is filtered off and the acetone is evaporated *in vacuo*. The residue is taken up in ether and washed several times with water. After drying with sodium sulphate, the hydrochloride is precipitated with ethereal hydrochloric acid. A recrystallization is effected with methanol/ether and 4 - [2 - (N,N - diethylamino) - ethoxy] - 2,6 - dimethyl - β,β - diphenylpropiophenone hydrochloride, having a melting point range of from 135 to 137°C, is obtained.

Example 11

24.4 grams of 3,6 - dimethylphenyl and 26.6 grams of aluminium chloride are dissolved in 250 mls chlorobenzene and 48.9 grams of 3,3 - diphenylpropionic acid chloride, dissolved in 150 mls chlorobenzene, are added while stirring. The stirring is continued for several days at 100°C. The chlorobenzene is evaporated *in vacuo*, the residue is mixed with ice and ether and washed several times with water. After drying with sodium sulphate, the ether is evaporated. 15.1 grams of 4 - hydroxy - 3,6 - dimethyl - β,β - diphenylpropiophenone are obtained.

15.0 grams of the propiophenone derivative together with 25.0 grams of potassium carbonate, are dissolved in 150 mls of dry acetone. While stirring, 15.6 grams of 2 - diethylaminoethylchloride in 50 mls of acetone are added dropwise. Boiling is effected under reflux, the precipitate is filtered off and the acetone is evaporated *in vacuo*. The residue is taken up in ether and washed several times with water. After drying with sodium sulphate, the hydrochloride is precipitated with ethereal hydrochloric acid.

After recrystallization with methanol/ether, 19.8 grams of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,6 - dimethyl - β,β - diphenylpropiophenone hydrochloride, having a melting point range of 148 to 150°C, are obtained.

Example 12

37.0 grams (0.086 mol) of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 200 mls of absolute ethanol. While stirring, 24.4 grams of methyliodide (0.1725 mol), dissolved in 100 mls of absolute methanol, are added dropwise. The reaction is completed after 5 hours. After distilling the solvent, the residue is recrystallized with methanol/ether. 30 grams of 4 - [2 - (N,N - diethyl - N - methylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - iodide (having a melting point of 209—210°C) are obtained.

Example 13

17.26 hundredths grams (0.0403 mol) of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 150 mls of dry acetone. 5.08 grams (0.0403 mol) of dimethylsulphate, dissolved in 100 mls of dry acetone, are added dropwise to this solution. The reaction is completed after 4 hours. The excess dimethylsulphate is destroyed by adding water and the sulphuric acid is neutralized with a methanolic caustic soda solution. The precipitated sodium sulphate is filtered. The filtrate is concentrated and the residue is recrystallized with acetic ester/petroleum ether.

4 - [2 - (N,N - diethyl - N - methylamino - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone-methosulphate (having a melting point of from 118 to 121°C) is obtained.

Example 14

20 grams (0.047 mol) of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenyl - propiophenone (prepared as in Example 3) are dissolved in 150 mls of dry acetone. To this solution 11.48 grams (0.094 mol) of propylbromide, dissolved in 75 mls of dry acetone, are added dropwise. The reaction is completed after 10 hours. After distilling the solvent, the residue is recrystallized from methanol/ether. Eleven grams of 4 - [2 - (N,N - diethyl - N - propylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenyl-propiophenone - bromide are obtained, having a melting point of 216°C.

Example 15

32.75 grams (0.0763 mol) of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 150 mls of dry acetone. While stirring thoroughly 29.8 grams (0.1526 mol) of 4 - chlorobenzylchloride dissolved in 100 mls of dry acetone, are added dropwise. After refluxing for 6 hours the reaction is completed.

The solvent is distilled off and the residue is recrystallized from methanol/ether. Eight grams of 4 - [2 - (N,N - diethyl - N - 4' - chlorobenzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - chloride are obtained, having a melting point of 153°C.

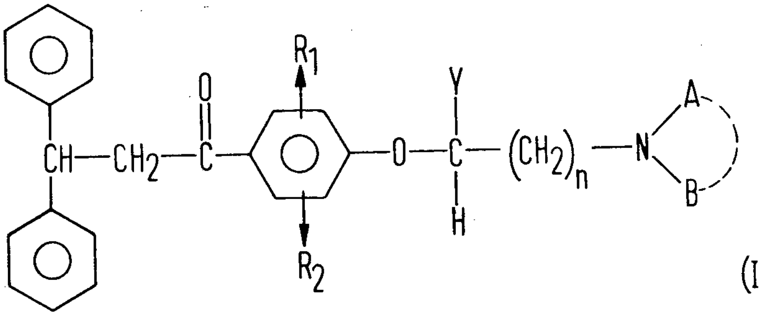
Example 16

6 grams (0.014 mol) of 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone (prepared as in Example 3) are dissolved in 75 mls of dry acetone. While stirring, 3.45 grams (0.028 mol) benzylchloride, dissolved in 75 mls of dry acetone, are added dropwise. The reaction is completed after 2 days.

The solvent is distilled off and the residue is recrystallized from methanol/ether. Five grams of 4 - [2 - (N,N - diethyl - N - benzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - chloride are obtained, melting at from 168 to 170°C.

WHAT WE CLAIM IS:—

1. Compounds having the formula:

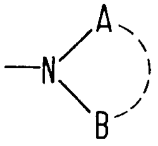


(I)

wherein Y represents hydrogen or an alkyl group;

A represents hydrogen, or a branched or straight chain alkyl group having 1 to 8 carbon atoms, or an arylalkyl group wherein the alkyl group is branched or straight chain and contains 1 to 8 carbon atoms, and

B represents hydrogen, or a branched or straight chain alkyl group having 1 to 8 carbon atoms, or an arylalkyl group wherein the alkyl group is branched or straight chain and contains from 1 to 8 carbon atoms, or the

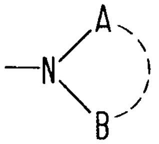


group represents a heterocyclic ring;

n is an integer of from 1 to 4; and

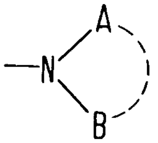
R_1 and R_2 represent the same groups and each is a branched or straight chain alkyl group having from 1 to 4 carbon atoms.

2. Compounds as claimed in Claim 1 wherein, in the formula,



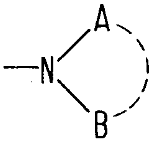
is a 5- or 6-membered heterocyclic group which contains a second hetero atom selected from nitrogen, sulphur and oxygen.

3. Compounds as claimed in Claim 1 wherein, in the formula,



is a pyrrolidino, piperidino, piperazino, morpholino, 1-pyrazolyl, 1-imidazolyl or 3-thiazolyl ring.

4. Compounds as claimed in Claim 1 wherein, in the formula,



is a heterocyclic group, or as claimed in Claim 2 or Claim 3, wherein the heterocyclic group is substituted with an alkyl, aryl or alkoxy group.

5. Compounds as claimed in any of the preceding Claims wherein R_1 and R_2 are methyl groups which are substituted on the benzene nucleus in the 2,6 or 3,5 or 3,6 positions.

6. 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone.

7. 4 - [2 - (N,N - diisopropylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone.

8. 4 - [2 - (N,N - dimethylamino) - 1 - methyl - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone.

9. 4 - [2 - (N,N - diethylamino) - ethoxy] - 3,6 - dimethyl - β,β - diphenylpropiophenone.

10. Pharmaceutically acceptable acid addition and quaternary ammonium salts of compounds as claimed in any of the preceding Claims.

11. 4 - [2 - (N,N - diethyl - N - methyl) - amino - ethoxy] - 3,5 - dimethyl - β,β - diphenypropiophenone - iodide.

12. 4 - [2 - (N,N - diethyl - N - methyl) - amino - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - methosulphate.

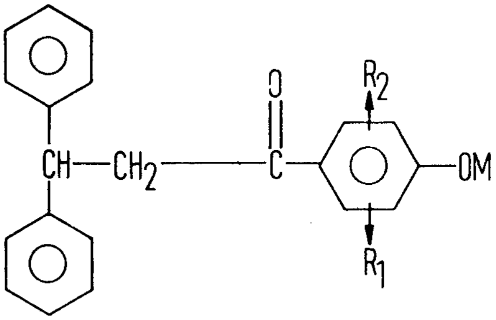
13. 4 - [2 - (N,N - diethyl - N - benzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - chloride.

14. 4 - [2 - (N,N,N - triethylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - ethosulphate.

15. 4 - [2 - (N,N - diethyl - N - 4′ - chlorobenzylamino) - ethoxy] - 3,5 - dimethyl - β,β - diphenylpropiophenone - chloride.

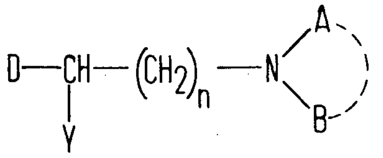
16. Compounds according to Claim 1 substantially as hereinbefore described, and their pharmaceutically acceptable acid addition and quaternary ammonium salts.

17. A process for preparing compounds as claimed in Claim 1 which comprises reacting an alkali metal salt of a phenol, the salt having the general formula:



(II)

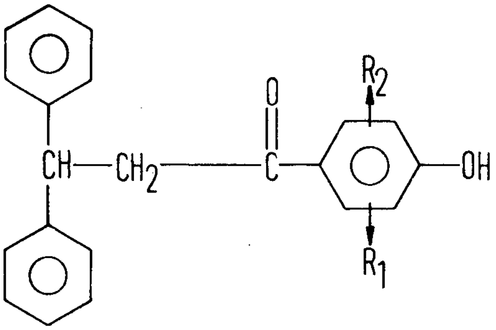
wherein M represents an alkali metal atom and R_1 and R_2 have the same meanings as in the formula of Claim 1 with a compound having the general formula



(III)

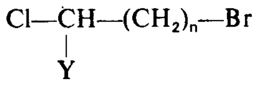
wherein Y, A, B and *n* have the same meanings as in the formula of Claim 1 and D represents a halogen atom.

18. A process for preparing compounds as claimed in Claim 1 which comprises (a) reacting a phenol having the general formula



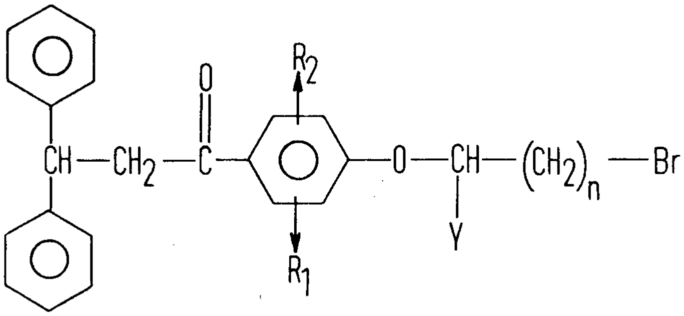
(V)

wherein R_1 and R_2 have the same meanings as in the formula of Claim 1 with a chloro- and bromo-substituted alkane having the general formula



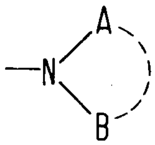
$$\underset{\displaystyle Y}{\underset{|}{Cl{-}CH}}{-}(CH_2)_n{-}Br$$

wherein Y and *n* have the same meanings as in the formula of Claim 1 in an alkaline medium to produce a bromoalkoxy - benzoyl derivative having the general formula:



(VII)

and (b) reacting the bromoalkoxybenzoyl derivative with an amine having the general formula



wherein A and B have the same meanings as in the formula of Claim 1.

19. Processes for preparing compounds as claimed in Claim 1 and acid addition or quaternary ammonium salts thereof, substantially as described in any of the Examples.

20. Compounds as claimed in Claim 1 or acid addition or quaternary ammonium salts thereof which have been prepared by a process as claimed in any of Claims 17 to 19.

21. A pharmaceutical composition comprising a compound or salt as claimed in any of Claims 1 to 16 or 20 and a pharmaceutically acceptable carrier and/or adjuvant.

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