

1.032.880



PATENT SPECIFICATION

NO DRAWINGS

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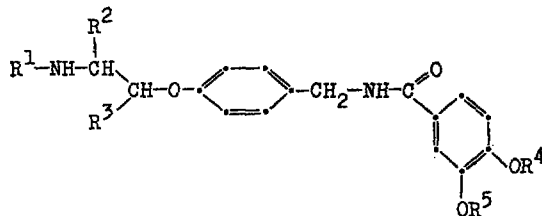
COMPLETE SPECIFICATION

Novel Benzamide Derivatives and a process for the manufacture thereof

We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel benzamide derivatives and a process for the manufacture thereof.

The novel benzamide derivatives provided by the invention are compounds of the general formula



(I)

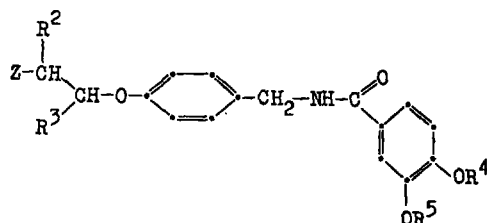
wherein R¹, R² and R³ each represent a lower-alkyl group and one of R² and R³ represents a hydrogen atom and the other represents a hydrogen atom or a lower-alkyl group, and acid addition salts thereof. They are useful as antiemetics; for example, for the suppression of nausea associated with gastrointestinal disturbances, motion sickness or pregnancy or induced by the administration of other therapeutic agents. They can be used as medicaments in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier. This may be an organic or inorganic, solid or liquid carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed compatible substances such as water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly or any other inert carrier useful for the preparation of medicaments. The pharmaceutical preparations may be in solid form (for example, as tablets, dragées, suppositories or capsules) or in liquid form (for example, as solutions, emulsions or suspensions). If desired, they may be sterilized and/or contain auxiliary substances such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain still other therapeutically useful substances.

The most interesting derivatives provided by the invention are the compounds N - [4 - (2 - methylamino - ethoxy) - benzyl] - 3,4 - diethoxy - benzamide, N - [4 - (2 - methylamino - 1 - methyl - ethoxy) - benzyl] - 3,4 - diethoxy - benzamide and N - [4 - (2 - methylamino - 2 - methyl - ethoxy) - benzyl] - 3,4 - diethoxy - benzamide and their acid addition salts (especially the hydrochlorides). The latter two

[Price 4s. 6d.]

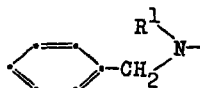
compounds and their acid addition salts may conveniently be used in the form of a mixture.

According to the process provided by the invention, the novel derivatives afore-
said are manufactured by replacing or converting the substituent Z of a compound of
the formula



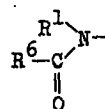
(II)

(wherein R^2 , R^3 , R^4 and R^5 have the significance given earlier and Z represents a halogen atom or a protected-amino group of the formula



(a)

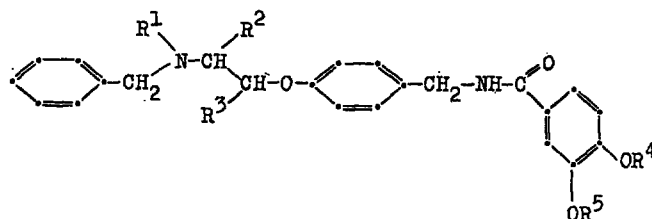
or



(b)

in which R^1 has the significance given earlier and R^6 represents a hydrogen atom or
a lower-alkyl, lower-alkoxy or lower carboxy-alkyl group) by or into the group
 R^1-NH- (in which R^1 has the significance given earlier) by animation, catalytic
debenzylation or hydrolysis as the case may require and, if desired, transforming the
product into an acid addition salt.

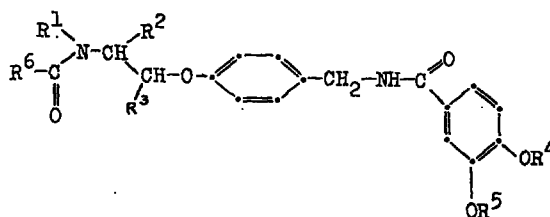
According to one embodiment of the process, the conversion is effected by
catalytically debenzylating a compound of the formula



IIa

wherein R^1 , R^2 , R^3 , R^4 and R^5 have the significance given earlier, by hydrogenolysis.
The compound of formula IIa (i.e. a compound of formula II in which Z represents
a group of formula a) is treated with a strong acid (e.g. with a mineral acid such as
hydrochloric acid or hydrobromic acid) in alcohol or aqueous alcohol, acetic acid, etc
and catalytically debenzylated with hydrogen in the presence of a noble-metal catalyst
(e.g. a palladium or platinum catalyst, or a nickel catalyst such as RANEY-nickel) to
give a compound of formula I or a mixture of compounds of formula I. When a
mixture of compounds is obtained, the mixture may, if desired, be separated into its
two components either by fractional crystallization or by chromatography.

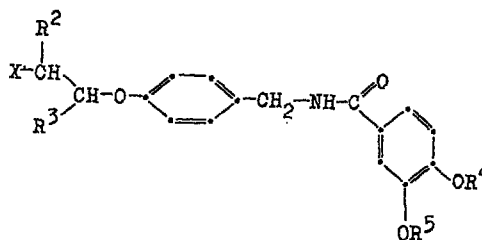
According to another embodiment of the process, the conversion is effected by
hydrolysing a compound of the formula



IIb

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 have the significance given earlier. The hydrolysis can be carried out using either aqueous acid or base (e.g. an aqueous mineral acid or aqueous alkali). The hydrolysis of the compound of formula IIb (i.e. a compound of formula II in which Z represents a group of formula b) is preferably carried out by heating an ethanol solution of the compound of formula IIb at reflux with about 2.5 parts of 48 per cent hydrobromic acid for 24 hours. Neutralization of the reaction mixture gives the compound of formula I. One particular aspect of this embodiment comprises using a compound of formula IIb in which R^6 represents a lower-alkoxy group. The hydrolysis of such a compound is conveniently carried out by dissolving same in 32 per cent hydrogen bromide in acetic acid, whereby the desired product of formula I is obtained by storing the mixture overnight at room temperature.

According to a further embodiment of the process, the replacement is effected by reacting a compound of the formula



IIc

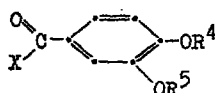
(wherein R^2 , R^3 , R^4 and R^5 have the significance given earlier and X stands for a halogen atom) with an amine of the formula



III

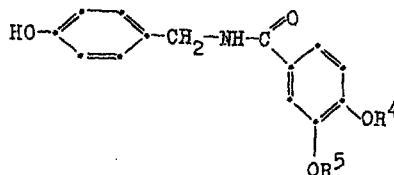
wherein R^1 has the significance given earlier. The reaction of a compound of formula IIc (i.e. a compound of formula II in which Z represents a halogen atom) with a primary amine R^1-NH_2 is preferably carried out in methanol containing a trace of sodium iodide at a temperature of about 100° C.

The compounds of formula IIa hereinbefore can be prepared by reacting 4-hydroxy-benzyl amine with a dialkoxy-substituted benzoyl halide of the formula



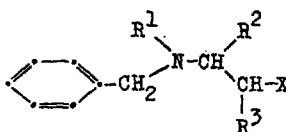
IV

(wherein R^4 , R^5 and X have the significance given earlier) and etherifying the resulting compound of the formula



V

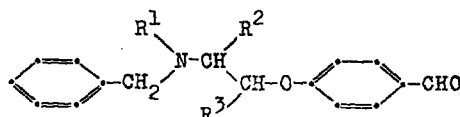
(wherein R^4 and R^5 have the significance given earlier) with a halide of the formula



VI

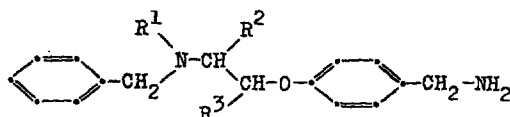
wherein R^1 , R^2 , R^3 and X have the significance given earlier. The reaction of the 4-hydroxy-benzyl amine with a dialkoxy-substituted benzoyl halide of formula IV to give the correspondingly substituted N-(4-hydroxy-benzyl)-benzamide of formula V is carried out under conditions which are commonly employed in SCHOTTEN-BAUMANN reactions; that is by the simultaneous addition of the dialkoxy-substituted benzoyl halide and aqueous alkali to a vigorously stirred mixture of a solvent (e.g. ethylene chloride and water) containing the 4-hydroxy-benzyl amine so as to maintain slightly alkaline reaction conditions. The compound of formula V is then etherified with an N-benzyl-N-(lower alkyl)aminoalkyl halide of formula VI or a mixture of halides of formula VI in which R^2 represents a lower-alkyl group in one halide component of the mixture and R^3 represents a lower-alkyl group in the other halide component of the mixture to form a compound of formula IIa or a mixture of compounds of formula IIa. This etherification is carried out under the following conditions: The compound of formula V is converted into its alkali-metal salt (preferably the sodium salt) by reaction with an alkali-metal lower-alkoxide. The alkali-metal salt is then reacted with the halide of formula VI in a non-polar organic solvent (e.g. a hydrocarbon solvent, a halogenated hydrocarbon solvent or the like).

The compounds of formula IIa hereinbefore can also be prepared by reacting 4-hydroxy-benzaldehyde with a halide of formula VI hereinbefore, condensing the resulting N,N-disubstituted-aminoalkoxy-benzaldehyde of the formula



VII

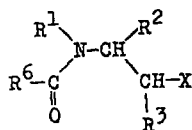
(wherein R^1 , R^2 and R^3 have the significance given earlier) with ammonia in the presence of hydrogen and a hydrogenation catalyst and reacting the resulting benzyl amine of the formula



VIII

(wherein R^1 , R^2 and R^3 have the significance given earlier) with a dialkoxy-substituted benzoyl halide of formula IV hereinbefore. Thus, 4-hydroxy-benzaldehyde is reacted with an N-benzyl-N-(lower alkyl)-aminoalkylhalide of formula VI to form an N-benzyl-N-(lower alkyl)aminoalkoxy-benzaldehyde of formula VII. The latter substituted-benzaldehyde is then reductively condensed with ammonia in a lower-alkanol (preferably ethanol) in the presence of hydrogen and a hydrogenation catalyst such as a noble-metal catalyst (e.g. platinum, palladium, etc. or nickel) to give the corresponding benzyl amine of formula VIII. The benzyl amine of formula VIII is then reacted with a dialkoxy-substituted benzoyl halide of formula IV to give the compound of formula IIa. It will be understood that where halides of formula VI are employed in which R^2 represents a hydrogen atom and R^3 represents a lower-alkyl group or in which R^2 represents a lower-alkyl group and R^3 represents a hydrogen atom mixtures of compounds VIII, IIa and I will be obtained by subsequent steps of the process.

The compounds of formula IIb hereinbefore can be prepared by reacting a compound of formula V with a halo-amide of the formula

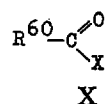


IX

wherein R^1 , R^2 , R^3 , R^6 and X have the significance given earlier. The preferred process

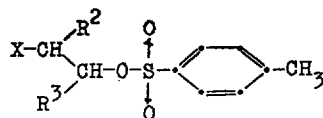
for the preparation of compounds of formula IIb is similar to that described for the preferred etherification process hereinbefore, namely by reacting the sodium salt of the compound of formula V with a halo-amide of formula IX in chloro-benzene under reflux. Also, when the halo-amide of formula IX is a chloro-amide, a trace of sodium iodide is preferably added to the reaction mixture.

The compounds of formula IIb hereinbefore in which R⁶ represents a lower-alkoxy group can also be prepared by reacting a compound of formula IIa with an alkyl haloformate of the formula



wherein R⁶ represents a lower-alkoxy group and X has the significance given earlier. The preferred procedure for reacting the compound of formula IIa with an alkyl haloformate of formula X comprises dissolving the compound of formula IIa in benzene under reflux and adding thereto ethyl chloroformate.

The compounds of formula IIc hereinbefore can be prepared by reacting a compound of formula V with a haloalkyl *para*-toluenesulphonate of the formula



XI

wherein R², R³ and X have the significance given earlier. The reaction of the compound of formula V with the toluenesulphonate of formula XI is preferably carried out according to the preferred procedure described hereinbefore in connection with the etherification of a compound of formula V.

The compounds of formula IIc in which R² and R³ each represent a hydrogen atom can also be prepared by reacting a compound of formula V with an ethylene dihalide such as ethylene dibromide, dichloride or diiodide. The reaction is preferably carried out by adding the dihalide to a solution of the potassium salt of the compound of formula V in methanol under reflux.

The dialkoxy-substituted benzoyl halides of formula IV hereinbefore can be produced by treating the corresponding acid with a 5-fold excess of thionyl chloride in benzene under reflux. Removal of the excess thionyl chloride by distillation leaves, as the residue, the desired chlorides of formula IV of sufficient purity to be used directly. The dialkoxy-substituted benzoic acids are either obtained by oxidation of the corresponding dialkoxy-substituted benzaldehydes or by etherification of the appropriate dihydroxy-benzoic acids.

The halides of formula VI hereinbefore can be produced by reacting thionyl chloride with the appropriate (N-benzyl-N-alkyl-amino)-alkanol. The latter are obtained by reacting a benzyl alkyl amine with an alkylene oxide or reductively condensing benzaldehyde with an alkylamino-alkanol or alkylating a benzylamino-alkanol.

The halo-amides of formula IX hereinbefore can be produced by reacting an acyl halide with an N-(2-halo-alkyl)alkyl amine hydrochloride. The latter is obtained from the corresponding alkylamino-alkanol and thionyl chloride. Alternatively, the appropriate alkylamino-alkanol is reacted with formamide to give the (N-formyl-N-methyl-amino)-alkanol which upon reaction with thionyl chloride gives an amide of formula IX in which R⁶ represents a hydrogen atom.

The compounds of formula IIa are novel and it will be appreciated that they also form part of the present invention.

The following Examples illustrate the invention.

EXAMPLE 1.

A) The preparation of the starting material:

100 ml of chloro-benzene are added to 46.2 g (0.2 mol) of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane hydrochloride dissolved in 50 ml of water. 75 ml of 50 per cent sodium hydroxide are added to the vigorously stirred mixture while the tem-

perature is maintained at 4° C. The upper layer of chloro-benzene extract is quickly decanted from the residual highly alkaline viscous aqueous phase. The latter is re-extracted with two 100 ml portions of chloro-benzene. The chloro-benzene extracts are combined and rapidly dried over anhydrous potassium carbonate, filtered, and stored at 4° C. until ready for use.

48 ml of a 25 per cent solution (by weight) of sodium methoxide in methanol (equivalent to 0.21 mol of sodium methoxide) are added, all at once, to a stirred suspension of 24.4 g (0.2 mol) of 4-hydroxy-benzaldehyde (practical) in 200 ml of chloro-benzene. The mixture becomes slightly warm and momentary solution occurs; it then changes to a pink coloured suspension. The mixture is stirred and heated at reflux for 2 hours, after which time the methanol is slowly distilled off until the vapour temperature is constant (about 165 ml of distillate is collected). A solution of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane in chloro-benzene (prepared as described in the preceding paragraph) is added portionwise over 0.75 hour to the stirred and refluxing yellow coloured suspension. After the addition is completed, the reaction mixture is stirred and heated at reflux for 20 hours and then cooled. The precipitate which forms is filtered off. The yellow coloured filtrate is washed with four 50 ml portions of water, dried over anhydrous sodium sulphate, filtered, and concentrated at water vacuum and steam temperature to give 51 g of an orange coloured oil. This is fractionally distilled in high vacuum to give 40.8 g of 4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzaldehyde.

350 ml of 13 per cent ammonia (2.7 mol) in ethanol are added to 179 g (0.67 mol) of 4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzaldehyde dissolved in 200 ml of ethanol. The yellow coloured solution is stored overnight at 4° C. and then hydrogenated at 100° C. and 400 pounds per square inch using 6 teaspoons of RANEY-nickel. The catalyst is filtered off and the volatile components distilled off at water vacuum and steam temperature to give 175 g of a yellow coloured residual oil. This oil is dissolved in 900 ml of anhydrous ether and at 4° C. is treated with carbon dioxide until no further precipitation occurs. The white amorphous precipitate which forms is filtered off, washed with petroleum ether (boiling range = 30° - 60° C.) and dried *in vacuo* to give 156 g of 4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl amine carbonate complex.

40 ml (65.5 g, 0.55 mol) of thionyl chloride are added over 0.5 hour to a stirred suspension of 10.7 g (0.059 mol) of veratric acid (previously dried overnight *in vacuo* at 60° C.) in 75 ml of dry benzene which is being heated at reflux. The mixture is stirred and heated at reflux for an additional 2 hours and the resulting solution taken to dryness with a water vacuum pump at steam temperature. The solid residue is dissolved in 75 ml of dry benzene and the volatile components distilled off. This benzene treatment is repeated. A solution of 18 g (0.057 mol) of 4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl amine carbonate complex is added over 0.5 hour to a stirred and refluxing solution of the resulting solid in 100 ml of acetonitrile, to give N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-dimethoxy-benzamide which melts at 89°-91° C. (after recrystallization from benzene/petroleum ether).

B. The process:

22 ml of 1-N hydrochloric acid are added to 9.55 g (0.022 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-dimethoxy-benzamide suspended in 200 ml of water. The resulting pale yellow solution is lyophilised, the residue dissolved in 150 ml of ethanol and hydrogenated at 25° C. and 100 pounds per square inch above theory using 2 g of 10 per cent palladium-on-carbon. The catalyst is filtered off, the filtrate concentrated *in vacuo* and the residue crystallized from ethanol to give 7.5 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-dimethoxy-benzamide hydrochloride of melting point 183°-185° C.

EXAMPLE 2.

A) The preparation of the starting material:

25 ml of thionyl chloride are added over 0.5 hour to a stirred and refluxing solution of 16.5 g (0.084 mol) of 4-ethoxy-3-methoxy-benzoic acid (previously dried over phosphorus pentoxide) in 400 ml of dry benzene. After stirring and heating at reflux for an additional 2 hours, the resulting solution is taken to dryness using a water vacuum and steam temperature. The residue is dissolved in 100 ml of dry benzene and the volatile components are distilled off. This benzene treatment is repeated. The residue crude 4-ethoxy-3-methoxy benzyl chloride is dissolved in 200 ml of methylene

chloride and the solution stored in a nitrogen atmosphere until ready for use.

100 ml of methylene chloride are added to 12.7 g (0.08 mol) of 4-hydroxy-benzyl amine hydrochloride dissolved in 50 ml of water. To the vigorously stirred mixture at 4° C., which is blanketed with nitrogen and adjusted to pH 7.5—8 with 15 per cent sodium hydroxide, there is added over 1.5 hour the solution of 4-ethoxy-3-methoxy-benzoyl chloride whose preparation is described in the preceding paragraph. Simultaneous addition of 15 per cent sodium hydroxide is made as needed, in order to maintain the pH at 7.5—8. A precipitate forms. The resulting mixture is stirred at 4° C. for an additional hour and then 3-N hydrochloric acid is added to adjust the pH to 5—6. The resulting crystals are filtered off, washed with water and recrystallized from acetone/water to give 18.1 g of N-(4-hydroxy-benzyl)-4-ethoxy-3-methoxy-benzamide of melting point 157°—158° C.

31.5 g (0.099 mol) of N-(4-hydroxy-benzyl)-4-ethoxy-3-methoxy-benzamide in 500 ml of chloro-benzene and 25.8 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.011 mol of sodium methoxide) are treated with a 600 ml chloro-benzene solution of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane [derived from 33.2 g (0.143 mol) of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane hydrochloride] to give 29 g of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-4-ethoxy-3-methoxy-benzamide which melts at 82°—84° C. after recrystallization from acetone/ether/(petroleum ether).

B) *The process:*

5.6 g (0.0125 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-4-ethoxy-3-methoxy-benzamide are converted into the hydrochloride using ethanolic hydrogen chloride and reduced in ethanol with 1 g of 10 per cent palladium-on-carbon, to give 2.5 g of N-[4-(2-methylamino-ethoxy)-benzyl]-4-ethoxy-3-methoxy-benzamide hydrochloride which melts at 171°—173° C. after recrystallisation from acetonitrile/ether.

EXAMPLE 3.

A) *The preparation of the starting material:*

15 g (0.072 mol) of 3-methoxy-4-propoxy-benzoic acid are treated with 21 ml of thionyl chloride according to the process of Example 1A to form 3-methoxy-4-propoxy-benzoyl chloride. The latter compound is then reacted with 10.5 g (0.066 mol) of 4-hydroxy-benzyl amine hydrochloride according to the method of Example 2 to give 14.3 g of N-(4-hydroxy-benzyl)-3-methoxy-4-propoxy-benzamide which melts at 174°—175° C. after recrystallization from acetone/water.

22 g (0.07 mol) of N-(4-hydroxy-benzyl)-3-methoxy-4-propoxy-benzamide in 500 ml of chloro-benzene and 17.2 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.075 mol of sodium methoxide) are treated with a 300 ml chloro-benzene solution of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane [derived from 22.2 g (0.096 mol) of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane hydrochloride] to give 21 g of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3-methoxy-4-propoxy-benzamide (melting point = 68°—70° C. after recrystallization from acetonitrile) according to Example 2A.

B) *The process:*

13 g (0.028 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3-methoxy-4-propoxy-benzamide are converted into the hydrochloride addition salt using ethanolic hydrogen chloride and reduced in ethanol with 3 g of 10 per cent palladium-on-carbon according to the method of Example 1B to give 8.6 g of N-[4-(2-methyl-amino-ethoxy)-benzyl]-3-methoxy-4-propoxy-benzamide hydrochloride which melts at 180°—182° C. after recrystallization from water/ethanol/ether.

EXAMPLE 4.

A) *The preparation of the starting material:*

96 ml (157 g, 132 mol) of thionyl chloride are added over 1.75 hours to a stirred and refluxing solution of 70 g (0.33 mol) of 3,4-diethoxy-benzoic acid (previously dried overnight at 60° C. *in vacuo*) in 500 ml of dry benzene. After stirring and heating at reflux for an additional 2 hours the volatile components are distilled off at water vacuum and steam temperature. The residual brown coloured oil is dissolved in 250 ml of dry benzene and the volatile components are once again distilled off. This benzene treatment is repeated once again to give a residual tan coloured solid containing a trace of oil. This crude 3,4-diethoxy-benzoyl chloride is dissolved in 400 ml of

methylene chloride and the solution stored in a nitrogen atmosphere at room temperature until used.

500 ml of methylene chloride are added to 49.5 g (0.31 mol) of 4-hydroxy-benzylamine hydrochloride dissolved in 250 ml of water. To the vigorously stirred mixture at 4° C., blanketed with nitrogen and adjusted to pH 7.5—8.0 with *ca* 90 ml of 15 per cent sodium hydroxide, there is added the above solution of 3,4-diethoxy-benzoyl chloride over 4 hour period. Simultaneous addition of 15 per cent sodium hydroxide is made as required in order to maintain a pH of 7.5—8.0. Crystals form during the reaction. The resulting viscous mixture is stirred for an additional hour at 4° C. and then 3-*N* hydrochloric acid is added to adjust the pH to 5—6. The tan coloured crystals are filtered off, washed with water and dried at 60° C. *in vacuo* to give 98 g of N-(4-hydroxy-benzyl)-3,4-diethoxy-benzamide, melting point 182°—185° C.

After recrystallization from acetone/ether, the melting point is 183°—185° C. To a stirred suspension of 60 g (0.19 mol) of N-(4-hydroxy-benzyl)-3,4-diethoxy-benzamide in 1500 ml of chloro-benzene there are added 45 ml of a 25 per cent solution (by weight) of sodium methoxide in methanol (equivalent to 0.20 mol of sodium methoxide). The suspension is stirred and heated at reflux for 2 hours. The methanol is slowly distilled off until the vapour temperature is constant (about 135 ml of distillate are collected). A solution of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane in chloro-benzene [prepared from 55 g (0.25 mol) of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane hydrochloride according to the procedure of Example 1A] is added over 2 hours to the residual coloured suspension while stirring and heating at reflux. After the addition is completed, the reaction mixture is stirred and heated at reflux for 20 hours, cooled and filtered. 300 ml of water are added to the filtrate and the pH is adjusted to 12 with 15 per cent sodium hydroxide. The lower chloro-benzene layer is separated off, washed with four 300 ml portions of water, dried over anhydrous sodium sulphate, filtered and concentrated at water vacuum and steam temperature. The residue, consisting of white solids and brown coloured oil, is crystallized from a mixture of 175 ml of benzene, 275 ml of ether and 1350 ml of petroleum ether (boiling range = 30°—60° C.) to give 74.2 g of off-white N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide of melting point 102°—104° C.

An aliquot, when treated with oxalic acid in acetone, gives N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide oxalate hemihydrate which melts at 137°—139° C. after recrystallization from 95 per cent acetonitrile/ether.

N - [4 - [2 - (N - benzyl - N - methyl - amino) - ethoxy] - benzyl] - 3,4-diethoxy-benzamide is also prepared in the following manner:

11 g (0.052 mol) of 3,4-diethoxy-benzoic acid are converted to the acid chloride and treated with 15.7 g (0.05 mol) of 4[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl amine carbonate complex (prepared as described in Example 1A) to give 17.6 g of N - [4 - [2 - (N - benzyl - N - methyl - amino) - ethoxy] - benzyl] - 3,4-diethoxy-benzamide which melts at 102°—104° C. after recrystallization from benzene/ether/(petroleum ether).

B) The process:

About 50 ml of 20 per cent hydrogen chloride in ethanol are added to 88 g (0.19 mol) of N - [4 - [2 - (N - benzyl - N - methyl - amino) - ethoxy] - benzyl] - 3,4-diethoxy-benzamide dissolved in 200 ml of ethanol until the pH is 2. The solution is immediately taken to dryness at water vacuum and steam temperature, the semi-solid residue dissolved in 150 ml of ethanol and the volatile components are distilled off. The residue is dissolved in 600 ml of ethanol and hydrogenated at 25° C. and 100 pounds per square inch above theory using 20 g of 10 per cent palladium-on-carbon. The catalyst is filtered off and washed with water to dissolve away the crystals that have deposited. The filtrate and washings are combined and the volatile components distilled off. The residue which is initially obtained as an oil crystallizes on standing. It is recrystallized from a mixture of acetonitrile and ether or water, ethanol and ether to give 64 g of white crystals of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride; melting point 171°—173° C., with sintering at 120° C. An aliquot of the hydrochloride, when dissolved in water and rendered alkaline with ammonium hydroxide, gives a crystalline precipitate. This is filtered off, washed with water, air-dried, and recrystallized from ethanol/water to give N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide of melting point 119°—121° C.

N - [4 - (2 - methylamino - ethoxy) - benzyl] - 3,4 - diethoxy - benzamide

hydrochloride can also be obtained from N-[4-(2-(N-benzyl-N-methyl-amino)-ethoxy)-benzyl]-3,4-diethoxy-benzamide as follows:

A mixture of 4.6 g (0.01 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide and 1.1 ml (0.011 mol) of freshly distilled ethyl chloroformate in 20 ml of dry benzene is heated at reflux for 18 hours. The resulting solution is washed with cold 1-N hydrochloric acid and then with water, and the volatile components distilled off *in vacuo*. The residue is crystallized from benzene/ether/(petroleum ether) to give 3.9 g of N-methyl-N-[2-[4-(3,4-diethoxy-benzamido-methyl)-phenoxy]-ethyl]-carbamic acid ethyl ester of melting point 121°—122° C.

A solution of 2.2 g (0.005 mol) of N-methyl-N-[2-[4-(3,4-diethoxy-benzamido-methyl)-phenoxy]-ethyl]-carbamic acid ethyl ester in 20 ml of 32 per cent hydrobromic acid in acetic acid is stored overnight at 25° C., then rendered alkaline with 10 per cent sodium hydroxide and extracted with ethyl acetate. The highly coloured extract is washed with water and extracted with 3-N hydrochloric acid. The pale yellow coloured acidic aqueous extract is adjusted to pH 10 with concentrated ammonium hydroxide and the crystalline precipitate which forms is filtered off, washed with water and air-dried to give 0.5 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide of melting point 118°—120° C.

EXAMPLE 5.

A) *The preparation of the starting material:*

15.8 g (0.05 mol) of N-(4-hydroxy-benzyl)-3,4-diethoxy-benzamide in 500 ml of chloro-benzene and 11.7 ml of a 25 per cent solution (by weight) of sodium methoxide in methanol (equivalent to 0.051 mol of sodium methoxide) are reacted according to the procedure of Example 4 with 11.7 g (0.05 mol) of 2-chloro-ethyl *paratoluene*-sulphonate to give 11.7 g of N-[4-(2-chloro-ethoxy)-benzyl]-3,4-diethoxy-benzamide which melts at 126°—128° C. after recrystallization from acetone/ether.

B) *The Process:*

150 mg (0.001 mol) of sodium iodide and 13.5 ml of 12 per cent methyl amine in methanol are added to 3.8 g (0.01 mol) of N-[4-(2-chloro-ethoxy)-benzyl]-3,4-diethoxy-benzamide dissolved in 20 ml of methanol. The solution is heated at 100° C. for 8 hours, the volatile components are distilled off and the orange-brown coloured oil is crystallized from ethyl acetate to give 2.0 g of unchanged N-[4-(2-chloro-ethoxy)-benzyl]-3,4-diethoxy-benzamide. The yellow coloured ethyl acetate filtrate is extracted with 1-N hydrochloric acid. The aqueous extract is adjusted to pH 10 with ammonium hydroxide and the crystals which form are filtered off and air-dried to give 1.4 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide of melting point 117°—120° C. A mixed melting point with N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide obtained via the benzyl intermediate (obtained according to part B of Example 4) gives no depression.

EXAMPLE 6.

A) *The preparation of the starting material:*

5.9 g (0.019 mol) of N-(4-hydroxy-benzyl)-3,4-diethoxy-benzamide in 150 ml of chloro-benzene and 4.5 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.019 mol of sodium methoxide) is treated according to the procedure of Example 2 A) with 2.7 g (0.02 mol) of N-(2-chloro-ethyl)-N-methyl-acetamide to give 5.0 g of N-[4-[2-(N-methyl-acetamido)-ethoxy]-benzyl]-3,4-diethoxy-benzamide of melting point 143°—145° C.

B) *The Process:*

1 ml of 48 per cent hydrobromic acid is added to a solution of 0.4 g (1 millimol) of N-[4-[2-(N-methyl-acetamido)-ethoxy]-benzyl]-3,4-diethoxy-benzamide in 5 ml of ethanol. The solution is heated at reflux for 24 hours, the volatile components are distilled off *in vacuo* and the residue is distributed between dilute sodium carbonate and ethyl acetate. The ethyl acetate extract is washed with water and then extracted with 3-N hydrochloric acid. The acidic aqueous layer is rendered alkaline to give 0.16 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide of melting point 117°—119° C.

EXAMPLE 7.

A) *The preparation of the starting material:*

24.4 g (0.2 mol) of 4-hydroxy-benzaldehyde in 200 ml of chloro-benzene and 48 ml of a 25 per cent solution (by weight) of sodium methoxide in methanol (equiva-

lent to 0.21 mol of sodium methoxide) are reacted with 47 g (0.2 mol) of 1-chloro-2-benzylethylamino-ethane hydrochloride according to the procedure of Example 2 A) to give 33.3 g of 4-[2-(N-benzyl-N-ethyl-amino)-ethoxy]-benzaldehyde as an orange coloured oil of boiling point 163°—167° C./0.1 mm, n_D^{21} —1.5721.

35 ml of 13 per cent ammonia (ca 0.25 mol) in ethanol are added to 14.2 g (0.05 mol) of 4-[2-(N-benzyl-N-ethyl-amino)-ethoxy]-benzaldehyde dissolved in 100 ml of ethanol. The yellow coloured solution is stored at 4° C. overnight and then hydrogenated at 100° C. and 400 pounds per square inch using 1 teaspoon of RANEY-nickel. When the hydrogen uptake ceases, the catalyst is filtered off and the volatile components are distilled off at water vacuum and steam temperature. The residual oil is dissolved in 150 ml of anhydrous ether and is saturated at 4° C. with carbon dioxide. The white amorphous precipitate which forms is filtered off, washed with petroleum ether (boiling range = 30°—60° C.) and dissolved in 150 ml of acetonitrile.

11 g (0.052 mol) of 3,4-diethoxy-benzoic acid is converted to the acid chloride according to the procedure of Example 1 A) and treated with the solution of 4-(2-benzylethylaminoethoxy)benzylamine carbonate complex in acetonitrile prepared as described in the preceding paragraph to give 18 g of N-[4-[2-(N-benzyl-N-ethyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide which melts at 96°—98° C. after recrystallization from (ethyl acetate)/ether/(petroleum ether).

B) The Process:

14 g (0.029 mol) of N-[4-[2-(N-benzyl-N-ethyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide are converted to the hydrochloride addition salt using ethanolic hydrogen chloride and this is reduced in ethanol with 3 g of 10 per cent palladium-on-carbon (according to the procedure of Example 1 B) to give 11.6 g of N-[4-(2-ethylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride of melting point 162°—163° C.

EXAMPLE 8.

A) The preparation of the starting material:

30.4 g (0.2 mol) of isovanillin are added to 12.8 g (0.2 mol) of potassium hydroxide (86.5 per cent pure) dissolved in 400 ml of ethanol. While stirring and heating at reflux, 32.0 g (0.2 mol) of propyl bromide are added over 2 hours to the resulting solution. After the addition is completed, the mixture is stirred and heated at reflux for 14 hours, the volatile components are distilled off and the residue is distributed between ether and water. The ether extract is separated off, washed with 5 per cent potassium hydroxide and then with water, dried over anhydrous sodium sulphate and filtered. The filtrate is concentrated to a small volume and stored overnight at 4° C. The crystals that form are filtered off and air-dried to give 31 g of 4-methoxy-3-propoxy-benzaldehyde of melting point 50°—52° C.

A solution of 34 g of potassium permanganate in 550 ml of water is added over 1.5 hours to a vigorously stirred suspension of 23.2 g (0.12 mol) of 4-methoxy-3-propoxy-benzaldehyde in 350 ml of water maintained at 90° C. After the addition is completed, the mixture is stirred and heated under reflux for 1.25 hours and cooled. 15 per cent potassium hydroxide is added until the pH is 10. The dark brown solids are filtered off and concentrated hydrochloric acid is added to the filtrate until the pH is 2. The crystalline precipitate which forms is filtered off and recrystallized from methanol/water to give 21.5 g of 4-methoxy-3-propoxy-benzoic acid of melting point 154°—156° C.

19.5 g (0.093 mol) of 4-methoxy-3-propoxy-benzoic acid are treated with thionyl chloride according to the procedure of Example 2 A) to form the acid chloride. This is reacted with 13.7 g (0.086 mol) of 4-hydroxy-benzylamine hydrochloride to give 19.8 g of N-(4-hydroxy-benzyl)-4-methoxy-3-propoxy-benzamide which melts at 170°—172° C. after recrystallization from ethanol/water.

22 g (0.07 mol) of N-(4-hydroxy-benzyl)-4-methoxy-3-propoxy-benzamide in 500 ml of chloro-benzene and 17.2 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.075 mol of sodium methoxide) when treated with a 250 ml of chloro-benzene solution of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane [derived from 22.2 g (0.096 mol) of 1-chloro-2-(N-benzyl-N-methyl-amino)-ethane hydrochloride according to the procedure of Example 2 A] gives 17.5 g of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-4-methoxy-3-propoxy-benzamide which melts at 124°—125° C. after recrystallization from acetone/ether.

B) *The process:*

12.5 g (0.027 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-4-methoxy-3-propoxy-benzamide are converted to the hydrochloride using ethanolic hydrogen chloride and the hydrochloride is reduced in ethanol with 3 g of 10 per cent palladium-on-carbon according to the procedure of Example 2B to give 10 g of N-[4-(2-methylaminoethoxy)-benzyl]-4-methoxy-3-propoxy-benzamide hydrochloride which melts at 158°—160° C. after recrystallization from acetonitrile.

EXAMPLE 9.

A) *The preparation of the starting material:*

20 g (0.084 mol) of 3,4-dipropoxy-benzoic acid are converted to the acid chloride using thionyl chloride according to the procedure of Example 1A and the acid chloride is treated with 25 g (0.08 mol) of 4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl amine carbonate complex (according to the procedure of Example 1A) to give 24 g of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-dipropoxy-benzamide which melts at 85°—88° C. after recrystallization from benzene/(petroleum ether).

B) *The process:*

15.2 g (0.031 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-ethoxy]-benzyl]-3,4-dipropoxy-benzamide (as the hydrochloride) are reduced with hydrogen using palladium-on-carbon catalyst according to the procedure of Example 1 B) to give 11.2 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-dipropoxy-benzamide hydrochloride which melts at 189°—190° C. after recrystallization from ethanol/acetone.

EXAMPLE 10.

A) *The preparation of the starting material:*

31.5 g (0.1 mol) of 3,4-diethoxy-N-(4-hydroxy-benzyl)-benzamide in 800 ml of chloro-benzene and 24 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.105 mol of sodium methoxide) are treated with 28.5 g (0.125 mol) of N-(2-chloro-ethyl)-N-butyl-benzyl amine according to the procedure of Example 4 (1)A to give 19.6 g of N-[4-[2-(N-benzyl-N-butyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide which melts at 60°—62° C. after recrystallization from ether/(petroleum ether).

B) *The process*

16.1 g (0.032 mol) of N-[4-[2-(N-benzyl-N-butyl-amino)-ethoxy]-benzyl]-3,4-diethoxy-benzamide (as the hydrochloride) are reduced with hydrogen using palladium-on-carbon catalyst according to the procedure of Example 1B) to give 12.1 g of N-[4-(2-butylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride which melts at 197°—198° C. after recrystallization from acetonitrile/(ethyl acetate).

EXAMPLE 11.

A) *The preparation of the starting material:*

15 g (0.05 mol) of N-(4-hydroxy-benzyl)-3-methoxy-4-ethoxy-benzamide in 350 ml of chloro-benzene and 14.4 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.053 mol of sodium methoxide) is treated with a 250 ml chloro-benzene solution of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane derived from 15.9 g (0.068 mol) of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane hydrochloride according to the procedure of Example 2 A to give 11.3 g of an oil.

B) *The process:*

The oily product of part A of this Example, as the hydrochloride salt, is reduced with hydrogen according to the procedure given in Example 1B using palladium-on-carbon catalyst. The hydrogenation product is rendered alkaline and extracted into ether. The ether extract is washed with water, dried over sodium sulphate, filtered and the filtrate taken to dryness. The residual oil is dissolved in ether and added to a solution of 12 g of anhydrous oxalic acid in 400 ml of ether. The precipitate that forms is filtered off, washed with ether and crystallized from methanol/acetonitrile/ether to give N-[4-(2-methylamino-1(and 2)-methyl-ethoxy)-benzyl]-4-ethoxy-3-methoxy-benzamide oxalate hemihydrate; melting point = 116°—118° C., with sintering at 112° C.

EXAMPLE 12.

A) *The preparation of the starting material:*

18.5 g (0.059 mol) of N-(4-hydroxy-benzyl)-4-methoxy-3-propoxy-benzamide in 300 ml of chloro-benzene and 14.2 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.062 mol of sodium methoxide) are treated with a 400 ml chloro-benzene solution of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane derived from 18.3 g (0.078 mol) of 1-benzylmethylamino-2-chloro-propane hydrochloride according to the procedure of Example 4 (1) A to give 20 g of N-[4-[2-(N-benzyl-N-methyl-amino)-1 (and 2)-methyl-ethoxy]-benzyl]-4-methoxy-3-propoxy-benzamide which melts at 63°—65° C. after recrystallization from ether/(petroleum ether).

B) *The process:*

18 g (0.038 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-1 (and 2)-methyl-ethoxy]-benzyl]-4-methoxy-3-propoxy-benzamide (as the hydrochloride) are reduced with hydrogen and palladium-on-carbon according to the procedure of Example 1B to give 13 g of N-[4-(2-methylamino-1 (and 2)-methyl-ethoxy)-benzyl]-4-methoxy-3-propoxy-benzamide hydrochloride which melts at 155°—157° C. after recrystallization from ethanol/ether.

EXAMPLE 13.

(1)

A) *The preparation of the starting material:*

59 g (0.19 mol) of N-(4-hydroxybenzyl)-3,4-diethoxy-benzamide in 1.5 litres of chloro-benzene and 45 ml of a 25 per cent solution of sodium methoxide (by weight) in methanol (equivalent to 0.198 mol of sodium methoxide) are treated with a solution of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane in 1.3 litres of chloro-benzene derived from 58.6 g (0.25 mol) of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane hydrochloride according to the procedure of Example 4(1) A to give 79.4 g of N-[4-[2-(N-benzyl-N-methyl-amino)-1 (and 2)-methyl-ethoxy)-benzyl]-3,4-diethoxy-benzamide which melts at 52°—54° C. after recrystallization from ether/(petroleum ether).

B) *The process:*

56.3 g (0.118 mol) of N-[4-[2-(N-benzyl-N-methyl-amino)-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide (as the hydrochloride) are reduced with hydrogen and palladium-on-carbon according to the process of Example 1 B) to give 41.5 g of N-[4-[2-methylamino-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide hydrochloride which melts at 156°—158° C. after recrystallization from acetone/ether. The crystalline free base of N-[4-[2-methylamino-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide hydrochloride is obtained by dissolving said hydrochloride in water and adding ammonium hydroxide until the pH is 10. The crystals that form are filtered off and air-dried to give N-[4-[2-methylamino-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide which melts at 104°—106° C. after recrystallization from acetone/ether.

2 g of N-[4-(2-methylamino-1 (and 2)-methyl-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride are recrystallized from 5 ml of isopropanol and the crystals thus obtained are recrystallized twice more from isopropanol to give 0.5 g of N-[4-(2-methylamino-2-methyl-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride of melting point 165°—167° C. The crystalline free base, obtained as described in the preceding paragraph melts at 120°—122° C. after recrystallization from (ethyl acetate)/ether/(petroleum ether).

EXAMPLE 14.

A) *The preparation of the starting material:*

65.5 g (0.55 mol) of 4-hydroxy-benzaldehyde in 600 ml of chloro-benzene and 131 ml of a 25 per cent solution (by weight) of sodium methoxide in methanol (equivalent to 0.58 mol of sodium methoxide) are reacted with a solution of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane in 1.5 litres of chloro-benzene derived from 160 g (0.68 mol) of 1-(N-benzyl-N-methyl-amino)-2-chloro-propane hydrochloride according to the process of Example 1 A to give 115.5 g of 4-[2-(N-benzyl-N-methyl-amino)-1 (and 2)-methyl-ethoxy]-benzaldehyde as a colourless oil of boiling point 66° C./0.1 mm, $n_D^{20} = 1.5731$. To this oil dissolved in 600 ml of ethanol there are

added 270 ml of 13 per cent ammonia (ca 1.95 mol) in ethanol. The solution is stored overnight at 4° C. and then hydrogenated at 60° C. and 1000 pounds per square inch using 4 teaspoons of RANEY-nickel. The catalyst is filtered off and the volatile components are distilled off under water vacuum and at steam temperature. The red coloured residual oil is dissolved in 300 ml of anhydrous ether and is treated at 4° C. with carbon dioxide until no further precipitation occurs. The white amorphous precipitate is filtered off, washed with ether, dissolved in ethanol, and alcoholic hydrogen chloride is added until the pH is 2. The solution is taken to dryness and the residue crystallized from ethanol/(ethyl acetate) to give 60 g of 4-[2-(N-benzyl-N-methyl-amino)-1-methyl-ethoxy]-benzyl amine dihydrochloride of melting point 235°—236° C.

15 per cent sodium hydroxide is added to 10.7 g (0.03 mol) of 4-[2-(N-benzyl-N-methyl-amino)-1-methyl-ethoxy]-benzyl amine dihydrochloride dissolved in 50 ml of water until the pH is 12. The oil which forms is extracted into ether. The ether extract is washed with water, dried over anhydrous sodium sulphate and the volatile components are distilled off. The residual oil is treated according to the procedure of Example 1 B with 3,4-diethoxy-benzoyl chloride (derived from 7.4 g of 3,4-diethoxy-benzoic acid) in 150 ml of acetonitrile to give 12 g of N-[4-[2-(N-benzyl-N-methyl-amino)-1-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide which melts at 89°—90° C. after recrystallization from ether (petroleum ether).

B) The process:

Hydrogenation of N - [4 - [2 - (N - benzyl - N - methyl - amino) - 1 - methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide (as the hydrochloride) using palladium-on-carbon catalyst gives N - [4 - (2 - methylamino - 1 - methyl - ethoxy) - benzyl]-3,4-diethoxy-benzamide hydrochloride which melts at 178°—180° C. after recrystallization from ethanol/ether. The crystalline free base [obtained as described in part (1) B of this Example] melts at 56°—58° C. after recrystallization from (ethyl acetate)/ether/(petroleum ether).

EXAMPLE 15.

A) The preparation of the starting material:

67.5 g (0.5 mol) of benzyl ethyl amine are added to a solution of 29 g (0.5 mol) of propylene oxide in 50 ml of water. The resulting turbid mixture is vigorously stirred for 0.5 hour at 50° C. and then for 20 hours at 25° C. Two layers form. The mixture is fractionally distilled to give 89.3 g of 1-(N-benzyl-N-ethyl-amino)-propanol-(2) as a colourless oil of boiling point 75°—82° C./1.5 mm, $n_D^{26} = 1.5085$.

65.4 g (0.34 mol) of 1-(N-benzyl-N-ethyl-amino)-propanol-(2) in 300 ml of chloroform which has been previously saturated with hydrogen chloride are treated at 4° C. over 1 hour with 32 ml (52.5 g, 0.45 mol) of thionyl chloride. After stirring at 4° C. for an additional 3 hours, the volatile components are distilled off under water vacuum and at steam temperature. The residual oil is crystallized from (ethyl acetate)/ether to give 54 g of 1-(N-benzyl-N-ethyl-amino)-2-chloro-propane hydrochloride of melting point 105°—106° C.

31.5 g (0.1 mol) of N-(4-hydroxy-benzyl)-3,4-diethoxy-benzamide in 600 ml of chlorobenzene and 24 ml of a 25 per cent solution (by weight) of sodium methoxide in methanol (equivalent to 0.105 mol of sodium methoxide) are reacted with 1-(N-benzyl-N-ethyl-amino)-2-chloro-propane obtained from 24.8 g (0.1 mol) of the corresponding hydrochloride by the procedure of Example 4 (1) A to give 33 g of N-[4-[2-(N-benzyl-N-ethyl-amino)-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide which melts at 57°—58° C. after recrystallization from ether/(petroleum ether).

B) The process:

15 g (0.03 mol) of N-[4-[2-(N-benzyl-N-ethyl-amino)-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide (as the hydrochloride) are reduced with hydrogen and palladium-on-carbon according to the procedure of Example 1B to give 10 g of N-[4-[2-ethylamino-1 (and 2)-methyl-ethoxy]-benzyl]-3,4-diethoxy-benzamide hydrochloride which exist in two crystalline forms of melting point 110—113° C. and 145°—147° C. (from acetone/ether or acetonitrile/ether).

The following Example illustrates pharmaceutical preparations containing the novel derivatives provided by the invention:

EXAMPLE 16.

A. *Tablet formulation*

Each table contains 100 mg of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride, 202 mg of lactose, 80 mg of corn starch, 20 mg of AMIJEL B011 and 8 mg of calcium stearate, and has a total weight of 410 mg.

B. *Suppository formulation*

Each suppository contains 210 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride, 30 mg of benzocaine, 96 mg of polyoxyethylene-(20) sorbitan monooleate, 39 mg of white beeswax and 1075 mg of propylene glycol mono-stearate, and has a total weight of 1.45 g.

C. *Parenteral formulation*

Each ml of parenteral formulation contains 25 mg of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride and water for injection q.s. ad 1 ml.

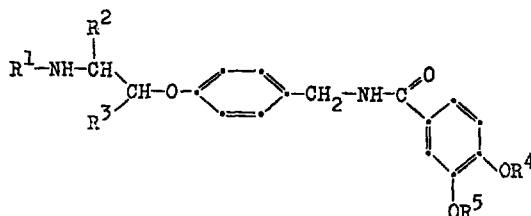
D. *Capsules formulation*

Each capsule contains 100 mg of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride, 200 mg of lactose, 50 mg of corn starch and 10 mg of talc, and has a total net weight of 360 mg.

It will be appreciated that the term 'lower alkyl' is used in the foregoing description and in the claims appended hereto to include straight- and branched-chain alkyl groups containing not more than seven carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, *tert*butyl, hexyl and heptyl). It will similarly be appreciated that the terms 'lower alkoxy' and 'lower carboxy-alkyl' include alkoxy and 'carboxy-alkyl' groups containing not more than seven and eight carbon atoms respectively. The term 'halogen' specifically relates to iodine, bromine or chlorine, with the latter two being preferred.

WHAT WE CLAIM IS:—

1) Compounds of the formula



wherein R^1 , R^4 and R^5 each represent a lower-alkyl group and one of R^2 and R^3 represents a hydrogen atom and the other represents a hydrogen atom or a lower-alkyl group, and acid addition salts thereof.

2) N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide and acid addition salts thereof.

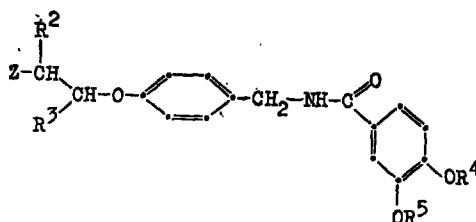
3) N - [4 - (2 - methylamino - 1 - methyl - ethoxy) - benzyl] - 3,4 - diethoxy-benzamide and acid addition salts thereof.

4) N - [4 - (2 - methylamino - 2 - methyl - ethoxy) - benzyl] - 3,4 - diethoxy-benzamide and acid addition salts thereof.

5) A mixture of the derivatives set forth in claims 3 and 4.

6) A pharmaceutical preparation comprising one or more of the derivatives set forth in claim 1 in admixture with a compatible pharmaceutical carrier.

7) A process for the manufacture of the derivatives set forth in claim 1, which process comprises replacing or converting the substituent Z of a compound of the formula





EXAMPLE 16.

A. *Tablet formulation*

Each table contains 100 mg of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride, 202 mg of lactose, 80 mg of corn starch, 20 mg of AMIJEL B011 and 8 mg of calcium stearate, and has a total weight of 410 mg.

B. *Suppository formulation*

Each suppository contains 210 g of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride, 30 mg of benzocaine, 96 mg of polyoxyethylene-(20) sorbitan monooleate, 39 mg of white beeswax and 1075 of propylene glycol mono-stearate, and has a total weight of 1.45 g.

C. *Parenteral formulation*

Each ml of parenteral formulation contains 25 mg of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride and water for injection q.s. ad 1 ml.

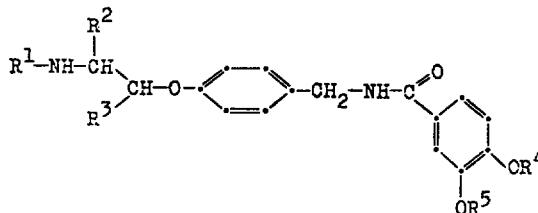
D. *Capsules formulation*

Each capsule contains 100 mg of N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide hydrochloride, 200 mg of lactose, 50 mg of corn starch and 10 mg of talc, and has a total net weight of 360 mg.

It will be appreciated that the term 'lower alkyl' is used in the foregoing description and in the claims appended hereto to include straight- and branched-chain alkyl groups containing not more than seven carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, *tert*butyl, hexyl and heptyl). It will similarly be appreciated that the terms 'lower alkoxy' and 'lower carboxy-alkyl' include alkoxy and 'carboxy-alkyl' groups containing not more than seven and eight carbon atoms respectively. The term 'halogen' specifically relates to iodine, bromine or chlorine, with the latter two being preferred.

WHAT WE CLAIM IS:—

1) Compounds of the formula



wherein R¹, R⁴ and R⁵ each represent a lower-alkyl group and one of R² and R³ represents a hydrogen atom and the other represents a hydrogen atom or a lower-alkyl group, and acid addition salts thereof.

2) N-[4-(2-methylamino-ethoxy)-benzyl]-3,4-diethoxy-benzamide and acid addition salts thereof.

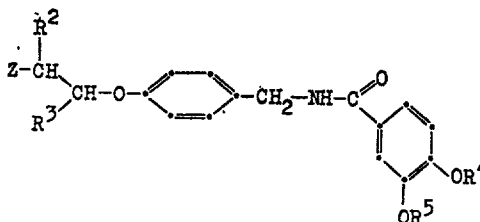
3) N - [4 - (2 - methylamino - 1 - methyl - ethoxy) - benzyl] - 3,4 - diethoxy-benzamide and acid addition salts thereof.

4) N - [4 - (2 - methylamino - 2 - methyl - ethoxy) - benzyl] - 3,4 - diethoxy-benzamide and acid addition salts thereof.

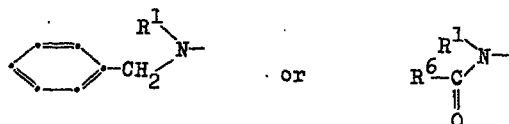
5) A mixture of the derivatives set forth in claims 3 and 4.

6) A pharmaceutical preparation comprising one or more of the derivatives set forth in claim 1 in admixture with a compatible pharmaceutical carrier.

7) A process for the manufacture of the derivatives set forth in claim 1, which process comprises replacing or converting the substituent Z of a compound of the formula



(wherein R^2 , R^3 , R^4 and R^5 have the significance given in claim 1 and Z represents a halogen atom or a protected-amino group of the formula



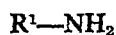
in which R^1 has the significance given in claim 1 and R^6 represents a hydrogen atom or a lower-alkyl, lower-alkoxy or lower carboxy-alkyl group) by or into the group $\text{R}^1\text{—NH—}$ (in which R^1 has the significance given in claim 1) by amination, catalytic debenzoylation or hydrolysis as the case may require and, if desired, transforming the product into an acid addition salt.

8) A process as set forth in claim 7, wherein a starting compound in which Z represents a protected-amino group of the second formula given in that claim is catalytically debenzoylated by hydrogenolysis.

9) A process as set forth in claim 7, wherein a starting compound in which Z represents a protected-amino group of the third formula given in that claim is hydrolysed.

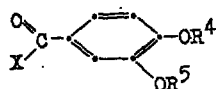
10) A process as set forth in claim 9, wherein a starting compound is used in which Z represents a protected-amino group of the third formula given in claim 7 wherein R^6 represents a lower-alkoxy group.

11) A process as set forth in claim 7, wherein a starting compound in which Z represents a halogen atom is aminated with an amine of the formula

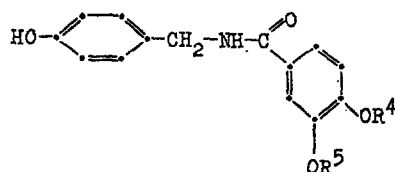


in which R^1 has the significance given in claim 1.

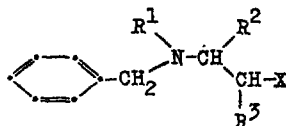
12) A process as set forth in claim 8 which includes the further and initial steps of preparing the starting compound used therein by reacting 4-hydroxy-benzyl amine with a dialkoxy-substituted benzoyl halide of the formula



(wherein R^4 and R^5 have the significance given in claim 1 and X stands for a halogen atom) and etherifying the resulting compound of the formula



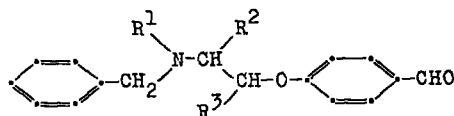
(wherein R^4 and R^5 have the significance given in claim 1) with a halide of the formula



(wherein R^1 , R^2 and R^3 have the significance given in claim 1 and X has the significance given earlier in this claim).

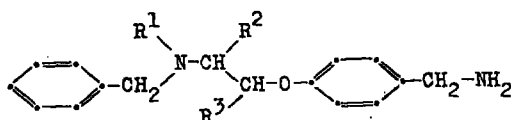
13) A process as set forth in claim 8 which includes the further and initial steps of preparing the starting compound used therein by reacting 4-hydroxy-benzaldehyde with a halide of the third formula given in claim 12, condensing the resulting N,N-disubstituted-aminoalkoxy-benzaldehyde of the formula





(wherein R^1 , R^2 and R^3 have the significance given in claim 1) with ammonia in the presence of hydrogen and a hydrogenation catalyst and reacting the resulting benzyl amine of the formula

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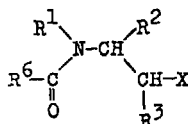
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(wherein R^1 , R^2 and R^3 have the significance given in claim 1) with a dialkoxy-substituted benzoyl halide of the first formula given in claim 12.

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14) A process as set forth in claim 9 which includes the further and initial step of preparing the starting compound used therein by reacting a compound of the second formula given in claim 12 with a halo-amide of the formula

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wherein R^1 , R^2 and R^3 have the significance given in claim 1, R^6 has the significance given in claim 7 and X has the significance given in claim 12.

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15) A process as set forth in claim 10 which includes the further and initial step of preparing the starting material used therein by reacting a compound of the first formula given in claim 2 in which Z represents a protected-amino group of the second formula given therein with an alkyl haloformate of the formula

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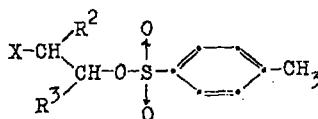


wherein R^{60} represents a lower-alkoxy group and X has the significance given earlier.

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16) A process as set forth in claim 11 which includes the further and initial step of preparing the starting compound used therein by reacting a compound of the second formula given in claim 12 with a haloalkyl *paratoluenesulphonate* of the formula

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(wherein R^2 and R^3 have the significance given in claim 1 and X has the significance given in claim 12).

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17) A process as set forth in claim 11 which includes the further and initial step of preparing the starting compound used therein in which R^2 and R^3 each represent a hydrogen atom by reacting a compound of the second formula given in claim 12 with an ethylene dihalide.

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18) A process for the manufacture of the derivatives set forth in claim 1, substantially as described with reference to Examples 1 to 15.

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19) Compounds of the formula given in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 7 to 18 inclusive.

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20) Compounds of the first formula given in claim 7, wherein Z represents a protected-amino group of the second formula given in that claim.

20) N - [4 - [2 - (N - benzyl - N - methyl - amino) - ethoxy] - benzyl] - 3,4-diethoxy-benzamide.



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