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THERAPEUTIC AGENTS

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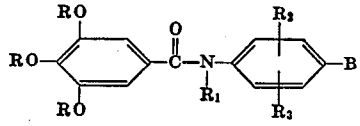
8 Claims. (Cl. 260—247.2)

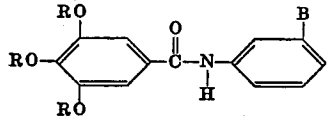
This invention relates to aromatic amides of trialkoxybenzoic acids of therapeutic value, e. g. as nonhypnotic sedatives and clinical tranquilizers, and more particularly to substituted anilides of 3,4,5-trialkoxybenzoic acid.

This application is a continuation-in-part of my prior copending applications Serial No. 679,765, filed August 22, 1957, and now abandoned, and Serial No. 631,390, filed December 31, 1956, and now abandoned. The latter application was, in turn, a continuation-in-part of my prior, copending application Serial No. 569,227, filed March 5, 1956, and now abandoned.

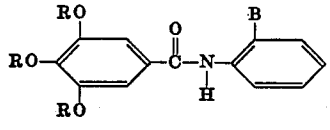
There is provided by the present invention a compound selected from the group consisting of a free base and the nontoxic acid addition salts thereof, said free base having a formula selected from the group consisting of



wherein R represents lower alkyl, R_1 is a member selected from the group consisting of hydrogen, (lower) alkyl, benzyl, phenethyl and cinnamyl, R_2 and R_3 are members selected from the group consisting of hydrogen, chloro, bromo, iodo, (lower) alkyl and nitro and B is a member selected from the group consisting of di(lower) alkylamino, piperidino, morpholino, thiomorpholino, 2,6-dimethylmorpholino, N'(lower) alkyl-piperazino, pyrrolidino and pipecolino; and

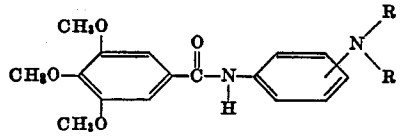


wherein R is lower alkyl and B represents di(lower) alkylamino; and



where R represents lower alkyl and B represents di(lower) alkylamino.

A preferred embodiment of the present invention is a free base having the formula



where R represents (lower)alkyl.

Lower alkyl includes radicals containing from one to six carbon atoms inclusive, e. g. methyl, ethyl, n-propyl, isopropyl, isobutyl, n-amyl, n-hexyl, isohexyl and the like.

Examples of nontoxic acid addition salts of said free bases with inorganic and organic acids, which may be prepared by the methods hereinafter disclosed, are the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, maleate, acetate, citrate, oxalate, succinate, benzoate, tartrate, fumarate, mandelate, malate, ascorbate, 8-chlorotheophyllinate and the like.

The compounds of this invention are useful as pharmaceuticals and as pharmaceutical intermediates. More specifically, compounds of this invention are nonhypnotic sedatives and clinical tranquilizers of use in anxiety states, neuroses, emotional disturbances, insomnia, hypertension and the like. The compounds of the present invention also possess other valuable therapeutic properties as local anesthetics, analgesics and as potentiators of drugs active on the central nervous system.

The useful depressant action on the central nervous system of man and animals of the compounds of the present invention is illustrated by their ability to prolong sleep caused by hexobarbital. Thus p-(3,4,5-trimethoxybenzamido)-dimethylaniline hydrochloride prolongs the duration of sleep induced in mice by hexobarbital by a factor of about four and is found in this procedure to be at least as effective as, and less toxic than, reserpine or chlorpromazine. The compounds of the present invention are also capable of eliminating conditioned responses for long periods of time.

The preferred embodiment of this invention is the base p-(3,4,5-trimethoxy-benzamido)-N, N-dimethylaniline and its nontoxic acid addition salts. In clinical trial using a daily dose of 400 to 2400 mg. p. o. this compound has produced no signs of behavioral or clinical toxicity while producing excellent remission in cases of severe psychoneurotic depression and severe psychotic depression. It was also found that this compound potentiated the analgesic action of morphine and codeine both in duration and degree. To ascertain acute toxicity, doses of 100 mg. were also given intravenously; they failed to produce any symptoms of toxicity.

The compounds of the invention are readily prepared by reacting a 3,4,5-trialkoxybenzoic acid halide, ester or azide with the appropriate substituted aniline.

The following examples are given to illustrate the scope of this invention without limiting it thereto.

EXAMPLE 1

To 11.5 g. of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there was added 8.6 g. of p-aminodimethylaniline monohydrochloride and 10 cc. triethylamine. The resulting solution was refluxed until all the solid dissolved (about 10–15 minutes). The cooled chloroform solution was washed with several portions of cold water and dried over anhydrous sodium sulfate. After removal of the chloroform by distillation in vacuo on the steam bath, the crystalline residue of p-(3,4,5-trimethoxybenzamido)-dimethylaniline (10.5 g.) was recrystallized from 95% ethanol and found to melt at 154°–155° C.

Analysis.—Calcd. for $C_{18}H_{22}O_4N_2$:C, 65.44; H, 6.71. Found: C, 65.7; H, 6.85.

EXAMPLE 2

To a solution of 69.0 g. of 3,4,5-trimethoxybenzoyl chloride in 500 ml. of chloroform there was added 40.9 g. of N-dimethyl-p-phenylenediamine in 200 ml. of chloroform and 22 g. triethylamine. The solution rose in temperature spontaneously and was allowed to cool and then washed with water. The chloroform layer was separated and dried over anhydrous potassium carbonate. After removal of the drying agent, the chloroform was removed by evaporation. The residue, containing p-(3,4,5-trimethoxybenzamido)-dimethylaniline, was dissolved in acetone and the solution was saturated with hydrogen

chloride. Addition of diethyl ether precipitated p-(3,4,5-trimethoxybenzamido)-dimethylamine hydrochloride, which was collected by filtration and dissolved in methanol (300 ml.) containing 25 grams activated charcoal. After boiling for about an hour, the carbon was removed by filtration and the solution was diluted with diethyl ether to precipitate p-(3,4,5-trimethoxybenzamido)-dimethylaniline hydrochloride which was collected by filtration, dried and found to weigh 52 g. and to melt at 203°–204° C.

Analysis.—Calcd. for $C_{18}H_{22}N_2O_4.HCl$: C, 59.0; H, 6.35. Found: C, 58.9; H, 6.28.

EXAMPLE 3

To 12 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 10 grams of N-[p-methyl aminophenyl] morpholine and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves N-[p-(3,4,5-trimethoxy-N-methyl-benzamido) phenyl]-morpholine as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

EXAMPLE 4

To 6 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 5 grams of N-[p-benzylamino-phenyl] piperidine and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves N-[p-(3,4,5-trimethoxy - N - benzyl-benzamido)-phenyl]-piperidine as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

EXAMPLE 5

To 9 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 8 grams of N-[p-phenethyl-aminophenyl]-pipecoline and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves N-[p-(3,4,5-trimethoxy-N-phenethyl-benzamido)-phenyl]-pipecoline as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

EXAMPLE 6

To 11 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 11 grams of p-dimethyl-amino-meta-dichloroaniline and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves p-(3,4,5-trimethoxybenzamido)-ortho-dichloro-dimethylaniline as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

EXAMPLE 7

To 10 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 8 grams of p-dimethylamino-meta-dinitroaniline and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves p-(3,4,5-trimethoxybenzamido) - ortho - dinitrodimethylaniline as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

EXAMPLE 8

To 12 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 10 grams of p-dimethylamino-meta-chloroaniline and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves p-(3,4,5-trimethoxybenzamido) - ortho - chlorodimethylaniline as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

The free base p-(3,4,5-trimethoxy-benzamido)-ortho-chlorodimethylaniline upon recrystallization from methanol melts at 134°–135° C. and is very insoluble in water.

Analysis.—Calcd. for $C_{18}H_{21}C_1N_2O_4$: C, 59.25; H, 5.76. Found: C, 59.5; H, 5.95.

This free base was suspended in methanol and dry hydrogen chloride was passed through the mixture, giving a clear solution. The resulting solution was cooled and diluted with a little ether. The pure colorless hydrochloride crystallized out slowly and was collected and found to melt at 216°–218° C. with decomposition.

EXAMPLE 9

To 6 grams of 3,4,5-trimethoxybenzoyl chloride in 200 cc. of chloroform there is added 5 grams of p-dimethylamino-meta-nitroaniline and 10 cc. triethylamine. The resulting solution is refluxed until substantially all the solid dissolves (at least fifteen minutes) and then cooled, washed with several portions of cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation in vacuo on the steam bath leaves p-(3,4,5-trimethoxybenzamido)-ortho-nitrodimethylaniline as the solid residue which is converted, if desired, to the hydrochloride by reaction with one equivalent of hydrogen chloride, preferably in an organic solvent such as acetone or diethyl ether.

EXAMPLE 10

N-(p-nitrosophenyl)-morpholine (28.8 g.; 0.15 mole) is dissolved in 250 cc. of methanol and the dark green solution is hydrogenated at 60 lbs. and 60° C., using Raney nickel as the catalyst. When the hydrogenation is complete (after about ten hours) an almost colorless solution is obtained. The catalyst is filtered off and the methanol is removed by distillation under reduced pressure to leave N-(p-aminophenyl) morpholine as a dark brown crystalline solid which is then dissolved in chloroform. After the addition of triethylamine (25 g.), this solution is added slowly, with stirring and cooling, to 3,4,5-trimethoxybenzoyl chloride (34.5 g.; 0.15 mole) in 100 cc. of chloroform. After the addition has been completed the reaction mixture is allowed to stand at room temperature for one hour, washed with cold water and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation under reduced pressure leaves as the residue 4'-morpholino-3,4,5-trimethoxy-benzanilide melting at 196°–197° C. after repeated re-

crystallizations from methanol or acetone to obtain colorless crystals.

Analysis.—Calcd. for $C_{20}H_{24}N_2O_6$: C, 64.51; H, 6.45. Found: C, 64.6; H, 6.65.

4'-morpholino-3,4,5-trimethoxybenzanilide hydrochloride is prepared by dissolving the basic amide in acetone, passing in dry hydrogen chloride and collecting the precipitated acid addition salt, which is found to be insoluble in water.

EXAMPLE 11

To a solution of 15.0 g. of N-benzyl-N', N'-dimethylphenylenediamine in ml. 200 chloroform there is added 10 g. triethylamine. To this solution there is added a solution of 15.5 g. trimethoxybenzoyl chloride in 100 ml. chloroform. This solution is allowed to stand for two hours, washed well with water and dried over anhydrous sodium sulfate. The chloroform is then removed by distillation under reduced pressure to leave as the residue N, N - dimethyl - N' - benzyl - N' - (3,4,5 - trimethoxybenzoyl) phenylenediamine. The hydrochloride of this basic amide is prepared by adding dry hydrogen chloride to a solution of the amide in ether and is found to be insoluble in ether and soluble in acetone. The citrate and the sulfate are also prepared and found to be soluble in acetone.

EXAMPLE 12

1-methyl-4-(p-nitrophenyl) piperazine (22.1 g., 0.1 mole) in 200 cc. methanol was hydrogenated at 50 lbs. pressure in the presence of Raney nickel. The absorption of hydrogen was very rapid and the temperature rose to 60°–65° C. The reaction was complete after 15–20 minutes; the catalyst was filtered off and the solvent was removed by distillation under reduced pressure to leave a residue which was taken up in acetone and added slowly with stirring to 3,4,5-trimethoxy-benzoyl chloride (23.0 g., 0.1 mole) in 100 cc. acetone. The product 4'-(1-methyl-piperazino) - 3,4,5 - trimethoxybenzanilide which precipitated was collected by filtration and dissolved in water. The addition to this aqueous solution of concentrated ammonium hydroxide to make it basic reprecipitated the product, which was recrystallized from isopropyl alcohol, M. P. 190°–191° C.

This base was converted to its dihydrochloride by dissolving it in methanol, bubbling dry hydrogen chloride through the resulting solution, diluting with ether and collecting the salt, 9.5 g., M. P. 253°–255° C. (dec.).

Analysis.—Calcd. for $C_{21}H_{27}N_3O_4.2HCl$: C, 55.02; H, 6.33. Found: C, 55.1; H, 6.56.

EXAMPLE 13

Five grams of Raney nickel was added to a solution of 20 g. p-nitroso-N,N-dimethyl-3-methylaniline dissolved in 150 ml. methanol and the mixture was hydrogenated at room temperature in 30 minutes. The catalyst was removed by filtration and the solvent by distillation in vacuo. The residue (13 g.) was dissolved in 100 ml. acetone and added to a solution in 50 ml. acetone of 20 g. of 3,4,5-trimethoxybenzoyl chloride. After standing for one hour and then cooling, the precipitated 2'-methyl-4'-dimethylamino-3,4,5-trimethoxybenzanilide hydrochloride was collected by filtration, recrystallized from methanol-ether and from 95% ethanol and found to weigh 17.3 g. and to melt at 213°–214° C.

Analysis.—Calcd. for $C_{18}H_{23}N_2O_4Cl$: C, 60.1; H, 6.61. Found: C, 60.4, 60.1; H, 6.74, 6.90.

The free base was prepared by slurrying the salt in dilute aqueous sodium hydroxide and melted at 195°–196° C.

EXAMPLE 14

To a solution of 10 g. 2-chloro-4-dimethylaminoaniline and 7.0 g. triethylamine in 100 ml. chloroform there was added slowly a solution of 14 g. 3,4,5-trimethoxybenzoyl chloride in 100 ml. chloroform. After standing for one hour, the chloroform was evaporated off. The residue of the product, 4'-dimethylamino-2'-chloro-3,4,5-trimethoxybenzanilide, was dissolved in 100 ml. boiling methanol and decolorized with carbon. After removal of the carbon by filtration, the solution was evaporated to dryness and the residue was dissolved in 50 ml. boiling methanol. Water (25 ml.) was added. The product precipitated and was collected, recrystallized from ethyl acetate, M. P. 164°–166° C., and dried two hours over P_2O_5 at 100° C.

Analysis.—Calcd. for $C_{18}H_{21}N_2O_4Cl$: C, 59.3; H, 5.81. Found: C, 60.0, 60.4; H, 5.81, 5.95.

This base was suspended in 50 ml. methyl isobutyl ketone and dissolved by heating on the steam bath. After passing hydrogen chloride into the solution, the hydrochloride precipitated and was collected and recrystallized from 25 ml. methanol, M. P. 206°–208° C. (dec.).

Analysis.—Calcd. for $C_{18}H_{21}N_2O_4Cl.HCl$: C, 54.2; H, 5.50. Found: C, 54.3, 54.2; H, 5.72, 5.72.

EXAMPLE 15

To 4-(p-nitrosophenyl)-thiomorpholine hydrochloride (30 g.) there was added 75 g. crystalline stannous chloride in concentrated hydrochloric acid (125 cc.). After exothermic reaction, the solution was cooled and the 4-thiomorpholinoaniline stannichloride separated and was collected by filtration. Upon solution in water and addition of 50% sodium hydroxide solution, the free amine, 4-thiomorpholinoaniline, was liberated and extracted into ether. The combined ethereal extracts were washed with water and dried over anhydrous potassium carbonate; upon removal of the solvent by evaporation there was obtained 12 g. of solid amine. The solid amine was dissolved in chloroform containing some triethylamine and the resulting solution was added slowly, with stirring, to a solution of 3,4,5-trimethoxybenzoyl chloride in chloroform. After exothermic reaction and cooling, 18 g. 4'-thiomorpholino-3,4,5-trimethoxy-benzanilide precipitated and was collected, dried, recrystallized from dimethylformamide and found to melt at 219°–220° C.

Anaylsis.—Calcd. for $C_{20}H_{24}N_2O_4S$: C, 61.85; H, 6.18; S, 8.24. Found: C, 61.8; H, 5.97; S, 7.92.

Upon suspending this basic amide in methanol and passing in hydrogen chloride, a solution was obtained from which the hydrochloride soon crystallized out, M. P. 269°–270° C. (dec.).

EXAMPLE 16

N,N,N'-trimethyl-p-phenylenediamine dihydrochloride (6.5 g., 0.029 mole) was dissolved in 150 ml. chloroform by the addition of 9.5 g. (0.95 mole) triethylamine. To this solution there was added 6.7 g. (0.030 mole) 3,4,5-trimethoxybenzoyl chloride in 25 ml. chloroform. The solution was refluxed for one hour and then washed with water; the choloroform was removed by distillation to leave the product, N-methyl-4'-dimethylamino-3,4,5-trimethoxybenzanilide as an oil which solidified on seeding and was recrystallized from methanol, M. P. 124°–125° C.

Analysis.—Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.25; H, 7.02. Found: C, 65.8; H, 6.88.

EXAMPLE 17

N,N-di-n-propyl-4-nitrosoaniline (20.6 g., 0.1 mole) was added to 200 cc. methanol and the resulting mixture was hydrogenated at 60° C. and 50 lbs. hydrogen pressure in the presence of Raney nickel during 30 minutes. After removal of the catalyst by filtration and the solvent by distillation in vacuo, the residue was taken up in 75 cc. acetone to give a solution which was added slowly with stirring to a solution of 3,4,5-trimethoxybenzoyl chloride (23 g., 0.1 mole) in 100 ml. acetone. Upon standing, 4'-(N,N-di-n-propylamino)-3,4,5 - trimethoxybenzanilide hydrochloride (38.5 g.) separated was collected, recrystallized from methanol and found to melt at 245°–246° C.

This salt was converted to the free base by refluxing

in a mixture of methanol, water and piperidine. The base precipitated and was recrystallized from methanol, M. P. 170°–171° C.

Analysis.—Calcd. for $C_{22}H_{30}N_2O_4$: C, 68.39; H, 7.77. Found: C, 68.6; H, 7.78.

EXAMPLE 18

N,N-diethyl-p-phenylenediamine (16.4 g., 0.1 mole) dissolved in 50 ml. acetone was added slowly with stirring to a solution of 3,4,5-trimethoxybenzoyl chloride (23 g., 0.1 mole) in 150 cc. acetone. Upon cooling at the end of the exothermic reaction, 4'-diethylamino-3,4,5-trimethoxybenzanilide hydrochloride precipitated and was collected by filtration, washed with a little cold acetone, recrystallized from methanol-ether and found to melt at 240°–241° C.

Analysis.—Calcd. for $C_{20}H_{26}N_2O_4.HCl$: C, 60.80; H, 6.84. Found: C, 6.11; H, 7.11.

Five grams of the hydrochloride was dissolved in water and the acidic solution was neutralized with sodium hydroxide. The free base which precipitated was collected by filtration and recrystallized from methanol, M. P. 158°–159° C.

EXAMPLE 19

A mixture of 60 g. p-nitrochlorobenzene and 75 ml. piperidine was heated at 95° C. on the steam bath for four hours in a flask attached to an air condenser. The reaction was violent at first; at the end of the refluxing period, the reaction mixture was diluted with 200 ml. water and stirred thoroughly. The precipitated 1-(p-nitrophenyl) piperidine was collected by filtration and recrystallized twice from 200 ml. methanol, M. P. 103° C.

1-(p-nitrophenyl) piperidine (20.6 g., 0.1 mole) was suspended in 200 ml. methanol and hydrogenated at 60° C. and 50 lbs. pressure using Raney nickel as the catalyst over about 30 minutes. After removal of the catalyst by filtration and the solvent by distillation in vacuo, the residue, 1-(p-aminophenyl) piperidine, 0.1 mole, was dissolved in 75 ml. acetone and added slowly with stirring to 3,4,5-trimethoxybenzoyl chloride (23 g., 0.1 mole) dissolved in 75 ml. acetone. After cooling, the crystalline 4'-piperidino-3,4,5-trimethoxybenzanilide which precipitated was collected and recrystallized from methanol, 38.5 g., M. P. 251°–253° C. (dec.).

Boiling this salt in a mixture of methanol, water and piperidine for a few minutes gave the free base, M. P. 161°–163° C.

Analysis.—Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.03. Found: C, 68.5; H, 7.25.

EXAMPLE 20

1-(p-nitrophenyl)-pyrrolidine (19.2 g., 0.1 mole) was suspended in 200 ml. methanol and the resulting mixture was hydrogenated at 60° C. and 50 lbs. pressure of hydrogen using a Raney nickel catalyst over 30 minutes. After removal of the catalyst by filtration and of the solvent by distillation in vacuo, the residue was dissolved in 75 ml. acetone and added slowly with stirring to a solution of 3,4,5-trimethoxybenzoyl chloride (23 g., 0.1 mole) in 100 ml. acetone. The crystalline precipitate of 4'-pyrrolidino-3,4,5-trimethoxybenzanilide hydrochloride (34.5 g.) was collected and recrystallized from methanol, M. P. 226°–228° C.

This hydrochloride was converted to the free base by boiling for a few minutes in a mixture of methanol, water and piperidine. The colorless crystals of free base thus obtained were collected by filtration, washed with cold water, recrystallized from methanol and found to melt at 174°–175° C.

Analysis.—Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.41; H, 6.74. Found: C, 67.4; H, 6.7.

EXAMPLE 21

The use of p-nitroso-N, N-dimethyl-2-methylaniline in the procedure of Example 13 yields 3'-methyl-4'-dimethylamino-3,4,5-trimethoxybenzanilide and its hydrochloride.

EXAMPLE 22

To a solution of 15 g. of N-cinnamyl-N',N'-dimethyl-p-phenylenediamine in 200 ml. chloroform there is added 10 g. triethylamine. To this solution there is added a solution of 15.5 g. 3,4,5-trimethoxybenzoyl chloride in 100 ml. chloroform. This solution is allowed to stand for two hours, washed well with water and dried over anhydrous sodium sulfate. The chloroform is then removed by distillation under reduced pressure to leave as the residue N,N-dimethyl-N'-cinnamyl-N'-(3,4,5-trimethoxybenzoyl)-p-phenylenediamine.

EXAMPLE 23

Materials

688 grams (3.24 moles) 3,4,5-trimethoxybenzoic acid
356 grams (488 ml.) (3.52 moles) triethylamine
378 grams (333 ml.) (3.50 moles) ethyl chloroformate
500 grams (3.67 moles) N,N-dimethyl-p-phenylenediamine
3.1 liters methylene chloride
700 ml. methanol for slurry
200 ml. methanol for wash
400 ml. methanol for recrystallization
135 grams (69 ml.) (1.28 moles) conc. sulfuric acid

Procedure

In a 5-liter, three-necked, round bottom flask equipped with a mechanical stirrer and a dropping funnel are placed 688 grams of 3,4,5-trimethoxybenzoic acid and 3 liters of methylene chloride. The mixture is stirred and while cooling in an ice-salt-acetone bath, 488 ml. of triethylamine is poured in rapidly. The trimethoxybenzoic acid dissolves completely as the triethylamine salt and the solution is cooled to −8° C. Then 333 ml. of ethyl chloroformate is added dropwise at such a rate that the temperature during the addition does not rise above 0° C. Ten minutes after the complete addition of the ethyl chloroformate, a previously prepared solution of 500 grams of N,N-dimethyl-p-phenylenediamine and 100 ml. of methylene chloride is added taking care again that the rate of addition does not raise the temperature above 0° C. The ice bath is removed and the mixture is stirred for 1 hour at room temperature. The solid triethylamine hydrochloride is removed by extraction of the mixture with 2 liters of water. The methylene chloride extract is transferred into a large, 5-liter round bottom flask and the solvent and water are removed by azeotropic distillation. The dark brown gummy solid is slurried with 700 ml. of methanol, filtered and washed with 200 ml. of ice cold methanol. The 4'-dimethylamino-3,4,5-trimethoxybenzanilide is recrystallized from 400 ml. of boiling methanol, filtered through a heated funnel to remove any impurities and filtered at 10° C. The crystalline solid weighs 420 grams (40% yield) and the melting point is 154–155° C. after air drying.

The 420 grams of 4'-dimethylamino-3,4,5-trimethoxybenzanilide is transferred to a large beaker containing 4.5 liters of acetone. The mixture is stirred and heated gently on the steam-bath until all of the basic amide has dissolved. Not much heating is required. The temperature is then regulated to 25–30° and 69 ml. of concentrated sulfuric acid is added dropwise with vigorous stirring. When nearly all of the acid has been added the solution becomes momentarily clear followed by rapid precipitation of the salt. The solution is cooled to 10° C., filtered and washed with 500 ml. of cold acetone. The 4'-dimethylamino-3,4,5-trimethoxybenzanilide hydrogen sulfate is air dried to constant weight and weighs 450 grams, M. P. 215°–217° C.

EXAMPLE 24

To 11 g. meta-dimethylphenylene diamine (also called

meta-dimethylaminoaniline) dissolved in 100 ml. chloroform there was added slowly a solution of 18.8 g. of 3,4,5-trimethoxybenzoyl chloride in 100 ml. chloroform. The reaction mixture was stored at room temperature for 90 minutes, washed with water and dried over anhydrous potassium carbonate. The chloroform was evaporated to leave 3'-dimethylamino-3,4,5-trimethoxybenzanilide as a solid residue which was recrystallized from 100 ml. methanol, dissolved in 300 ml. acetone and decolorized by treatment with carbon. After removal of the carbon, hydrogen chloride was added and on cooling 3'-dimethylamino-3,4,5-trimethoxybenzanilide hydrochloride precipitated and was collected, 11 g., M. P. 219°–220° C.

Analysis.—Calcd. for $C_{18}H_{22}N_2O_4.HCl$: C, 59.3; H, 6.30. Found: C, 59.2; H, 6.47.

EXAMPLE 25

A solution of 25 g. (0.15 mole) of o-nitrodimethylaniline in 150 ml. of methanol was hydrogenated over 9 g. of methanol-washed Raney nickel. Total uptake of hydrogen was 39 pounds (theory—40.5 lbs.). The catalyst was removed by filtration and the purple solution was saturated with dry hydrogen chloride. Collected the crystalline solid by suction to precipitate crystalline o-dimethylaminoaniline dihydrochloride (26 g.) which was collected by filtration.

To a stirred mixture of 26 g. (0.125 mole) o-dimethylaminoaniline dihydrochloride and 35 g. (0.15 mole) of 3,4,5-trimethoxybenzoyl chloride in 200 ml. of chloroform at room temperature was added 105 ml. (76 g.) (0.75 mole) of triethylamine during ten minutes. The mixture was stirred and heated under reflux for four hours, cooled, washed thrice with water and stripped of solvent by distillation in vacuo on the steam bath, leaving 52.3 g. 2'-dimethylamino-3,4,5-trimethoxybenzanilide as a dark oil. This was dissolved in ether and saturated with dry hydrogen chloride to precipitate 51.4 g. 2'-dimethylamino-3,4,5-trimethoxybenzanilide hydrochloride. This product on recrystallization from acetonitrile and then from 95% ethanol melted at 193.5–194.5° C.

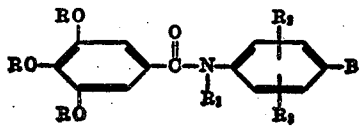
Analysis.—Calcd. for $C_{18}H_{23}ClN_2O_4$: C, 58.9; H, 6.31. Found: C, 58.86; H, 5.77.

A sample of this hydrochloride (0.7 g.) was converted to the free base by neutralizing with 10% sodium hydroxide, extracting into ether, and removing the ether by distillation to leave the base as a gum which crystallized when triturated with petroleum ether (Skelly solve B) and melted at 96–97.5° C. upon recrystallization from benzene-n-pentane.

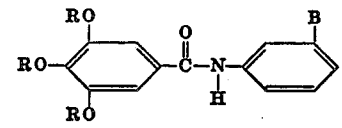
Analysis.—Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.4; H, 6.70. Found: C, 65.25; H, 6.68.

I claim:

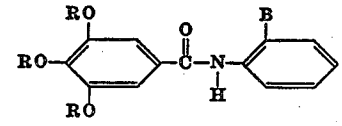
1. A compound selected from the group consisting of a free base and the nontoxic acid addition salts thereof, said free base having a formula selected from the group consisting of



wherein R represents lower alkyl, R_1 is a member selected from the group consisting of hydrogen, (lower) alkyl, benzyl, phenethyl and cinnamyl, R_2 and R_3 are members selected from the group consisting of hydrogen, chloro, bromo, iodo, (lower) alkyl and nitro and B is a member selected from the group consisting of di(lower) alkylamino, piperidino, morpholino, thiomorpholino, 2,6 - dimethylmorpholino, N'(lower)alkyl - piperazino, pyrrolidino and pipecolino; and

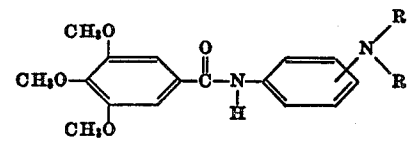


wherein R is lower alkyl and B represents di(lower)alkylamino; and



where R represents lower alkyl and B represents di-(lower) alkylamino.

2. A free base having the formula



where R represents (lower)alkyl.

3. p - (3,4,5 - trimethoxybenzamido) - N,N dimethylaniline.

4. m - (3,4,5 - trimethoxybenzamido) - N,N - dimethylaniline.

5. o - (3,4,5 - trimethoxybenzamido) - N,N - dimethylaniline.

6. 4'-morpholino-3,4,5-trimethoxybenzanilide.

7. p - (3,4,5 - trimethoxybenzamido) - ortho - chloro-N,N-dimethylaniline.

8. 2' - methyl - 4' - dimethylamino - 3,4,5 - trimethoxybenzanilide.

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