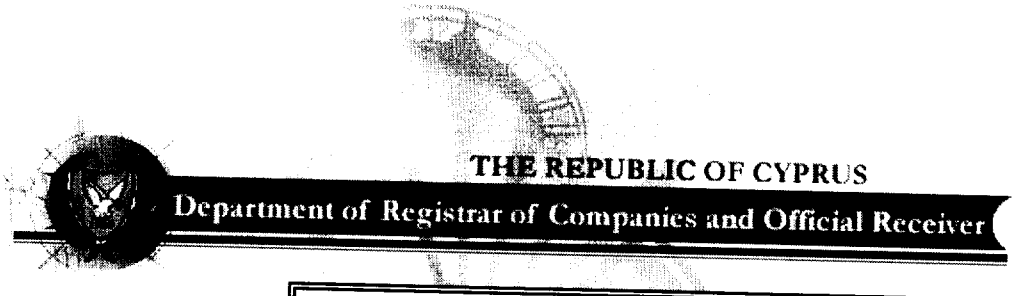

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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Michel Thominet, Jacques Acher, Jean-Claude Monier
(74) Agents
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(54) New substituted heterocyclic benzamides, methods of preparing them, compositions containing them, and their use as behaviour modifiers

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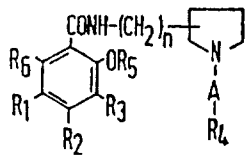

in which R_4 is a cycloalkyl, cycloalkenyl, bicycloalkyl or tricycloalkyl group; A is a single bond or a saturated or unsaturated hydrocarbon chain containing 1 to 3 carbon atoms; *n* is 0, 1, 2 or 3; R_5 is a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an alkenyl or alkynyl group; and each of R_1, R_2, R_3 and R_6, which are the same or different, is a hydrogen or halogen atom or an alkyl, alkoxy, amino, acetamido, sulphamoyl, alkylsulphamoyl, dialkylsulphamoyl, alkylsulphonyl or alkylsulphinyl group, or any two of them bonded together to form an azimido group; with the following provisos (a) that when R_4 is a cycloalkyl group, R_5 a hydrogen atom or an alkyl group, A a single bond and *n* equal to 0, at least one or R_1, R_2, R_3 and R_6 is an alkylsulphonyl or alkylsulphinyl group or two of them are bonded together to form an azimido group; and (b) that when R_4 is a cycloalkyl group, R_5 is a methyl group, A is an alkylene group with one to three carbon atoms, *n* is 1 and the amide chain is bonded at the 2 position of the pyrrolidine, R_1 can be a halogen atom or a sulphamoyl, alkylsulphamoyl, dialkylsulphamoyl or alkylsulphonyl group only when R_2, R_3, R_6 are not all hydrogen atoms. The compounds are made by aminating a benzoic acid having the appropriate R_1, R_2, R_3, OR_5 and R_6 substituents. The compounds can be made up into pharmaceutical compositions and their action on the central nervous system makes them valuable antimetic compounds, but with substantially no cataleptic action.

ERRATA

SPECIFICATION NO 2013662A

Page 3, line 42, *for* –5– *read* –4–

Page 19, line 49, *for cyclooctylmethyl read cyclooctyl*

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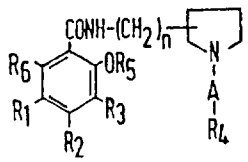

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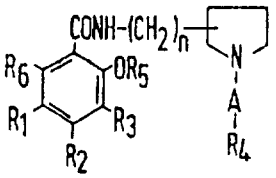
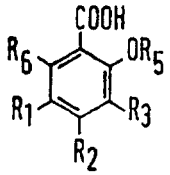


(I)

in which R_4 is a cycloalkyl, cycloalkenyl, bicycloalkyl or tricycloalkyl group; A is a single bond or a saturated or unsaturated hydrocarbon chain containing 1 to 3 carbon atoms; *n* is 0, 1, 2 or 3; R_5 is a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an alkenyl or alkynyl group; and each of R_1, R_2, R_3 and R_6, which are the same or different, is a hydrogen or halogen atom or an alkyl, alkoxy, amino, acetamido, suphamoyl, alkylsulphamoyl, dialkylsulphamoyl, alkylsulphonyl or alkylsulphinyl group, or any two or them are bonded together to form an azimido group; with the following provisos (a) that when R_4 is a cycloalkyl group, R_5 a hydrogen atom or an alkyl group, A a single bond and *n* equal to 0, at least one of R_1, R_2, R_3 and R_6 is an alkylsulphonyl or alkylsulphinyl group or two of them are bonded together to form an azimido group; and (b) that when R_4 is a cycloalkyl group, R_5 is a methyl group, and A is an alkylene group with one to three carbon atoms, *n* is 1 and the amide chain is bonded at the 2 position of the pyrrolidine, R_1 can be a halogen atom or a sulphamoyl, alkylsulphamoyl, dialkylsulphamoyl or alkylsulphonyl group only when R_2, R_3, R_6 are not all hydrogen atoms.

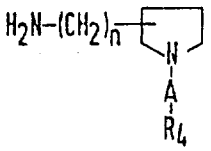
The invention also provides salts of addition of the compounds of formula (1) with pharmacologically acceptable acids, and their quaternary ammonium salts and oxides, including a laevorotatory and dextrorotatory isomers of such compounds.

In accordance with the invention, the novel compounds are prepared by reacting an acid of the formula:



(II)

where R_1, R_2, R_3, R_5, R_6 are defined as above, or one of its reactive derivatives with an amine of the formula:



(III)

where A, R_4 and *n* are defined as above, or one of its reactive derivatives.

Reactive derivatives of the acid (II) include its acid halides, azide, hydrazide, azolide, acid isothiocyanate, trichloroacetophone or triphenylphosphine derivative, alkyl esters, reactive esters, e.g. its methoxymethyl or cyanomethyl ester, aromatic esters, N-hydroximide esters, symmetrical anhydride or mixed anhydrides, e.g. those formed with a carbonic acid ester or a haloformic ester.

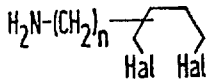
Reactive derivatives of the amine (III) include the derivative obtained by reacting the amine with a phosphorus chloride, phosphorus oxychloride, a dialkyl, diaryl or orthophenylenechlorophosphite, an alkyl or aryldichlorophosphite, an isothiocyanate of the amine, a sulphamide or a substituted urea.

The invention is not limited to derivatives of the acid and amine mentioned above.

The amidifying reaction may be carried out *in situ* or when the intermediate derivative has been isolated.

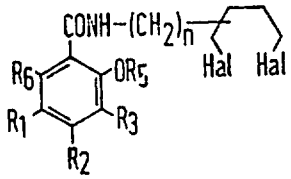
It is also possible to react the free acid and the free amine in the presence of a condensing agent such as silicon tetrachloride, trichlorophenylsilane, phosphoric anhydride, a carbodiimide or an alkoxyacetylene.

The formula (I) compounds may alternatively be prepared by reacting the acid of formula (II) or one of its reactive derivatives defined as above, with a dihaloalkylamine of the formula:



(IV)

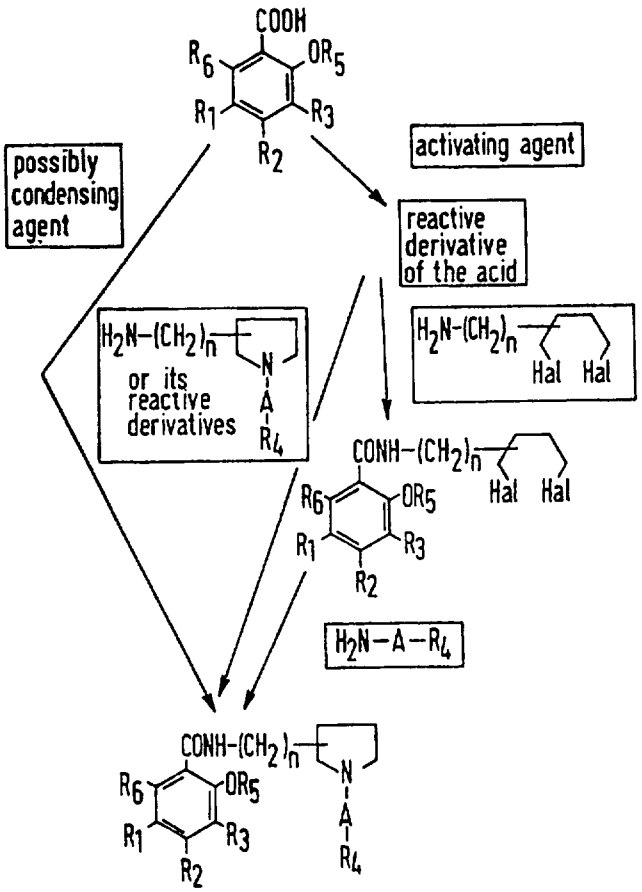
where *n* is defined as above and the halogen is a chlorine, bromine or iodine atom to produce a compound of the formula:



and reacting the latter with an amine of the formula $H_2N—A—R_4$ where R_4 and A are as defined above.

The methods of preparing the compounds according to the invention are set out in the following diagram:

DIAGRAM OF REACTION



The amidifying reactions may take place with or without a solvent.

Some examples of the systems used as solvents, which are inert relative to the amidifying reaction, are alcohols, polyols, ketones, benzene, toluene, dioxan, chloroform and diethyleneglycol-dimethyl ether. It is also possible to take an excess of the amine used as raw material as the solvent. It may be preferable to heat the reaction mixture during amidification, e.g. to the boiling point of the above mentioned solvents.

The compound obtained by the method of the invention may, if necessary, react with pharmaceutically acceptable inorganic or organic acids such as hydrochloric, hydrobromic, sulphuric, phosphoric, oxalic, acetic, tartaric, citric or methane-sulphonic acid, to give acid-addition salts.

It may equally react, if necessary, with alkyl sulphates or halides to give quaternary ammonium salts.

It may also be oxidised in known manner, e.g. with hydrogen peroxide and manganese dioxide, to give the corresponding N-oxide.

Some examples will now be given to illustrate the technical features of the invention. It should be

understood that the invention is not limited to these embodiments nor to the purposes to which they can be applied.

EXAMPLE 1

N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-chlorobenzamide

240g of 2-methoxy-4-acetamido-5-chloro-benzoic acid (0.985 mole), 960ml of acetone and 99.5g of triethylamine (0.985 mole) are placed in a 3-litre flask fitted with an agitator, a thermometer and a dropping funnel. The acid dissolves almost entirely. The reaction medium is cooled to 0°C: the triethylamine salt of the acid crystallises.

107g of ethyl chloroformate (0.985 mole) is added to the suspension, drop by drop, and the temperature is kept between 0° and +5°C. This takes about 1 hour 30. Agitation is continued for a further 30 minutes, then 188g of 1-cyclohexyl-2-amino-methyl pyrrolidine is added drop by drop over about 1 hour while the temperature is kept between +10 and +15°C. When all the pyrrolidine has been added agitation is continued for a further $\frac{1}{2}$ hour at +10°C then for 1 hour at room temperature. The base crystallises. It is drained and washed with acetone. The precipitate is immediately dissolved in 1 litre of water in order to dissolve the triethylamine hydrochloride; it is drained, washed with water until the Cl^- ions have been eliminated, and dried at 50°C. Weight obtained 262 g.

The acetone mother liquor is evaporated under vacuum to constant weight. Weight 161g for 139g theory.

790ml of 2.5N alcoholic potash (2 x 0.985 mole) and the 423g of crude acetylated base are placed in a 2-litre flask fitted with a reflux condenser. The mixture is heated to reflux for 2 hours. The solution is filtered with charcoal then diluted with 6 litres of water. The deacetylated base is precipitated in liquid form then crystallises after standing overnight. It is drained, washed with water and then dried in air at 40°C. 324g of the product is obtained, melting at 115—116°C.

The 324g of base is dissolved hot in 625ml of aceto-nitrile. The turbid solution is filtered, boiling, through charcoal, then cooled. The base re-crystallises and is drained, washed with aceto-nitrile then dried. 290g of a beige substance is obtained. The base obtained is re-crystallised a second time in 580ml of aceto-nitrile with filtration through charcoal.

271g of the product, which is still beige, is obtained.

The 271g of base is dissolved in 2.7 litres of water and the necessary hydrochloric acid. The solution is filtered with charcoal, then the base is precipitated by adding 20% ammonia. It is liquid at first and crystallises after 24 hours.

The crystals are drained, washed with water and dried in an oven at 40°C. 256g is obtained and re-crystallised in 510ml of acetonitrile. The boiling solution is filtered. After cooling, the re-crystallised base is drained, washed with acetonitrile and dried in air, then at 50°C.

235g of N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-chlorobenzamide is obtained, melting at 123—124°C. Yield 65%.

EXAMPLE 2

N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-chloro-5-ethyl sulphonylbenzamide

2-methoxy-4-chloro-5-chlorosulphonylbenzoic acid

4 litres of chlorosulphonic acid is placed in a 3-necked 6 litre flask, fitted with an agitator and a thermometer, and cooled to +15°C.

563g of 2-methoxy-5-chlorobenzoic acid (3.01 moles) is added in fractions and the temperture is allowed to develop. The benzoic acid takes 20 min. to add, and the temperature reaches 50°C. The mixture is immediately heated to 80°C, then the temperature is allowed to drop to 40°C.

The reaction mixture is poured over 30kg of ice, then the precipitate is drained, washed with water and dried at 50°C. 764g (89%) of product is obtained, melting at 179°C.

2-methoxy-4-chloro-5-ethylsulphonyl benzoic acid.

3 litres of water, 740g of sodium sulphite and 535g of sodium bicarbonate are placed in a 3-necked 10 litre flask fitted with an agitator, a thermometer and a condenser. The mixture is heated to 70°C and 903g of 2-methoxy-4-chloro-5-chlorosulphonyl benzoic acid is added in fractions while the temperature is kept between 70 and 75°C.

The temperature is kept at 75°C for 3 hours then reduced to 25°C. 750ml of ethanol is introduced, then 950g of sodium bicarbonate is added with care. Finally 1,270g of ethyl iodide and 2,250ml of ethanol are added. The medium is heated gently to reflux (35°C) and the reflux is maintained for 17 hours (82°C).

3 litres of a mixture of alcohol, water and ethyl iodide is distilled under vacuum, then 3 litres of water is added to the concentrate. It is acidified to pH 1 with about 1,100ml of hydrochloric acid and cooled to about 10°C, after which it is drained and washed with 3 litres of water. The product is dissolved in 3 litres of water containing 300g of sodium bicarbonate. It is agitated for 2 hours, then the insoluble part is filtered off. 100g of vegetable black is added to the filtrate, then it is agitated and the black is filtered off. The product is precipitated by acidifying it with about 300 ml of hydrochloric acid at 1.18 sp.gr. The product is drained, washed several times with water and dried in an oven at 60°C.

550g (62.5%) of acid is obtained, melting at 180°C.

2-methoxy-4-chloro-5-ethylsulphonyl benzoyl chloride.

139g of 2-methoxy-4-chloro-5-ethylsulphonyl benzoic acid, 200ml of thionyl chloride and 0.5ml of dimethylformamide are placed in a flask fitted with an agitator, a thermometer and a condenser.

The mixture is heated to reflux, left to stand, then the solution is evaporated dry.

The residue is treated with 200ml of toluene, then the crystals are washed with toluene and dried in a vacuum desiccator.

117g of 2-methoxy-4-chloro-5-ethylsulphonyl benzoyl chloride is obtained (M.P. = 115—117°C, yield = 79%.

N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-chloro-5-ethyl sulphonylbenzamide.

54g of 1-cyclopentyl-2-aminomethyl-pyrrolidine (0.32 mole) and 300ml of methyl ethyl ketone are placed in a 1-litre flask fitted with an agitator and a thermometer. The solution is cooled to +10°C, then 89g of 2-methoxy-4-chloro-5-ethylsulphonyl benzoyl chloride (0.30 mole) is added in stages. The reaction medium is agitated for 2 hours at room temperature then left to stand overnight. The crystals are filtered, washed three times with 100ml of methyl ethyl ketone, then dried in an oven at 60°C.

85g of product is obtained, melting at 165—170°C.

The hydrochloride is re-crystallised in 400ml of methyl ethyl ketone. The product is filtered, washed with a little solvent and dried in an oven at 50°C.

69g (49.5%) of product is obtained, which melts and decomposes at 160°C.

EXAMPLE 3

N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl benzamide.

2,3-dimethoxy-5-sulphamoyl benzoyl chloride.

419g (1.6 mole) of 2,3-dimethoxy-5-sulphamoyl benzoic acid and 1,351g (11.35 moles) of thionyl chloride are placed in a 2-litre flask fitted with an agitator, a thermometer and a condenser connected to a soda bubbler. The mixture is brought to reflux for 1 hour, after which the excess thionyl chloride is expelled under vacuum. The residue is dissolved in 1,000ml of hexane, filtered, washed twice with 500ml of petroleum ether and dried in a desiccator under vacuum. 424g (yield 94.8%) of 2,3-dimethoxy-5-sulphamoyl benzoyl chloride is obtained, with a melting point of 153°C.

N-(1-cyclopropyl-methyl-2-pyrrolidinyl-methyl)-2,3-dimethoxy-5-sulphamoyl benzamide.

20g (0.13 moles) of 1-cyclopropyl-methyl-2-amino-methyl-pyrrolidine and 150ml of methyl-ethyl-ketone are placed in a 500ml flask fitted with an agitator, a thermometer and a condenser. 36.3g (0.13 mole) of 2,3-dimethoxy-5-sulphamoyl benzoyl chloride is also introduced in stages and the temperature is kept between 15 and 20°C. The thick paste obtained is diluted with 170ml of water and reacted for 1 hour at ambient temperature. It is then evaporated dry and the residue is dissolved in 200ml of water and made alkaline with an excess of ammonia. The base is precipitated and crystallises slowly. The crystals are filtered, washed with water and dried in an oven at 50°C. 50g (yield 97%) of N-(1-cyclopropyl-methyl-2-pyrrolidinyl-methyl) 2,3-dimethoxy-5-sulphamoyl benzamide is obtained. This is re-crystallised three times in butyl acetate, and 26g (50.5%) of crystals is obtained. The crystals are dissolved in normal hydrochloric acid, filtered, made alkaline with normal soda and re-filtered. They are washed with water until the Cl^- ions have completely disappeared and dried in an oven (50°C), to give 24g (46.6%) of crystals which melt at 136°C (they are insoluble in water).

Analyses	Calculated	Found
S%	8.06	8.13

EXAMPLE 4

N-(1-cyclopropyl-methyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

2-methoxy-4-amino-5-ethylthiobenzoic acid.

159g of 2-methoxy-4-amino-5-mercaptobenzoic acid, 355cm³ of water and 160cm³ of soda lye are placed in a flask fitted with a condenser. The mixture is heated till the solids have dissolved, then 123g of ethyl sulphate is added. The mixture is heated to reflux, treated with 10cm³ of 30% of soda lye, then heated to reflux for 1 hour. It is cooled, 800cm³ of water is added and the solution is filtered. The precipitate, obtained by adding 100cm³ of concentrated hydrochloric acid in the presence of ether, is drained, washed with water and dried.

162g of 2-methoxy-4-amino-5-ethylthio benzoic acid is obtained (yield 88%).

2-methoxy-4-amino-5-ethylsulphonyl benzoic acid.

123g of 2-methoxy-4-amino-5-ethyl thiobenzoic acid is dissolved hot in 542cm³ of acetic acid. The solution obtained is cooled to 35°C, then 185cm³ of 131 vol. hydrogen peroxide is added in small

quantities and the temperature is raised to 80°C.

The temperature is lowered to 40°C and the mixture is kept at that temperature for a few hours, then cooled to 10°C.

The precipitate formed is drained, washed with acetic acid and dried, then dissolved in 600cm³ of water and 100cm³ of 20% ammonia.

The precipitate formed by adding 70cm³ of concentrated hydrochloric acid is cooled, drained, washed with water and dried.

65.1g of hydrated 2-methoxy-4-amino-5-ethylsulphonyl benzoic acid is obtained (yield = 42% — M.P. = 95—100°C).

N-(1-cyclopropyl-methyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

31.3g (0.31 mole) of triethylamine, 400ml of tetrahydrofuran and 80.3g (0.31 mole) of 2-methoxy-4-amino-5-ethylsulphonyl benzoic acid are placed in a 1 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. A rubbery precipitate is formed which gradually crumbles. After 30 minutes at room temperature it is cooled to 0°C and 33.6g (0.31 mole) of ethyl chloroformate is added drop by drop.

This is kept under agitation for 1 hour between 0 and 5°C and 62g (0.40 mole) of 1-(cyclopropylmethyl)-2-amino-methyl-pyrrolidine is added drop by drop while the temperature is kept at the same level. A thick precipitate is formed. The reaction medium is agitated for a further 2 hours at room temperature then left to stand overnight. The crystals obtained are filtered, washed twice with 100ml of tetrahydrofuran and dried in an oven at 50°C. 137g of product is obtained and is dissolved with boiling water. After filtering and drying, 91g (74.3%) of crystals is obtained; these are re-crystallised in 600ml of 90% alcohol. They are filtered, washed twice with 50ml of alcohol and dried in an oven at 40°C. 81.5g (yield 66.5%) of N-(1-cyclopropyl-methyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphonyl benzamide is obtained, melting at 181°C.

Analyses	Calculated	Found
S%	8.11	8.06

EXAMPLE 5

N-(1-cyclopropyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl benzamide

2,5-dichloropentylamine hydrochloride.

1,010g (10 moles) of tetrahydrofurfurylamine is placed in a 10 litre flask fitted with a mechanical agitator, a condenser connected to a bubbler which contains sulphuric acid, and a gas inlet tube, and a stream of hydrochloric acid, previously dried by bubbling through sulphuric acid, is passed through while the temperature is kept at 100—110°C.

The reaction is exothermic at the beginning. When the flow of gas at the inlet and the outlet is identical, the tube is removed, the reaction medium cooled to 60°C and 4 litres of chloroform is stirred in. The temperature is lowered to 30°C and 1,500ml of thionyl chloride is added drop by drop. After 2 hours at reflux the 2,5-dichloropentylamine hydrochloride is precipitated. It is filtered, washed with chloroform and dried at 70°C. 1,512g (yield 78.5%) of product is obtained, which melts at 160°C.

2-methoxy-5-sulphamoyl-benzoyl chloride.

23.1g (0.1 mole) of 2-methoxy-5-sulphamoyl-benzoic acid in 400ml of dichloroethane and 1ml of dimethylformamide is placed in a 1-litre flask fitted with a mechanical agitator, a dropping funnel and a condenser. 11ml (0.15 mole) of thionyl chloride is stirred in rapidly and the medium is heated to reflux until the solids are completely dissolved.

After cooling to 50°C the medium is filtered, and the chloride obtained is dried in a vacuum desiccator.

20.2g of 2-methoxy-5-sulphamoyl-benzoyl chloride is obtained; this melts at 167°C (with decomposition).

Analyses	Calculated	Found
Cl%	14.22%	14.6%

N-(2,5-dichloropentyl)-2-methoxy-5-sulphamoyl-benzamide.

77.5g (0.4 mole) of 2,5-dichloropentylamine hydrochloride dissolved in 500ml of dichlorethane is placed in a 2-litre flask fitted with an agitator, a thermometer, a condenser and dropping funnel, followed by 112ml of triethylamine. A solution of 100g (0.4 mole) of 2-methoxy-5-sulphamoyl-benzoyl chloride in 1 litre of methyl ethyl ketone is then poured in, while the temperature is kept at 20°C.

After a reaction lasting 1 hour the precipitate of triethylamine hydrochloride is filtered and the filtrate is evaporated dry under vacuum. The precipitate is dissolved in 1 litre of water. Crystals are left,

which are filtered and washed twice with 100ml of isopropanol. They are added to the residue of the evaporated filtrate, and the soid is re-crystallised in 1,600ml of isopropanol. The crystals are filtered, washed with isopropanol and dried in an oven at 40°C. 101g (68.4%) of N-(2,5-dichloropentyl)-2-methoxy-5-sulphamoyl-benzamide is collected, melting at 148°C.

N-(1-cyclopropyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl benzamide.

36.9g (0.1 mole) of N-(2,5-dichloropentyl)-2-methoxy-5-sulphamoyl-benzamide and 57g of cyclopropylamine are placed in 250ml bottle. They are brought to reflux for 6 hours, left to stand for 1 night then brought back to reflux for 5 hours. The suspension obtained is poured into 300ml of water and 50g of ice. The white precipitate is washed with water and dried in an oven at 60°C. It melts at 163°C and weighs 29.5g (83.6%). It is dissolved in 2 litres of acetonitrile and filtered in the presence of carbon black. The filtrate is left to crystallise. The crystals obtained are filtered, washed with acetonitrile and dried at 40°C. 67g (yield 74.9%) of N-(1-cyclopropyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl-benzamide is collected, melting at 180°C.

Analysis	Calculated	Found
N%	11.89	11.74
S%	9.07	9.19

EXAMPLE 6

N-(1-cyclopropyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-dimethyl-sulphamoylbenzamide.

2-methoxy-4-amino-5-dimethylsulphamoyl benzoic acid.

In a 4-litre flask fitted with a reflux condenser, 300g of 2-methoxy-4-amino-5-sulphamoyl benzoic acid (1.22 mole) is dissolved in 735ml of water and 365ml of soda lye (3 x 1.22 mole). 308g of methyl sulphate (2 x 1.22 mole) is added and the medium is heated to reflux. It is cooled and methylation is recommenced, once with 122ml of soda lye and 154g of methyl sulphate, and once with 61m of soda lye and 77g of methyl sulphate. The reaction medium is heated to reflux for about $\frac{1}{4}$ hour each time. When the reaction is over 22ml of soda lye is added and the medium is heated to reflux for $\frac{1}{2}$ hour. The solution is cooled then filtered with charcoal. The acid is precipitated by adding 140ml of concentrated hydrochloric acid. It is drained, washed with water and dried at 50°C. 304.5g of product is obtained; this melts to about 150°C, then re-crystallises and melts at 176—178°C.

The product is re-crystallised in 609ml of acetic acid, drained, washed with 60ml of acetic acid then with water, and dried at 50°C. 239g (71%) of white product is obtained, melting at 187—189°C.

N-(1-cyclopropyl-2-pyrrolidylmethyl)-2-methoxy-4-amino-5-dimethylsulphamoyl benzamide.

68.5g of 2-methoxy-4-amino-5-dimethylsulphamoyl benzoic acid (0.25 mole), 740ml of water and 25.4g of triethylamine (0.25 mole) are placed in a 2-litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The solution is cooled to about 0°C, and 34.1g of isobutyl chloroformate (0.25 mole) is poured in drop by drop. The mixture is reacted for 40 minutes at room temperature then cooled, and 42g of 1-cyclopropyl-2-aminomethyl-pyrrolidine is added drop by drop, while the temperature is kept between 0 and +5°C. The medium is reacted for 3 hours at room temperature, then the solution is evaporated dry under vacuum. The residue is dissolved in 250ml of water and 50ml of hydrochloric acid. The solution is extracted twice with 125ml of methylene chloride, which is eliminated. The aqueous phase is made alkaline with 70ml of soda lye.

An oil is precipitated. It crystallises slowly. The crystals are drained, washed with water and dried in an oven at 50°C.

79g of product is obtained and is re-crystallised in 1,975ml of ethyl acetate. 38.2g of amide is obtained, melting at 170°C.

EXAMPLE 7

N-(1-cyclohexyl-2-pyrrolidylmethyl)-2-methoxy-4,5-azimido benzamide.

117g of 5-carbomethoxy-6-methoxy-benzotriazol (0.565 mole), 52ml of water and 154g of 1-cyclohexyl-2-aminomethyl-pyrrolidine (0.565 mole + 50% excess) are placed in a 500ml flask fitted with a reflux condenser. The suspension is heated in a water bath and dissolves rapidly. Heating is continued for 8 hours 30. A sample which is then taken is entirely soluble in dilute acids.

The solution is diluted with 500ml of water; the base crystallises rapidly. It is drained, washed with water and dried in an oven at 50°C. 143g of product is obtained; it melts, but not in a clear cut way, at 115—118°C.

140g of base is suspended in 450ml of water. 33ml of hydrochloric acid (sp. gr. 1.18) is added. The hydrochloride forms immediately. It is brought to the boil, and the solution obtained is filtered, then cooled. The hydrochloride crystallises in a thick mass, which is drained, washed with 50ml of ice water and dried. Draining takes a long time and the product retains a great deal of water. 144g of product is obtained (melting point 153—155°C). The 144g of hydrochloride is dissolved in 700ml of hot water.

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and the solution is filtered with charcoal and the base precipitated by adding 400ml of 20% ammonia. It is liquid at first but crystallises rapidly. The crystals are drained, washed with water and dried at 50°C. 126g of product is obtained; this melts, but not in a clear cut way, at 110 to 115°C.

This base is dissolved in 250ml of isopropanol and heated. The suspension is cooled, drained, washed with 30ml of isopropanol and dried in air, then at 50°C.

114g of N-(1-cyclohexyl-2-pyrrolidylmethyl)-2-methoxy-4,5-azimidobenzamide is obtained, melting at 173—174°C. Yield = 56%.

EXAMPLE 8

N-(1-cyclopropylmethyl-2-pyrrolidylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

2-methoxy-3-isopropyl-6-methylbenzoic acid.

262g of *o*-thymotic acid (1.35 mole), 270ml of 40% soda lye and 400ml of water are placed in a 3 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The solution is heated to reflux and 255ml of dimethyl sulphate is added drop by drop. The reflux is maintained for 30 minutes, then 70ml of soda lye is added and 65m of dimethyl sulphate is dripped in. The reaction is allowed to proceed for 15 minutes, the pH is adjusted to 8—9 by adding 20ml of soda, and the suspension is cooled to about 10°C. It is acidified with 80ml of hydrochloric acid, and the suspension is extracted 3 times with 200ml of ether. The organic phase is evaporated dry under vacuum.

The oily residue is added to a solution of 180g of potash in pellet form in 675ml of ethanol at 95°. It is heated to reflux for 1 hour and cooled, then the suspension is evaporated and the residue dissolved in water. The liquid is acidified to pH = 1 with hydrochloric acid, and the suspension is extracted 3 times with 300ml of ether. The organic phase is washed with water, dried over magnesium sulphate and filtered, and the solvent is evaporated under vacuum.

The residue is re-crystallised in 250ml of petroleum ether, drained and washed 3 times with 100ml of petroleum ether, and the white crystals are dried in an oven at 40°C.

217g (77%) of product is obtained, melting at 68°C.

2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzoic acid.

1,200ml of chlorosulphonic acid is placed in a 4-litre flask fitted with an agitator and a thermometer. 250g of 2-methoxy-3-isopropyl-6-methyl benzoic acid (1.20 moles) is added in stages between 10 and 15°C. The mixture is agitated for 9 hours at room temperature then left to stand, and the solution is poured drop by drop into a 20 litre reactor containing crushed ice. Effective agitation is necessary, and the temperature is always kept below +5°C by periodically adding ice. Altogether 10 to 11kg of ice is used.

The precipitate is filtered, washed with water then introduced in stages into 800ml of 23% ammonia kept between —5 and +5°C.

When the solids have completely dissolved, the solution is left to stand then filtered in the presence of carbon black. The filtrate is acidified with 500ml of hydrochloric acid (sp. gr. 1.18). It is crystallised in a refrigerator, filtered and washed with water. The crystals, which are white, are dried in an oven at 50°C. 291g (84%) of product is obtained, melting at 198°C.

2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzoyl chloride.

72g of 2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzoic acid (0.25 mole), 250 ml of chloroform, 23ml of thionyl chloride and 3 drops of dimethylformamide are placed in a 1-litre flask fitted with an agitator and a condenser. The mixture is heated to reflux for 1.5 hours, then 18ml of thionyl chloride is added and the reflux is continued for 1.5 hours. The solids dissolve completely.

The solution is cooled and evaporated dry under vacuum, then 100ml of chloroform is added to the residue and evaporation is continued. There is an oily residue.

N-(1-cyclopropylmethyl-2-pyrrolidylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

4.3g of 1-cyclopropylmethyl-2-aminomethyl-pyrrolidine (0.028 mole) and 40ml of methylethyl ketone are placed in 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is cooled to about 10°C and a soution of 7.6g of 2-methoxy-3-isopropyl-5-sulphamoyl-6-methyl benzoyl chloride (0.025 mole) in 50ml of methyl ethyl ketone is poured in drop by drop. The mixture is reacted for 1 hour at room temperature then evaporated dry under vacuum, and the residue is dissolved in 100ml of water and 10ml of hydrochloric acid (density 1.18). The solution is subjected to reduced pressure to remove the last traces of solvent, an insoluble component is filtered off and the filtrate is made alkaline with 15ml of ammonia (density = 0.91). The precipitate formed is filtered, washed with water and re-crystallised moist in 50ml of ethyl acetate. 2.5g (24%) of product is obtained, melting at about 125°C.

EXAMPLE 9

N-(1-cyclopentyl-2-pyrrolidylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

3.4g of 1-cyclopentyl-2-aminomethylpyrrolidine (0.020 mole) and 40ml of methyl ethyl ketone

are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is cooled to about +10°C, then a solution of 5.5g of 2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzoyl chloride (0.018 mole) in 40ml of methyl ethyl ketone is poured in drop by drop. The mixture is reacted 1 hour at room temperature, then the solvent is evaporated under vacuum and the residue dissolved in 100ml of hydrochloric acid (density 1.18). An insoluble rubbery product is filtered off, and the filtrate is made alkaline with 15ml of ammonia (sp. gr. 0.91). The precipitate formed is filtered, washed with water then re-crystallised in 30ml of ethyl acetate. The crystals are filtered, washed with a little solvent and dried in an oven at 50°C. 1.3g (17%) of product is obtained, melting at 196°C.

EXAMPLE 10

N-(1-cyclohexylmethyl-2-pyrrolidylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

4.4g of 1-cyclohexylmethyl-2-aminomethylpyrrolidine (0.22 mole) and 40ml of methyl ethyl ketone are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is cooled to about 10°C, and a solution of 6.1g of 2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzoyl chloride (0.20 mole) in 40ml of methyl-ethyl-ketone is added drop by drop. The reaction medium is agitated for 1 hour at room temperature, then the solution is evaporated under vacuum. The residue is dissolved in 100ml of water and 10ml of hydrochloric acid (density 1.18). An insoluble viscous product is filtered off. The filtrate is made alkaline with 15ml of ammonia (sp. gr. 0.91). An oil is salted out, then crystallises slowly. The crystals are filtered off, washed with water and re-crystallised moist in 50 ml of isopropyl ether. 1.4g of product is obtained.

It is dissolved in 50ml of water, 1ml of hydrochloric acid (sp. gr. 1.18) and 30ml of acetone. 50ml of water is added, and the acetone is distilled under vacuum. The remaining aqueous solution is made alkaline with 2ml of ammonia (sp. gr. 0.91). The precipitate formed is filtered, washed with water and dried in an oven at 50°C.

1.2g (13%) of product is obtained, which melts to a viscous consistency at about 90°C. The NMR and IR spectra are compatible with the structure proposed.

EXAMPLE 11

N-(1-norbornyl-2-pyrrolidylmethyl)-2-methoxy-5-methyl-sulphonyl benzamide.

69g of 2-methoxy-5-methylsulphonylbenzoic acid (0.30 mole), 360ml of acetone, 120ml of water and 30.3g of triethylamine (0.30 mole) are placed in a 1-litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The solution is chilled to 0°C, then 40.8g of isobutyl chloroformate (0.30 mole) is added drop by drop. The mixture is agitated for 30 minutes at room temperature, then chilled to 0°C again, and 58.2g of 1-norbornyl-2-aminomethyl pyrrolidine (0.30 mole) is poured in drop by drop. The reaction mixture is agitated for 3 hours at room temperature then evaporated dry. The residue is dissolved in 500ml of water and 80ml of hydrochloric acid (sp. gr. 1.18). The solution is filtered with acticarbone 3S and the filtrate is made alkaline with 120ml of soda lye. A thick oil is decanted off, washed with 500ml of water then dissolved hot, at about 60°C, in 90ml of ethyl acetate. The product crystallises. The crystals are frozen, filtered and washed in water and dried in an oven at 60°C. 72g of product is obtained (melting point 125°C). This is re-crystallised in 150ml of isopropanol to give 62g (51%) of amide melting at 132°C.

EXAMPLE 12

N-(1-(-2-norbornyl)-2-pyrrolidyl)methyl)-2-methoxy-4-amino-5-ethyl sulphonyl-benzamide.

26g of 2-methoxy-4-amino-5-ethylsulphonylbenzoic acid (0.1 mole), 100ml of acetone, 26m of water and 10g of triethylamine (0.1 mole) are placed in a 500ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. When the acid has dissolved, the solution is cooled to 5°C and 14g of isobutyl chloroformate (0.102 mole) is added drop by drop. The reaction medium is agitated for 30 minutes between +5 and +10°C then cooled to +5°C again. 20g of 1-(-2'-norbornyl)-2-aminomethyl pyrrolidine (0.103 mole) is added drop by drop, then the medium is reacted from 2 hours at room temperature. The solvents are evaporated under vacuum, and the viscous residue is dissolved in 200ml of water and 50ml of acetic acid. The solution is filtered, and the filtrate is made alkaline with 500ml of soda lye. The product is crystallised in the refrigerator, filtered, washed with water, dried in an oven, then re-crystallised in 200ml of methanol. The white crystals are filtered, washed with a little chilled methanol and dried in an oven at 50°C. 25g (57%) of product is obtained, melting at 175°C.

EXAMPLE 13

N-(-1-norbornyl-2-pyrrolidylmethyl)-2-methoxy-4-bromo-5-sulphamoyl benzamide.

2-methoxy-4-bromo-5-chlorosulphonyl-benzoic acid.

300ml of chlorosulphonic acid of sp. gr. 1.766 (4.55 mole) is placed in a 1-litre flask fitted with an agitator, a thermometer and a condenser, and 69.3g of 2-methoxy-4-bromobenzoic acid (0.30 mole) is added in stages. The reaction is slightly exothermic and the temperature reaches 40°C by the time all

the benzoic acid has been added. The reaction medium is heated to 80°C then returned to room temperature. The solution, which is brown, is poured slowly over 2kg of crushed ice.

The precipitate formed is filtered, washed with water and dried in an oven at 50°C for 4 hours. 94g of product is obtained, melting at 194°C.

2-methoxy-4-bromo-5-sulphamoyl-benzoic acid.

1,290ml of 22°Bé. ammonia is placed in a 3-litre flask fitted with an agitator and a thermometer. It is cooled, and 805g of 2-methoxy-4-bromo-5-chlorosulphonyl-benzoic acid is added in stages between 0 and +10°C. The reaction medium is agitated for 1 hour at about +10°C then the solution is filtered with charcoal. The filtrate is diluted with 300ml of water and the acid precipitated by adding hydrochloric acid (sp. gr. 1.18). The precipitate is drained, washed with water and dried in an oven at 50°C. 645g (85%) of product is obtained; melting at 256°C.

2-methoxy-4-bromo-5-sulphamoyl-benzoyl chloride.

183ml of thionyl chloride (sp. gr. 1.64), 61g of 2-methoxy-4-bromo-5-sulphamoyl-benzoic acid (0.197 mole) and 2 drops of dimethylformamide are placed in a 500 ml flask fitted with an agitator, a condenser and a thermometer and are gradually heated to reflux. The reflux is maintained for 2 hours, then the excess $SOCl_2$ is expelled by distillation under vacuum. The residue is dissolved in 100ml of toluene which is then expelled under vacuum. The product is dissolved in 180ml of hexane, drained, washed with 40ml of hexane and dried in an oven for 2 hours.

62g (96%) of product is obtained; this decomposes at 185°C.

N-(1-norbornyl-2-pyrrolidylmethyl)-2-methoxy-4-bromo-5-sulphamoyl-benzamide.

65g of 1-norbornyl-2-amino-methyl-pyrrolidine (0.335 mole) and 500ml of methyl ethyl ketone are placed in a 3 litre flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to +5°C, then a filtered solution of 109g of 2-methoxy-4-bromo-5-sulphamoyl-benzoyl chloride in 2,000ml of methyl ethyl ketone is poured in drop by drop. The reaction medium is allowed to return to room temperature then left for 24 hours. The precipitate formed is filtered, washed with water and dried in an oven at 60°C. 146g of product is obtained, with a melting point of over 250°C. This is suspended in 4 litres of boiling water, 200ml of ammonia is added and the suspension is agitated for 1 hour at 80°C. It is cooled to 40°C and filtered. The white crystals are washed with water then re-suspended in 200ml of water. 100ml of acetic acid is added, the solution obtained is filtered with charcoal and the base precipitated by adding 350ml of ammonia. The crystals are drained, washed with water and dried in an oven at 60°C. 115g (71%) of amide is obtained, melting at 202°C.

EXAMPLE 14

N-(1-cycloheptyl-2-pyrrolidinylmethyl)-2-methoxy-4-chloro-5-ethylsulphonyl-benzamide.

39g of 1-cycloheptyl-2-aminomethylpyrrolidine (0.200 mole) and 150ml of methyl ethyl ketone are placed in a 1 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The solution is cooled to +10°C, then 55g of 2-methoxy-4-chloro-5-ethyl-sulphonyl-benzoyl chloride is added in stages. The reaction medium is agitated for 8 hours at room temperature then left to stand.

The precipitate is filtered, washed with a little ethanol and dried in an oven. Yield 78g (85.5%). Melting point—160—170°C with decomposition.

The hydrochloride is dissolved hot in 500ml of water. The solution is filtered in the presence of 3S black, then the filtrate is rendered alkaline with 60m of soda lye. An oil is precipitated. After 2 days in an ice chamber the crystals formed are filtered, washed with water and dried in an oven at 40°C. 52.5g of product is obtained and is dissolved in 200ml of water and 7g of acetic acid. The solution is diluted to 10% and filtered in the presence of carbon black. The product is re-precipitated by rendering the solution alkaline with 130ml of 1N soda. The oil is crystallised, then the crystals are filtered, washed with water and dried in an oven. The product is re-crystallised in a 100ml of isopropanol. 43g (51%) of product is obtained, with a melting point of 110°C.

EXAMPLE 15

N-(1-cyclohexyl-methyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-chlorobenzamide.

8g of 2-methoxy-4-amino-5-chlorobenzoic acid (0.040 mole), 50ml of acetone and 4g of triethylamine (0.040 mole) are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The suspension is cooled and 5.5g of isobutyl chloroformate (0.040 mole) is added drop by drop between 0 and +5°C. The reaction medium is agitated for 45 minutes with the temperature kept between 0 and +5°C, then 8g of 1-cyclohexyl-methyl-3-aminopyrrolidine (0.044 mole) is added drop by drop. The reaction is allowed to continue for 2 hours at room temperature, then 80ml of water is added and the acetone is expelled. The product crystallises in the residual water. It is filtered and re-dissolved in 150ml of water and 5ml of concentrated hydrochloric acid. The solution is filtered with charcoal and the filtrate is made alkaline with 10ml of ammonia (sp. gr. 0.91). The viscous precipitate is decanted and dissolved in 80ml of water and 5ml of hydrochloric acid. The product is dissolved and the hydrochloride is precipitated very rapidly. It is drained, washed with water and dried at 50°C. 10.4g of product is obtained and is dissolved hot in 100ml of water. The solution is rendered

alkaline with 10ml of soda lye. The oily precipitate is crystallised by cooling. It is drained, washed with water and dried in an oven at 50°C.

The product is re-crystallised in 50ml of diethylcarbonate. 7.7g (53%) of product is obtained. Melting point about 110°C.

EXAMPLE 16

N-(1-cyclopropylmethyl-3-pyrrolidyl)-2-methoxy-4-bromo-5-methyl-sulphonyl-benzamide.

2-methoxy-4-bromo-5-methylsulphonyl benzoic acid.

66g of sodium sulphite, 80g of sodium bicarbonate and 280ml of water are placed in a flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The mixture is heated to 60°C, then 92.4g of 2-methoxy-4-bromo-5-chlorosulphonyl benzoic acid is added in stages.

When the reaction medium has been heated to 60—70°C for 3 hours 60g of sodium bicarbonate is added then 106g of dimethylsulphate is introduced slowly. The mixture is heated to reflux then cooled and acidified with hydrochloric acid. The precipitate formed is drained and dried in an oven at 50°C, then poured into 250ml of boiling water. The suspension formed is agitated at boiling point, filtered hot, then the crystals are dried in an oven at 50°C. 34g of 2-methoxy-4-bromo-5-methylsulphonyl benzoic acid is obtained (melting point 225—258°C. Yield = 39.3%).

N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-4-bromo-5-methylsulphonyl-benzamide.

9.3g of 2-methoxy-4-bromo-5-methylsulphonyl benzoic acid (0.030 mole), 70ml of acetone, 10ml of water and 4.2ml of triethylamine of density 0.72 (0.030 mole) are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. A solution is obtained and cooled to about 0°C. 4.2g of isobutyl chloroformate (0.030 mole) is added drop by drop, the reaction medium is agitated for 30 minutes with the temperature between 0 and +5°C, then 4.7g of 1-cyclopropylmethyl-3-aminopyrrolidine (0.033 mole) is poured in drop by drop. The reaction is continued for 2 hours at room temperature then 50ml of water and 5ml of soda lye are added. The acetone is evaporated under vacuum and the oil, which is insoluble in water, is extracted twice, each time with 50ml of methylene chloride. The organic solution is dried over magnesium sulphate and filtered, and the filtrate is evaporated under vacuum. The viscous residue is dissolved hot in 90ml of isopropanol. The solution is acidified with 7ml of 6N hydrochloric ethanol. The hydrochloride is crystallised in the refrigerator, then the crystals are filtered, washed with a little isopropanol and dried in an oven at 50°C.

The product is dissolved in 400ml of tepid water and the solution is filtered, then rendered alkaline with 5ml of soda lye. The base is precipitated in the form of an oil. The aqueous phase is decanted and the residue is dissolved hot in 100ml of methyl isobutyl ketone. It is crystallised in a refrigerator. The product is filtered, washed with a little methyl isobutyl ketone then with water and dried in an oven at 50°C. 5.4g (42%) of product is obtained, with a melting point of 147°C.

EXAMPLE 17

N-1-(cyclohexenyl)-methyl-2-pyrrolidylmethyl-2,3-dimethoxy-5-sulphamoyl-benzamide.

13g of 2,3-dimethoxy-5-sulphamoyl-benzoic acid (0.05 mole), 150ml of acetone, 35ml of water and 5g of triethylamine (0.05 mole) are placed in a 500ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The mixture is cooled to between 0 and +5°C and 5.5g of ethyl chloroformate (0.05 mole) is poured in drop by drop. The reaction medium is agitated until the precipitate is completely dissolved, then re-cooled to 0°C and 9.7g of 1-(1-cyclohexenyl)-methyl-2-aminomethyl-pyrrolidine (0.05 mole) is poured in drop by drop.

The medium is reacted for 5 hours at room temperature then left to stand. The solvents are evaporated under vacuum and the residue is dissolved in 150ml of hydrochloric acid (sp. gr. 1.18). An insoluble oil is decanted off, then the aqueous solution is made alkaline with 13ml of ammonia (sp. gr. 0.91). The precipitate formed is filtered, washed with water and re-crystallised in 120ml of isopropanol. 6.1g of product is obtained and is re-crystallised in 250ml of isopropanol. Yield = 4.5g (21%). M.P. = 169°C.

EXAMPLE 18

N-(1-cyclohexyl-2-pyrrolidyl-methyl)-2-propargyloxy-3,5-dichlorobenzamide.

Methyl 2-propargyloxy-3,5-dichlorobenzoate

A 5-litre flask fitted with a sealed agitator, a condenser and a thermometer is used. 320g of methyl 3,5-dichlorosalicylate (1.45 mole), 1,280ml of methyl ethyl ketone and 177g of propargyl bromide (1.45 mole + 3% excess) are placed in it, then 200g of potassium carbonate (1.45 mole) and 21.5g of sodium iodide (0.145 mole). A thick pulp is obtained, which becomes fluid when brought to reflux. The reflux is maintained for 8 hours.

Part of the methyl ethyl ketone is distilled, then the residue is dissolved in 2.8 litre of water in order to dissolve the mineral salts.

The precipitate is drained, washed with water until neutral and dried in air. 372g (99%) of ester is obtained, melting at 78 to 79°C.

2-propargyloxy-3,5-dichloro-benzoic acid.

372g of methyl 2-propargyloxy-3,5 dichlorobenzoate (1.45 mole) is dissolved hot in 720ml of ethanol (95°) in a 2-litre flask fitted with a reflux condenser. 145ml of 30% soda lye (1.45 mole) is added and the solution is heated to reflux for 1 hour 30. With the reflux still maintained, 1 litre of water is added to finish the reaction. The solution is cooled, poured into 6.2 litres of water then filtered with charcoal. The acid is precipitated by adding 170ml of concentrated hydrochloric acid. The white precipitate is drained, washed with water then dried in an oven at 60°.

340g of 2-propargyloxy-3,5-dichloro-benzoic acid is obtained. Yield 95.5%. M.P. = 163—164°C.

2-propargyloxy-3,5-dichloro-benzoyl chloride.

86g of 2-propargyloxy-3,5-dichlorobenzoic acid (0.35 mole) is reacted.

83.5g of thionyl chloride (2 × 0.35 mole) is placed in a 500ml flask fitted with a reflux condenser, followed by about half the organic acid, and the resultant suspension is heated gently in a water bath. Within an hour everything is dissolved. The solution is cooled and the second portion of acid is added. The mixture is heated until everything has dissolved, which takes 45 minutes.

The excess thionyl chloride is distilled under vacuum to constant weight. The remaining acid chloride crystallises. Weight obtained: 90g. Yield: 97%. M.P.: 63—64°C

N-(1-cyclohexyl-2-pyrrolidyl-methyl)-2-propargyloxy-3,5-dichlorobenzamide.

64g of 1-cyclohexyl-2-aminomethyl-pyrrolidine (0.35 mole) is dissolved in 190ml of chloroform in a 500ml flask fitted with an agitator and a thermometer. The solution is cooled to +5°C, then 92g of finely powdered 2-propargyloxy-3,5-dichlorobenzoyl chloride (0.35 mole) is gradually added in the course of about an hour, with the temperature kept between +5 and +10°C. The acid chloride gradually dissolves as this is added. The temperature is then raised to finish the reaction. The reaction mixture is dissolved in 1 litre of water then the chloroform is distilled. The aqueous solution which is left is filtered with charcoal, and the base is precipitated by adding 20% ammonia. It crystallises slowly. It is drained, washed with water and dried in an oven at 40°C. 137g of product is obtained, melting at 79—80°C.

The 137g of base is re-crystallised in 275ml of isopropanol. Weight obtained: 106g of product. M.P.: 84—85°C.

The product is purified by dissolving it in 1.5 litre of water and 29ml of concentrated hydrochloric acid, filtering the solution with charcoal then adding 20% ammonia. The base crystallises slowly. It is drained, washed with water until the Cl^- ions are eliminated, then dried in an oven at 40°C.

104g of N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-propargyloxy-3,5-dichloro-benzamide is obtained. This is a white substance which melts at 84 to 85°C.

EXAMPLE 19

N(1-(1'-adamantyl)-2-pyrrolidyl-methyl)-2-methoxy-5-sulphamoyl benzamide.

55g of 1-(1'adamantyl)-2-amino-methyl-pyrrolidine (0.235 mole), 300ml of methyl ethyl ketone and 100ml of water are placed in a 2 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel.

A filtered solution of 58g of 2-methoxy-5-sulphamoyl-benzoyl chloride (0.23 mole) in 700ml of methyl-ethyl-ketone is poured in drop by drop while the temperature is kept at about 20°C.

The reaction medium is agitated for 1 hour then filtered. The crystals are washed with water and dried in an oven at 50°C. 60g of product is obtained, melting between 250—270°C.

It is dissolved in 1 litre of water containing 80ml of glacial acetic acid. A light insoluble component is filtered off and the product is precipitated by adding ammonia to pH = 8—9.

52g of product is obtained, with a melting point of 245°C. After re-crystallisation in 700ml of methyl acetoacetate, then acidification and neutralisation in dioxan, 28g of product is obtained with a melting point of 250°C.

EXAMPLE 20

N(1-(1'-adamantyl)-2-pyrrolidinyl-methyl)-2-methoxy-5-methyl-sulphonyl benzamide.

46g of 1-(1'-adamantyl)-2-amino-methyl-pyrrolidine (0.2 mole), 300ml of methyl-ethyl-ketone and 50ml of water are placed in a 1-litre flask fitted with an agitator, a thermometer and a condenser, then 41g of 2-methoxy-4-methyl-sulphonyl-benzoyl chloride (0.16 mole) is added in stages.

The medium is reacted for 2 hours at 20°C, then the solution is evaporated under vacuum. 300ml of water and 30ml of 40% soda lye are added to the residue. The supernatant solution is decanted off and the viscous substance dissolved in 500ml of boiling ethanol. The product is filtered and crystallised by chilling.

The product is filtered and re-crystallised twice running in 500ml of ethanol. 35g (49%) of white crystals is obtained, with a melting point of 174°C.

EXAMPLE 21

N(1-(1'-adamantyl)-2-pyrrolidinyl-methyl)-2-methoxy-4-5-azimido benzamide.

56.5g of methyl 2-methoxy-4,5-azimido-benzoate (0.27 mole) in 400ml of butanol containing 70g of 1-(1'-adamantyl)-2-amino-methyl-pyrrolidine (0.3 mole) is fed at 80°C into a 1-litre flask fitted with a thermometer, and left to react for 60 hours in an oven at 70°C.

A light insoluble substance is filtered off hot and the filtrate is cooled and evaporated dry. The residue is dissolved hot in 600ml of water and 60m of hydrochloric acid (sp. gr. 1.18). The solution is filtered with carbon black then put in an ice chamber. The hydrochloride precipitate is filtered and dried in an oven. 87g of product is obtained. This is dissolved in 800ml of hot water then filtered with charcoal, and the base is precipitated by adding 195ml of 1*N* soda. It is cooled and 500ml of chloroform is added. The mixture is filtered, washed with water then with a little chloroform and isopropanol and dried in an oven at 50°C.

53g of base is obtained and is dissolved hot in 500ml of water and 20ml of concentrated hydrochloric acid. The hydrochloride is precipitated by cooling. It is filtered off, washed with water and dried in an oven at 50°C. 48g is obtained and is re-dissolved in 500ml of hot water. 107ml of 1N soda is added. The mixture is cooled, 500ml of chloroform is added and the white precipitate is filtered off. This is washed with water then with a little isopropanol. 40g of product is obtained. The hydrochloride formation and neutralisation are repeated to give 31.5g (28.6%) of base with a melting point of 251°C.

EXAMPLE 22

N(1-(1'-adamantyl)-2-pyrrolidinyl-methyl)-2-methoxy-5-ethyl-sulphonyl-benzamide.

70g of 1-(1'-adamantyl)-2-aminomethylpyrrolidine (0.3 mole), 400ml of methyl ethyl ketone and 150ml of water are placed in a 1 litre flask fitted with an agitator and a thermometer.

78g of 2-methoxy-5-ethylsulphonylbenzoyl chloride (0.297 mole) is added to the solution in stages. The reaction is exothermic and the temperature rises to 40°C. The medium is reacted for 3 hours then evaporated to dryness, and the residue is dissolved in 500ml of methylene chloride. The organic solution is washed with 200ml of 10% soda then dried over magnesium sulphate. It is filtered then the methylene chloride is evaporated. The viscous residue is dissolved in 500ml of boiling methanol. The product is crystallised by cooling, filtered and re-crystallised a second time in 400ml of methanol.

51.5g (37.7%) is obtained with a melting point of about 103°C.

EXAMPLE 23

N-(1-cyclopentyl-2-pyrrolidinyl-methyl)-2-methoxy-5-sulphamoyl-benzamide.

23g of methyl 2-methoxy-5-sulphamoyl benzoate (0.09 mole) is dissolved hot, at about 90°C, in 115m of glycol in a 500ml flask fitted with an agitator and a thermometer. The solution is cooled to 50°C and the ester re-crystallises. 19g of 1-cyclopentyl-2-amino-methyl-pyrrolidine is added. The suspension obtained is kept at 50°C. After 30 hours the ester is completely dissolved. The solution continues to be heated until a sample taken is found to be completely soluble in acetic acid. The solution is then cooled and the benzamide crystallises slowly. 150ml of water is added and the precipitate is drained, washed with water and dried. 23g (68%) of benzamide is obtained with a melting point of 147—148°C. Since the benzamide hydrochloride is relatively insoluble in water, the benzamide is purified by dissolving the base at boiling point in water and HCl then filtering the solution obtained with 1g of charcoal.

The hydrochloride is precipitated when cooled. It is drained, washed with 25m of cold water and dried. 21g (84%) of hydrochloride is obtained with a melting point of 237—238°C. The hydrochloride is dissolved in 150ml of hot water, the solution is filtered with 3g of charcoal and 6ml of NH_4OH is added. The base is precipitated, initially in a viscous state, then solidifies. It is drained, washed with water and dried. 18g of white crystals is obtained with a melting point of 156—157°C. Total yield 53%.

EXAMPLE 24

N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-methoxy-5-sulphamoyl-benzamide.

118g of ethyl 2-methoxy-5-sulphamoyl-benzoate, 41ml of water and 100g of 1-cyclohexyl-2-amino methyl-pyrrolidine are placed in a 500ml flask fitted with a condenser. The suspension obtained is heated in a water bath at 90—95°C. The ester dissolves gradually and after 2 hours 30 solubilisation is almost complete; the base formed then crystallises. Heating is continued until a sample taken is found to be totally soluble in dilute acids. The product obtained is dissolved in dilute acetic acid, the solution is filtered with charcoal, then the base is precipitated with 20% ammonia. The precipitate is initially in a viscous state, then solidifies. It is drained, washed with water until neutral and dried at 45°C. 152.5g (85%) of product is obtained with a melting point from 191—193°C.

148.5g of base is suspended in 1,200ml of water, 33ml of hydrochloric acid (sp. gr. 1.18) is added and the medium is heated to reflux until complete solubilisation is obtained. The solution is filtered with charcoal. The hydrochloride crystallises rapidly on cooling. It is drained, washed with 150ml of iced water then dried in an oven at 45°C.

150g of hydrochloride is collected, with a melting point of 245—250°C.

It is re-dissolved hot in 1,200ml of water, the solution is filtered with charcoal, then the base is precipitated by adding 40ml of 20% ammonia. The base is initially in a liquid state, then solidifies. It is drained, washed with water and dried at 50°C; the product is white and contains Cl^- ions.

The following treatment is therefore applied:

119g of base is dissolved in 480ml of water and the necessary acetic acid. The solution obtained is filtered with charcoal then the base is re-precipitated by adding 20% ammonia. It is drained, washed with water and dried at 45°C.

111g of N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-methoxy-5-sulphamoyl-benzamide is obtained, with a melting point of 194—195°C. Total yield 70%.

I.R. spectrum analysis shows that the product is a mixture of 2 polymorphic forms.

EXAMPLE 25

N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

Using a 1-litre flask fitted with an agitator, a thermometer and a dropping funnel, 98g of 2-methoxy-4-amino-5-ethylsulphonyl-benzoic acid (0.378 mole) is dissolved in 392ml of acetone, then 38g of triethyl amine (0.378 mole) is added. The triethyl amine salt of the organic acid crystallises immediately.

The suspension is cooled to 0°C then 41g of ethyl chloroformate (0.378 mole) is added drop by drop between 0 and 5°C. The salt is dissolved gradually and the triethylamine hydrochloride is precipitated in fine white crystals.

Once the introduction stage is over the medium is agitated for $\frac{1}{2}$ hour at 5°C, then 72g of 1-cyclohexyl-2-amino-methyl-pyrrolidine is added drop by drop while the temperature is kept between 5 and 10°C. Agitation is continued for 1 hour with a rise in temperature. The suspension is cooled, then the triethylamine hydrochloride is drained and washed with acetone.

The filtrate is distilled under vacuum to constant weight. The residue obtained is dissolved in 800ml of water and 35ml of concentrated hydrochloric acid. The solution is filtered with charcoal then made alkaline with 40ml of 20% ammonia. The base is precipitated in the form of oil, which is decanted off and extracted with methylene chloride. The organic solution obtained is washed several times with water and dried over potassium carbonate. The methylene chloride is then evaporated under vacuum to constant weight. The residue of 151g is dissolved in 300ml of hot isopropyl alcohol. The base is crystallised by cooling. It is drained, washed with isopropanol and dried at 45°. 125g of product is obtained, melting at 162—163°C. It is re-dissolved in 1 litre of water and 38ml of concentrated hydrochloric acid. The solution obtained is filtered with charcoal then made alkaline by adding 20% ammonia. The base precipitated is initially viscous then crystallises. It is drained, washed with water and dried in an oven at 50°C.

123g is obtained. The base contains a little water. It is crystallised in 355ml of methanol. 100g of N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphonyl benzamide is collected.

EXAMPLE 26

N-(1-cyclohexylmethyl-2-pyrrolidinyl-methyl)-2,3-dimethoxy-5-sulphamoyl benzamide.

26.1g of 2,3-dimethoxy-5-sulphamoyl-benzoic acid (0.10 mole), 40ml of water, 200ml of acetone and 10.1g of triethylamine (0.10 mole) are placed in a 500m flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to between 0 and +5°C and 10.9g of ethyl chloroformate (0.10 mole) is added drop by drop. It is agitated for 1 hour 30 with the temperature kept at about +5°C, then 19.6g of 1-cyclohexylmethyl-2-aminomethyl pyrrolidine (0.10 mole) is added drop by drop. A precipitate forms progressively as more and more is added. The reaction medium is then agitated at room temperature, after which it is left to stand. The crystals are filtered, washed three times with water then with 100ml of 10% ammonia and dried in an oven at 50°C. 50g is obtained.

The product is dissolved in 300ml of water and 10ml of acetic acid, the solution is filtered and the filtrate is rendered alkaline with 20ml of ammonia (density 0.91). It is crystallised in a refrigerator, filtered, washed with water and dried in an oven at 50°C. 28.5g of product is obtained. Yield: 65%. M.P.: 189°C.

EXAMPLE 27

N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2,3-dimethoxy-5-methylsulphamoyl benzamide.

125.5g of methyl 2,3-dimethoxy-5-methylsulphamoyl benzoate (0.434 mole) and 500ml of ethylene glycol are placed in a 1-litre flask, heated to 90° to dissolve everything, then cooled to 50°C. 95g of 1-cyclohexyl-2-aminomethylpyrrolidine is added. The reaction mixture is kept at 50°C for 106 hours. In the course of the reaction the base which forms is precipitated. The suspension is dissolved in 1.7 litres of water and 52ml of concentrated hydrochloric acid (density 1.18). The solution obtained is filtered with charcoal and the base is precipitated with 60ml of 20% ammonia. It is liquid at first, then solidifies. It is drained, washed with water and dried at 40°C. 176.5g of product is collected, with a melting point of 161—162°C.

The base is suspended in 2 litres of boiling water, after which a solution of 43g of 85% phosphoric acid and 200ml of water is added. The resultant solution is filtered with charcoal then chilled. The

phosphate which crystallises is drained, washed with 200ml of iced water and dried at 45°. 151g of white product is obtained.

The phosphate is dissolved hot in 1,800ml of water and the base is precipitated by 42ml of soda lye. The suspension is cooled and filtered. The precipitate is washed in water and dried at 45°C.

121g of benzamide is obtained, melting at 162—163°C. Yield: 64%.

EXAMPLE 28

N-(1-cyclohexyl-2-pyrrolidinylmethyl)2,3-dimethoxy-5-methylsulphamoyl benzamide.

55g of 2,3-dimethoxy-5-methylsulphamoyl benzoic acid, 300ml of tetrahydrofuran and 20.2g of triethylamine are placed in a 1-litre flask fitted with an agitator, a thermometer and a dropping funnel. The suspension is agitated for 30 minutes then cooled. 27.3g of isobutyl chloroformate is dripped in between 0 and +5°C then left to react for 45 minutes at the same temperature. 40g of 1-cyclohexyl-2-amino-methyl-pyrrolidine is next added drop by drop, between 0 and 5°C, agitated at that temperature for 30 minutes then for 2 hours at room temperature. It is left to stand, then the precipitate is filtered off, washed with 100ml of chilled tetrahydrofuran and dried in an oven at 40°C. The 91g of product obtained is suspended in 500ml of boiling water, which is agitated for 1 hour. The product is filtered off hot and dried in an oven at 60°C.

60g of product is obtained. This is dissolved in 290ml of 0.5*N* hydrochloric acid and filtered with acticarbone 3S.

The filtrate is made alkaline with 20% ammonia. The precipitate is drained, washed with water then re-dissolved hot in 420ml of 90% ethanol. It is re-crystallised in a refrigerator, filtered, washed with water and dried in an oven at 50°C.

55g of product is obtained, melting at 166°C. Yield: 63%.

EXAMPLE 29

N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphamoyl-benzamide.

123g of ethyl 2-methoxy-5-methylsulphamoyl benzoate, 40ml of water and 98g of 1-cyclohexyl-2-aminomethyl-pyrrolidine are placed in a 500ml flask fitted with a reflux condenser. The suspension is heated in a water bath at 90—95°C. In 10 minutes the ester is completely dissolved. Heating is continued for 8 hours. The reaction medium is cooled and the base crystallises. It is re-dissolved in 800ml of water and the necessary acetic acid. The solution is filtered with charcoal and the base is precipitated by adding 20% ammonia, with ether present to encourage crystallisation.

The precipitate is drained, washed with water and dried in an oven at 45°C. 153g of product is obtained, melting at 142—145°C.

The base is re-crystallised, with filtration through charcoal, in 310ml of absolute ethanol. 118g is obtained, with a melting point of 149—151°C.

A second re-crystallisation is carried out in 240ml of absolute ethanol with filtration through charcoal. The N-(1-cyclohexyl-2-pyrrolidinyl methyl) 2-methoxy-5-methyl-sulphamoyl-benzamide is obtained in the form of yellowish white crystals which melt 149—151°C. Yield = 57%.

The infra-red spectrum shows the product obtained to be a mixture of 2 crystalline forms.

EXAMPLE 30

N-(1-cyclopropyl-2-pyrrolidinyl methyl)-2-methoxy-5-methyl sulfinyl benzamide.

53.5g of 2-methoxy-5-methyl sulfinyl benzoic acid, 740ml of acetone, 140ml of water and 35ml of triethylamine (density 0.726) are placed in a 2 litre flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to between 0 and +5°C, after which 34.1g of isobutyl chloroformate is dripped in. The mixture is agitated for 45 minutes at 20°C then cooled to 0°C, and 42g of 1-cyclopropyl-2-amino methyl pyrrolidine is poured in drop by drop. The mixture is reacted at room temperature and then left to stand. The solvents are evaporated under vacuum. The oily residue is dissolved in 250ml of water and 50ml of hydrochloric acid (density 1.18) and extracted twice with 125ml of methylene chloride. The aqueous phase is then made alkaline with 70ml of soda lye. A yellow oil is salted out. It is extracted 3 times with 250ml of methylene chloride and the organic phase is washed 3 times with 100ml of water and dried over magnesium sulphate. The solution is filtered and the solvent evaporated. An oily residue is obtained. It is dissolved in 500ml of ethanol and an equimolar quantity of citric acid is added. It is evaporated under vacuum and the residue is dissolved in a 1,000ml of boiling isopropanol then cooled. The supernatant solution is decanted off and the residual paste dissolved in 600ml of water. The solution is filtered with charcoal then the filtrate is evaporated under vacuum.

A very hygroscopic crystallised residue is obtained. Melting point about 70°C. NMR spectrum compatible.

EXAMPLE 31

N-(1-cyclopentyl-2-pyrrolidinyl methyl)-2-methoxy-4-amino-5-sulphamoyl benzamide.

104g of methyl 2-methoxy-4-amino-5-sulphamoyl benzoate (0.40 mole), 100.8g of 1-cyclopentyl-2-aminomethyl pyrrolidine (0.60 mole) and 36g of water are placed in a 1 litre flask fitted

with an agitator, a thermometer and a condenser. The mixture is heated to 90—95°C, left to stand then heated again to 95°C, distilling off the methanol formed. A sample of the reaction medium taken at that stage is completely soluble in a dilute solution of acetic acid. 500ml of water is added to the suspension, which is cooled and then filtered. The precipitate is washed with water, re-suspended in 500ml of water and acidified with 50ml of acetic acid. The solution obtained is filtered in the presence of carbon black and the filtrate is made alkaline with 150ml of ammonia. The precipitate is drained, washed with water and dried. 123g of product is obtained, melting at 225°C. It is re-crystallised twice in a solution of 600ml of dimethyl formamide and 210ml of water.

93g of product is obtained, containing a little solvent. The crystals are re-dissolved in 500ml of water and 30ml of acetic acid and are filtered with charcoal. The base is precipitated by adding 100ml of ammonia to the filtrate. The white precipitate is drained, washed with water and dried in an oven at 60°C.

80g of amide is obtained, melting at 232°C. Yield 50.5%.

EXAMPLE 32

N-(1-cyclohexyl-2-pyrrolidinylmethyl-2-methoxy-4-amino-5-methylsulphamoyl benzamide.

58.5g of 2-methoxy-4-amino-5-methylsulphamoyl benzoic acid and 585ml of acetone are placed in a 2-litre flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is agitated and 22.7g of triethylamine is added. A rubbery precipitate forms which then crystallises slowly. After being agitated for 45 minutes the suspension is cooled to 0°C and 24.4g of ethyl chloroformate is added drop by drop between 0 and 5°C. This is agitated for 45 minutes between 0 and 5°C, then 45.5g of 1-cyclohexyl-2-aminomethyl-pyrrolidine is dripped in. The medium is reacted cold for 30 minutes then left to stand at room temperature. The triethylamine hydrochloride precipitate is filtered off and washed with 100ml of acetone. The organic solution is evaporated to dryness under vacuum. The residue is dissolved in 500ml of water and 50ml of concentrated hydrochloric acid. The aqueous phase is extracted with 250ml of methylene chloride, which is expelled. The aqueous phase is made alkaline with 70ml of soda lye and the suspension is extracted twice with 250ml of methylene chloride. The organic phase is washed twice with 250ml of water, dried over magnesium sulphate then evaporated to dryness under vacuum. The residue is dissolved in 400ml of isopropanol, 100ml of hydrochloric isopropanol (≃5N) is added and the hydrochloride is crystallised in a refrigerator. The precipitate is drained, made into a paste with 300ml of acetone and dried in an oven at 50°C.

76g is obtained (M.P. about 200° with decomposition).

The product is re-crystallised in 500ml of ethanol. It is placed in an ice chamber for 3 days, then the white crystals are drained, washed twice with 60ml of iced ethanol and dried in an oven at 30° then at 60°C.

64g of hydrochloride is obtained. This melts at about 208°C with decomposition.

EXAMPLE 33

N-(1-cyclohexyl methyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

25.9g of 2-methoxy-4-amino-5-ethylsulphonyl benzoic acid, 40ml of water, 200ml of acetone and 13.9ml of triethylamine (density 0.726) are placed in a 500ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to about 0 to 5°C and 10.9g of ethyl chloroformate is dripped in. The mixture is agitated for 40 minutes at about 0°C, then 19.6g of 1-cyclohexyl-methyl-2-aminomethyl pyrrolidine is added drop by drop. The mixture is agitated for 2 hours at room temperature then left to stand. The acetone is evaporated under vacuum and the residue is dissolved in 100ml of water and 25ml of acetic acid and filtered in the presence of vegetable black. The filtrate is made alkaline with 100ml of 40% soda lye. A precipitate is formed; this is filtered, washed with plenty of water and dissolved moist in 230ml of boiling acetone. The hot solution is filtered in the presence of vegetable black and the filtrate is crystallised. The product is drained, washed with a little acetone and dried in an oven at 50°C.

25g (57%) of product is collected: melting point 155°C.

EXAMPLE 34

N-(1-cyclohexyl-2-pyrrolidinyl methyl)-2-methoxy-4-amino-5-methylsulphinyl benzamide.

2-methoxy-4-amino-5-methylthio benzoic acid.

3600ml of methanol is placed in a 6 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel, and 495g of potash (84% in pellet form) is added in stages. The temperature reaches 60°C and the potash is completely dissolved. 357g of methyl 2-methoxy-4-amino-5-thiocyano benzoate is then added and 280ml of methyl iodide (density 2.28) is poured in drop by drop while the temperature is kept between 55 and 60°C. The mixture is heated to reflux then cooled to 15°C and the mineral salts are filtered off. The filtrate is evaporated to dryness under vacuum. The solid residue is dissolved in 1,500ml of water; the solution is filtered in the presence of vegetable black, after which the filtrate is acidified to pH 2—3 with hydrochloric acid. The precipitate which appears is drained, washed with water and dried in an oven at 50°C. Yield: 260g (81%). M.P.: 143°C.

2-methoxy-4-acetamido-5-methyl-thio-benzoic acid.

260g of 2-methoxy-4-amino-5-methyl-thio-benzoic acid and 520ml of acetic acid are placed in a 2 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. 123ml of acetic anhydride (density 1.082) is poured in slowly. The temperature rises to reach 40°C. The reaction mixture is heated for 1 hour 30 at 85°C, cooled and poured over 1,000g of ice and 1,000ml of water. The precipitate which forms is filtered, washed with water and dried in an oven at 50°C.

278g (89%) of product is obtained, melting at 165°C.

2-methoxy-4-acetamido-5-methyl-sulphinyl-benzoic acid.

127.5g of 2-methoxy-4-acetamido-5-methyl thio-benzoic acid and 200ml of acetic acid are placed in a 500ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. A solution of 50ml of 110 vol. hydrogen peroxide in 100ml of acetic acid is poured drop by drop onto the suspension obtained. The reaction is exothermic. The temperature is kept between 20 and 30°C by cooling. 30 minutes after the introduction stage is over the solution is clear. It is kept at from 25—30°C for a further 2 hours, the solvent is evaporated to dryness under vacuum, and the viscous residue is dissolved in 250ml of acetone. The crystals formed are filtered, washed with a little acetone and dried in an oven at 50°C.

110g (81%) of product is obtained, melting at 196°C.

N-(1-cyclohexyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-methyl-sulphinyl-benzamide.

81.3g of 2-methoxy-4-acetamido-5-methylsulphinyl-benzoic acid (0.30 mole), 600ml of acetone, 120ml of water and 41.7ml of triethylamine with a density of 0.726 (0.30 mole) are placed in a 1 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The mixture is cooled to 0°C and 40.8g of isobutyl chloroformate (0.30 mole) is poured in drop by drop. It is agitated for 30 minutes with the cooling bath removed, cooled to 0°C again and 54.6g of 1-cyclohexyl-2-aminomethyl-pyrrolidine (0.30 mole) is poured in drop by drop. The mixture is reacted for 1 hour at room temperature with agitation, and left to stand. The solution is evaporated to dryness. A paste is obtained and is dissolved in 200ml of soda and 400ml of water. It is heated to reflux for 2 hours, and 50ml of a mixture distilling over at low temperature is distilled off then put back under reflux. The reaction medium is left to stand, then the suspension is extracted four times with 200ml of methylene chloride. The organic phase is washed twice with 300ml of 10% hydrochloric acid, the aqueous phase is filtered with carbon black and the filtrate is made alkaline with 300ml of 40% soda. The suspension is extracted 3 times, each time with 300ml of methylene chloride. The organic solution is washed with water and dried over magnesium sulphate. The solution is filtered and evaporated to dryness. 42.5g (36%) of benzamide is obtained; this does not crystallise.

The product is solubilised in 150ml of isopropanol, and a soution of 22.7g of citric acid, H_2O in 200ml of isopropanol is added hot. This is evaporated to dryness, dissolved in 500ml of water and filtered in the presence of 3S carbon black, and the filtrate is evaporated to dryness under vacuum.

50.3g (29%) of product is obtained, melting at about 125°C.

The NMR and IR spectra are compatible with the structure of the product.

EXAMPLE 35

N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethyl-sulphinyl benzamide.

2-methoxy-4-acetamido-5-ethylsulphinyl benzoic acid.

123.7g of 2-methoxy-4-acetamido-5-ethyl thiobenzoic acid and 184ml of acetic acid are placed in a 1 litre flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. A solution of 46.5ml of 110 vol. hydrogen peroxide in 103ml of acetic acid is poured in drop by drop. The reaction is exothermic and the temperature is kept at about 30°C. The product is completely dissolved, then a white precipitate appears. Agitation is continued for 1 hour, after which the suspension is cooled to 10°. The precipitate is drained, washed with acetic acid and dried in an oven at 50°C.

90g of product is obtained, melting at 199°C (yield 69%).

N-(1-cyclopentyl-2-pyrrolidinyl-methyl)-2-methoxy-4-amino-5-ethylsulphinyl benzamide.

85.5g of 2-methoxy-4-acetamido-5-ethylsulphinyl benzoic acid, 85ml of water, 342ml of acetone and 31g of triethylamine are placed in a 1-litre flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is agitated until the solids dissolve, then 32.5g of ethyl chloroformate is added drop by drop while the temperature is kept at about 10°C. The reaction medium is agitated for 30 minutes at room temperature then cooled to 5—10°C and 50.4g of 1-cyclopentyl-2-aminomethyl-pyrrolidine is added drop by drop in the course of 1 hour. Agitation is continued for 2 hours at room temperature, then the reaction mixture is evaporated to dryness under vacuum. The residue is dissolved in 300ml of water and the suspension is extracted with 500ml then twice with 300ml of methylene chloride. The organic phase is washed twice with 200ml of water and evaporated under vacuum. The oily residue is dissolved hot in 300ml of water. 90ml of soda lye is added and the medium is heated to reflux for 2 hours 30. An oil appears rapidly. It is cooled, the suspension is extracted twice with 250ml

methylene chloride, and the organic solution is washed three times with 200ml of water. It is dried over magnesium sulphate, filtered and evaporated to dryness under vacuum. The residue is dissolved in 320ml of ethyl acetate, then the product is left to crystallise in a refrigerator. The crystals are filtered off and dried in an oven at 50°C.

65g of product is obtained (melting point 168°C). It is re-crystallised in 200ml of isopropanol and 10ml of water. The solution is chilled for 24 hours, then the crystals are filtered off and dried.

33g of product is obtained, melting at 183°C (yield 28%).

EXAMPLE 36

N-(1-cyclopentyl-2-pyrrolidinyl methyl)-2,4-dimethoxy-5-ethylsulphonyl benzamide.

2,4-dimethoxy-5-chlorosulphonyl benzoic acid.

1,800ml of chlorosulphonic acid is placed in a 4 litre flask fitted with an agitator and a thermometer, and is cooled to 10°C. 328g of finely powdered 2,4-dimethoxy benzoic acid is added in stages in the course of 45 minutes, between 10 and 15°C. The acid dissolves gradually as it is introduced. When all the acid has been added the solution is gradually heated to 55°C and that temperature is maintained for 5 hours. The solution is left to stand overnight, then poured little by little into 17kg of ice, with agitation and with external cooling. The acid which is precipitated is drained, washed with water and dried in air.

456g is obtained. Yield 90%.

2,4-dimethoxy-5-mercaptobenzoic acid.

145g of 2,4-dimethoxy-5-chlorosulphonyl benzoic acid, 393ml of acetic acid and 230.5g of tin are placed in a 6 litre flask fitted with an agitator, a thermometer and a dropping funnel, and the thick suspension is heated to 40°C. 1,009ml of hydrochloric acid (density 1.18) is added drop by drop while cooling so as to keep the temperature at from 40 to 45°. The reaction is exothermic. The suspension dissolves gradually, the more acid is added, but the tin salts are precipitated about midway through the adding process. When all the acid has been added the water bath is heated to 55—60° until the tin has dissolved. 2 litres of water is drained and washed with 460ml of 10% hydrochloric acid, then with water. It is immediately re-dissolved in water and the necessary soda, the solution is filtered with charcoal, and the acid is re-precipitated by adding concentrated hydrochloric acid. The precipitate is drained, washed with water and dried in an oven at 40°.

86.5g is obtained. Yield 78%.

2,4-dimethoxy-5-ethylthiobenzoic acid.

In a 2 litre flask fitted with a reflux condenser, 173g of 2,4-dimethoxy-5-mercapto benzoic acid is dissolved in 525ml of water and 162ml of soda lye, and 135g of ethyl sulphate is added. The solution obtained is heated to reflux. It is cooled, then ethylation is recommenced with 40.5ml of soda lye and 76g of ethyl sulphate, and the medium is heated in the same way till it has very low alkalinity.

40ml of soda lye is added and the medium is heated for $\frac{1}{2}$ hour under reflux. The solution is then diluted with 1.4 litre of water and filtered through charcoal.

The acid is precipitated by adding hydrochloric acid, drained and washed with water. It is immediately re-dissolved in water and sodium carbonate, the solution is filtered with charcoal to eliminate an insoluble substance, and the acid is re-precipitated by adding concentrated hydrochloric acid. It is drained, washed with water and dried in an oven at 40°.

144g (74%) of product is obtained, with a melting point from 94 to 96°C.

2,4-dimethoxy-5-ethylsulphonyl benzoic acid.

124g of 2,4-dimethoxy-5-ethylthiobenzoic acid and 765ml of acetic acid are placed in a 3-litre flask fitted with a reflux condenser and are heated gently to dissolve all the solids. 306ml of 112 volume hydrogen peroxide is added; the solution immediately becomes clear. It is boiled gently for 3 hours and finally heated for 1 hour with the naked flame in order to destroy the excess hydrogen peroxide.

The 2,4-dimethoxy-5-ethylsulphonyl benzoic acid is crystallised by cooling. It is drained, washed with 120ml of acetic acid then water and dried at 40°C.

99g of product is collected with a melting point of 207—208°C. Yield 70%.

2,4-dimethoxy-5-ethylsulphonyl benzoyl chloride.

82.2g of 2,3-dimethoxy-5-ethylsulphonyl benzoic acid, 165ml of thionyl chloride and 3 drops of D.M.F. are placed in a 500ml flask fitted with an agitator, a reflux condenser and a thermometer.

The suspension is heated slowly to reflux. After 1 hour 30 the temperature is stabilised at 78—79°C. Heating is continued for another 2 hours, after which the solution is cooled slightly and the excess thionyl chloride expelled by distillation under vacuum. The solid residue is dissolved in 125ml of isopropyl ether and the crystals are filtered off. They are washed with 125ml of isopropyl ether, dried for 1 hour in an oven at 45—50°C, then kept in a desiccator under vacuum.

86g of acid chloride (98%) is obtained, with a melting point of 186°C.

N-(1-cyclopentyl-2-pyrrolidinyl methyl)-2,4-dimethoxy-5-ethyl sulphonyl-benzamide.

33.6g of 1-cyclopentyl-2-amino-methyl pyrrolidine and 200ml of methyl-ethyl-ketone are placed in a litre flask fitted with an agitator, a thermometer and a condenser. The solution is cooled, then 58.5g of 2,4-dimethoxy-5-ethylsulphonyl benzoyl chloride (0.2 mole) is added in stages over about 45 minutes, while the temperature is kept between 0 and +5°C. The solution obtained is kept at +5°C for 30 minutes and at room temperature for 2 hours 30. A precipitate forms after 1 hour's agitation at room temperature. The hydrochloride crystals are filtered, washed with 50ml of methyl-ethyl-ketone and dried in an oven at 50—60°C.

82g of hydrochloride is obtained, M.P. 186°C.

The product is dissolved in 400ml of water and filtered in the presence of charcoal. The filtrate is made alkaline with 25ml of soda lye diluted with 75ml of water. The precipitate crystallises rapidly. It is drained, washed with water and dried in an oven at 50—60°C.

69g of product is obtained, with a melting point of 113°C.

The base is re-crystallised in 210ml of 90% ethanol. The crystals are chilled overnight, drained and washed with 70ml of 90° ethanol then twice with 100ml of water. They are dried in an oven at 50°C.

62g (73%) of benzamide is obtained with a melting point of 162°C.

EXAMPLE 37

N-(1-cycloheptyl-2-pyrrolidinylmethyl)-2-methoxy-5-methyl sulphonyl-benzamide.

52g of 1-cycloheptyl-2-amino-methyl-pyrrolidine and 240ml of water are placed in a 500ml flask fitted with an agitator, a condenser and a thermometer. They are cooled to 0°, then 62.1g of 2-methoxy-5-methylsulphonyl-benzoyl chloride (0.250 mole) is added in stages while the temperature is kept at from 0 to +5°C. The temperature is raised; at about 20° an exothermic reaction commences and the temperature rises to 30°C. After 1 hour's agitation everything is dissolved. The reaction is continued for a further 30 minutes, then the solution is filtered in the presence of acticarbone 3S. The filtrate is made alkaline with 20ml of soda lye diluted with 80ml of water. The precipitate is initially rubbery, then crystallises. It is drained, washed with water and dried in an oven at 50°C.

90.5g is obtained, with a melting point from 112 to 114°C.

The base is re-crystallised twice, respectively in 225ml and 200ml of methanol containing 30% of water. The white crystals are drained and dried in an oven at 40°C.

54g of product is obtained with a melting point of 118°C. Yield 53%.

EXAMPLE 38

N-(1-cycloheptyl-methyl-2-pyrrolidinyl methyl)-2-methoxy-4-amino-5-methylsulphamoyl benzamide.

6.5g of 2-methoxy-4-amino-5-methylsulphamoyl benzoic acid, 75ml of acetone, 14ml of water and 3.5ml of triethylamine (density 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The solution is cooled to between 0 and +5°C and 2.7g of ethyl chloroformate is added drop by drop. The reaction medium is agitated for 45 minutes at room temperature then cooled to 0°C again. 6.8g of 1-cycloheptyl methyl-2-amino methyl pyrrolidine is added drop by drop. The medium is reacted for 2 hours then left to stand. The solvents are expelled and the solid residue dissolved in 50ml of water and 20ml of hydrochloric acid (density 1.18). The suspension obtained is made alkaline with ammonia. It is extracted 3 times with 50ml of methylene chloride. The organic phase is washed twice with 50ml of water, dried over magnesium sulphate and filtered. The filtrate is evaporated to dryness under vacuum. The residue is dissolved in 80ml of water and 20ml of hydrochloric acid (density 1.18). The hydrochloride crystallises. It is drained, washed with water and dried in an oven at 50°C.

7g of product is obtained, with a melting point of about 230°C.

It is re-crystallised in 300ml of ethanol.

4.3g (35%) of benzamide hydrochloride is obtained, with a melting point of 223°C.

EXAMPLE 39

N-(1-cycloheptyl methyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl benzamide.

4.9g of 2-methoxy-4-amino-5-ethylsulphonyl benzoic acid, 57ml of acetone, 10ml of water and 2.6ml of triethylamine (sp. gr. 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The solution is cooled to between 0 and +5°C and 2.1g of ethyl chloroformate is added drop by drop. The reaction medium is agitated for 45 minutes at room temperature then cooled to 0°C and 5.3g of 1-cycloheptyl methyl-2-amino methyl pyrrolidine is poured in drop by drop. The medium is agitated for 4 hours then left to stand overnight. The solvents are evaporated to dryness and the residue is dissolved in 60ml of water and 15ml of hydrochloric acid (sp. gr. 1.18). Extraction is carried out 3 times with 50ml of methylene chloride, the organic phase is dried over magnesium sulphate and filtered, and the solvent is evaporated under vacuum. The residue is dissolved in 100ml of water. The solution is filtered in the presence of carbon black and the filtrate is made alkaline with about 7ml of ammonia (sp. gr. 0.91). A gum is precipitated. It is extracted 3 times with 50ml of methylene chloride. The organic phase is washed twice with 50ml of water, dried over

magnesium sulphate and filtered. The solvent is evaporated under vacuum and the residue is re-crystallised in 100ml of isopropanol.

4.5g (52%) of product is obtained, with a melting point of 156°C.

EXAMPLE 40

N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2,4-dimethoxy-5-methylsulphonyl benzamide.

2,4-dimethoxy-5-methylsulphonyl benzoic acid.

930ml of water, 208g of sodium sulphite and 277g of sodium bicarbonate are placed in a 6 litre flask fitted with a sealed agitator, a reflux condenser and a thermometer. They are heated to 70—80° and 309g of 2,4-dimethoxy-5-chlorosulphonyl benzoic acid is added gradually.

A large amount of CO_2 is given off simultaneously with the dissolving of the acid. The acid takes 45 minutes to introduce. Heating is continued for a further 2 hours at 70—80° to complete the reaction. The pH of the solution is about 7.

220 cc of 30% soda lye, 1,120ml of absolute alcohol and 470g of methyl iodide are added to the reaction mixture and it is heated with a gentle reflux. After 3 hours 30 a weight loss of 50g is noted and the solution is found to be only very slightly alkaline to phenolphthalein.

50g of methyl iodide and 110 cc of soda lye are added and the medium is heated to reflux again. The initial reflux temperature rises progressively to 65° then to 75°. Another weight loss is observed but the solution remains alkaline. Heating is continued for 8 hours altogether.

500ml of alcohol is then distilled off. The residue is dissolved in 2 litres of water and the mineral salts dissolved. The solution obtained, which is slightly turbid, is filtered with charcoal. The 2,4-dimethoxy-5-methylsulphonyl benzoic acid is precipitated by adding concentrated hydrochloric acid until it turns Congo red. It is drained, washed with water and dried at 60°C.

255g of product is obtained (89%).

2,4-dimethoxy-5-methylsulphonyl-benzoyl chloride.

161g of 2,4-dimethoxy-5-methylsulphonyl-benzoic acid is reacted. 590g of thionyl chloride, 5 drops of dimethylformamide and about half of the organic acid are placed in a 2 litre flask fitted with a reflux condenser. The resultant suspension is heated in a water bath at 55° for about 5 minutes. The second half of the organic acid is added and heating is continued for 20 minutes at 60—65° then for 45 minutes at 70—75°. The medium becomes fluid and turns yellow. The acid dissolves gradually, while the acid chloride begins to crystallise. When the reaction is over the excess thionyl chloride is distilled to constant weight, finishing up under vacuum.

169g (98%) of acid chloride is obtained. This melts with decomposition at 200°C.

N-(1-cyclopropyl methyl-2-pyrrolidinyl methyl)-2,4-dimethoxy-5-methyl sulphonyl benzamide.

74g of 1-cyclopropylmethyl-2-aminomethyl-pyrrolidine and 460ml of chloroform are placed in a litre flask fitted with an agitator and a thermometer. 134g of finely powdered 2,4-dimethoxy-5-methylsulphonyl benzoyl chloride is added gradually. The temperature is kept between 5 and 10° by cooling in an iced bath. Each portion of acid chloride dissolves immediately. It takes 1 hour to introduce. Agitation is then continued for 1 hour at 5° then for 1 hour at room temperature.

The solution obtained is dissolved in 1 litre of water and the chloroform is distilled off. This leaves in suspension a light precipitate which is drained, washed and dried. 6g of 2,4-dimethoxy-5-methylsulphonyl benzoic acid is recovered in this way (M.P. 208—310°).

The aqueous solution is then made alkaline by adding 20% ammonia until it turns phenolphthalein. Ether is present to aid in crystallising the base. The product is drained, washed with water and dried at 45°C.

153g (81%) of product is obtained, with a melting point of 193—196°C.

After re-crystallising in 900ml of acetonitrile, 133g of benzamide is collected, with a melting point of 190—191°C. Total yield 70%.

EXAMPLE 41

N-(1-cyclooctylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl benzamide.

13g of 2,3-dimethoxy-5-sulphamoyl benzoic acid, 130ml of acetone, 28ml of water and 7ml of triethylamine (density 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The resultant suspension is cooled to 0°C, then 5.4g of ethyl chloroformate is poured in drop by drop and allowed to react at room temperature. It is then cooled to 0°C again and 13.8g of 1-cyclooctyl-2-aminomethyl-pyrrolidine is added drop by drop. The reaction medium is brought back to room temperature and left to stand.

The solvents are evaporated under vacuum and the residue is dissolved in 100ml of water and 20ml of hydrochloric acid (density 1.18). The solution is extracted 3 times with 25ml of methylene chloride. 3 phases are formed. The aqueous solution and imtermediate phase are made alkaline with 25ml of ammonia (sp. gr. 0.91). A gum is precipitated and crystallises slowly. The product is filtered, washed with water and dried in an oven at 40°C. It is re-crystallised in 100ml of isopropanol. The

product is filtered, washed with a little isopropanol and dried at 50°C.
Yield 8.6g (38%). M.P. 164°C.

EXAMPLE 42
N-(1-cycloheptylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl benzamide.
13g of 2,3-dimethoxy-5-sulphamoyl benzoic acid, 150ml of acetone, 28ml of water and 7ml of triethylamine (sp. gr. 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The resultant solution is cooled from 0 to +5°C. 5.4g of ethyl chloroformate is added drop by drop and the reaction medium is agitated for 45 minutes at room temperature and cooled to 0°C again. 13.7g of 1-cycloheptylmethyl-2-aminomethyl-pyrrolidine is added drop by drop. The medium is agitated for 1 hour at room temperature then left to stand. The crystals formed are drained, washed with water and dried in an oven at 30°C.
Yield 22.3g (98%). M.P. 180°C.
The product is re-crystallised in 400ml of isopropanol.
14.3g (63%) of amide is collected, melting at 180°C.

EXAMPLE 43
N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-5-sulphamoyl-benzamide.
30g of 1-cyclopropylmethyl-3-amino-pyrrolidine and 300ml of water are placed in a litre flask fitted with an agitator, a thermometer and a condenser. The mixture is cooled to about 10°C and 50g of 2-methoxy-5-sulphamoyl-benzoyl chloride is added in stages. The temperature of the resultant suspension is raised to about 20°C then it is heated for 1 hour at 30°C. The solution obtained is filtered with charcoal then made alkaline with 20% ammonia. A rubbery precipitate forms and crystallises shortly afterwards. The crystals are filtered, washed with water and dried in an oven at 50°C. 66g of product with a melting point of 142°C is obtained.
The product is re-crystallised in 400ml of ethanol.
45g of N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-5-sulphamoyl-benzamide is obtained: melting point 150°C. Yield 64%.

EXAMPLE 44
N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-5-methylsulphonyl benzamide.
36.4g of 1-cyclohexylmethyl-3-amino-pyrrolidine and 200ml of water are placed in a 500ml flask fitted with an agitator and a thermometer. The solution is cooled to +5°C, then 47.4g of 2-methoxy-5-methylsulphonyl benzoyl chloride is added in stages. The suspension is then agitated for 2 hours at 20°C followed by 1 hour at 30°C. The reaction medium is left to stand then strongly acidified with 30ml of hydrochloric acid (density 1.18). A light insoluble substance is filtered off and the base is precipitated by making it alkaline with 60ml of soda lye. The base is initially oily, then crystallises. The white crystals are filtered off, washed with water and dried in an oven at 50°C. 57.2g of product is obtained, with a melting point of 152°C.
The product is re-crystallised with filtration in a hot state in 600ml of methanol. It is left to re-crystallise overnight in a refrigerator. The crystals are filtered, washed with a little methanol and dried in an oven at 60°C.
51g of N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-5-methylsulphonyl-benzamide is obtained, with a melting point of 157°C. Yield 68%.

EXAMPLE 45
N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-methylsulphamoyl benzamide.
7.8g of 2-methoxy-4-amino-5-methylsulphamoyl benzoic acid, 70ml of acetone, 10ml of water and 3g of triethylamine are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to about 0°C and 4.3g of isobutyl chloroformate is added drop by drop. It is agitated for 45 minutes at a temperature of from 0 to +5°C, after which 4.6g of 1-cyclopropylmethyl-3-amino-pyrrolidine is added drop by drop. The medium is reacted for 2 hours at room temperature and 70ml of water and 7ml of soda lye is added. The acetone is evaporated under vacuum and the aqueous phase acidified with 10ml of hydrochloric acid (density 1.18).
The aqueous phase is made alkaline with 15ml of ammonia. A gum is precipitated. This is decanted then washed by decantation 3 times with 30ml of water. The viscous residue is dissolved hot in 90ml of isopropanol and 10ml of water. The solution is filtered hot then put in a refrigerator to crystallise. The crystals are filtered, washed with water and dried in an oven at 50°C.
5.8g (50%) of product is obtained with a melting point of 177°C.

EXAMPLE 46
N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-ethyl-sulphonyl-benzamide.
64.8g of 2-methoxy-4-amino-5-ethylsulphonyl benzoic acid, 650ml of acetone and 25.2g of triethylamine are placed in a litre flask fitted with an agitator, a thermometer and a dropping funnel. The solids dissolve completely then the triethylamine salt is precipitated rapidly. The reaction medium is

cooled to 0°C and 35g of isobutyl chloroformate is poured in drop by drop. The medium is agitated for 45 minutes between 0 and 5°C, after which 37g of 1-cyclopropylmethyl-3-aminopyrrolidine is added drop by drop. The reaction is continued for 2 hours at room temperature, after which 500ml of water is added and the acetone evaporated under vacuum. An oil is decanted and is extracted with methylene chloride. The organic phase is dried over magnesium sulphate, filtered and evaporated to dryness under vacuum. The residue is dissolved hot in 500ml of diethylcarbonate and the product is put in an ice chamber to crystallise. The crystals are filtered, washed with a little ether and dried in an oven at 40°.

78g of product is obtained with a melting point of 71—72°C.

EXAMPLE 47

N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-ethyl-sulphonyl-benzamide.

7.8g of 2-methoxy-4-amino-5-ethylsulphonyl benzoic acid, 70ml of acetone, 10ml of water and 3g of triethylamine are placed ina 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is cooled to 0°C and 4.1g of isobutyl chloroformate is poured in drop by drop. It is agitated for 45 minutes at 0°C and 6g of 1-cyclohexylmethyl-3-amino-pyrrolidine is dripped in. The reaction is continued for 2 hours at room temperature, 80ml of water and 5ml of soda lye are added, then the acetone is evaporated under vacuum. An oil is decanted; it is washed twice with 100ml of water then dissolved hot in 50ml ethyl acetate. It is chilled in a refrigerator. The crystals are filtered off, washed with a little ethyl acetate then dried in an oven at 50°C.

9.4g of benzamide is obtained with a melting point of 146°C (74%).

EXAMPLE 48

N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-ethylsulphinyl benzamide.

8.5g of 2-methoxy-4-acetamino-5-ethylsulphinyl benzoic acid, 70ml of acetone, 10ml of water and 3g of triethylamine are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to about 0°C, after whcih 4.2g of isobutyl chloroformate is poured in drop by drop. It is agitated for 45 minutes at 0°C then 6g of 1-cyclohexyl-methyl-3-amino-pyrrolidine is dripped in. It is reacted for 2 hours at room temperature, 50 ml of water is added and the acetone is evaporated under vacuum. 10ml of soda and 50ml of water are added to the aqueous residue and it is heated to reflux for 5 hours then cooled. The suspension is extracted twice with 50ml of methylene chloride, and the organic phase is dried over magnesium sulphate and filtered. The filtrate is evaporated dry under vacuum, and the residue is dissolved in 70ml of hot ethyl acetate. The product is re-crystallised by cooling and filtered. It is washed with a little ether and dried in an oven at 50°C.

8.2g of product is obtained, with a melting point of 143°C. This is re-crystallised a second time in 90ml of ethyl acetate. 6.8g of amide is collected, with a melting point of 146°C.

EXAMPLE 49

N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2,4-dimethoxy-5-ethylsulphonyl benzamide.

8.2g of 2,4-dimethoxy-5-ethylsulphonyl benzoic acid, 70ml of acetone, 10ml of water and 4.2ml of triethylamine (density 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution obtained is cooled, then 4.2g of isobutyl chloroformate is poured in drop by drop while the temperature is kept at about 0°C. The medium is reacted for 45 minutes at that temperature, after which 4.6g of 1-cyclopropylmethyl-3-aminopyrrolidine is added drop by drop. It is agitated for 2 hours at normal temperature, then 50ml of water and 5ml of soda lye are added. The acetone is evaporated under vacuum and the insoluble oil extracted 3 times with 50ml of methylene chloride. The organic phase is washed twice with 50ml of water then dried over magnesium sulphate, filtered and evaporated to dryness. The oily residue is dissolved hot in 80ml of butyl acetate. The solution is filtered then put in a refrigerator to crystallise. The crystals are drained, washed with a little ether and dried in an oven at 50°C.

8g (67%) of product is obtained, with a melting point of 106°C.

EXAMPLE 50

N-(1-cyclopropylmethyl-3-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl benzamide.

6.6g of 2,3-dimethoxy-5-sulphamoyl benzoic acid, 50ml of acetone, 10ml of water and 3.6ml of triethylamine (sp. gr. 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to 0—+5°C and 3.6g of isobutyl chloroformate is poured in drop by drop. It is reacted for 30 minutes with the same temperature maintained, after which 4.8g of 1-cyclopropylmethyl-3-aminomethyl-pyrrolidine is added drop by drop. The reaction medium is agitated for 1 hour at room temperature, whereupon 50ml of water is added and the acetone evaporated under vacuum. A further 50ml of water is added and the solution is made alkaline with 5ml of ammonia (sp. gr. 0.91). An oil is precipitated. The suspension is extracted 3 times with 50ml of methylene chloride. The organic phase is dried over magnesium sulphate, filtered, then evaporated under vacuum. The residue is dissolved in boiling ethyl acetate. It crystallises hot. The crystals are cooled, filtered and dried in an oven at 50°C.

2.7g (27%) of product is obtained, with a melting point of 146°C.

EXAMPLE 51

N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2,3-dimethoxy-5-sulphamoyl benzamide.

7.85g of 2,3-dimethoxy-5-sulphamoyl benzoic acid, 50ml of acetone, 10ml of water and 3g of triethylamine are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The mixture is cooled to 0° and 4.2g of isobutyl chloroformate is poured in drop by drop. The mixture is agitated for 45 minutes at 0°C, after which 6g of 1-cyclohexylmethyl-3-amino-pyrrolidine is dripped in. It is agitated for 2 hours at room temperature, then 80ml of water is added and the acetone evaporated under vacuum. The product crystallises. It is filtered, washed with water then re-dissolved in 150ml of water and 20ml of hydrochloric acid. The solution is filtered with charcoal and the filtrate made alkaline with ammonia. An oil is precipitated and crystallises slowly. The crystals are drained, washed with water and dried in an oven at 50°C.

6.8g (53%) of product is obtained, with a melting point of 167°C.

EXAMPLE 52

N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-5-ethylsulphonyl-benzamide.

7.3g of 2-methoxy-5-ethylsulphonyl benzoic acid, 70ml of acetone, 10ml of water and 4g of triethylamine are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to about 0°C and 4.2g of isobutyl chloroformate is added drop by drop. The reaction medium is then agitated for 45 minutes between 0 and +5°C, after which 4.6g of 1-cyclopropylmethyl-3-amino-pyrrolidine (0.033 mole) is poured in drop by drop. The medium is reacted for 2 hours.

50ml of water and 5ml of 40% soda lye are added, the acetone is evaporated under vacuum and the resultant suspension is extracted twice with 50ml of methylene chloride. The organic phase is dried over magnesium sulphate and filtered and the solvent is evaporated under vacuum. The residual oil is dissolved in 80ml of isopropanol. It is acidified with 7ml of hydrochloric ethanol ≃4.7N and left to stand in a refrigerator. The crystals are filtered off and dried in an oven at 50°C. The hydrochloride obtained melts at 170°C.

Yield 5.5g (46%).

EXAMPLE 53

N-(1-cyclopropylmethyl-3-pyrrolidinyl methyl)-2-methoxy-5-sulphamoyl benzamide.

5.8g of 2-methoxy-5-sulphamoyl benzoic acid, 50ml of acetone, 10ml of water and 3.6ml of triethylamine (sp. gr. 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer and a dropping funnel. The solution is cooled to about +10°C, then 3.6g of isobutyl chloroformate is added drop by drop. The medium is reacted for 30 minutes at 0°C, after which 4.5g of 1-cyclopropylmethyl-3-aminomethyl-pyrrolidine is poured in drop by drop. The medium is reacted for 1 hour at room temperature, 50ml of water is added and the acetone is evaporated under vacuum. The reaction medium is further diluted with 50ml of water and made alkaline with 10ml of ammonia (density 0.91). The viscous product which is precipitated crystallises slowly. The solid is filtered off, washed with water and re-crystallised in 50ml of ethanol.

3.8g (41%) of benzamide is obtained, melting at 177°C.

EXAMPLE 54

N-(1-cyclooctyl-2-pyrrolidinyl methyl)-2,4-dimethoxy-5-methyl-sulphonyl benzamide.

13g of 2,4-dimethoxy-5-methyl sulphonyl benzoic acid, 150ml of acetone, 28ml of water and 7ml of triethylamine (sp. gr. 0.726) are placed in a 250ml flask fitted with an agitator, a thermometer, a condenser and a dropping funnel. The suspension is cooled to from 0 to +5°C, then 5.4g of ethyl chloroformate is added drop by drop. The mixture is agitated for 45 minutes at room temperature and cooled to about 0°C then 13.8g of 1-cyclooctyl-2-aminomethyl-pyrrolidine is added drop by drop. There is complete solubilisation. The reaction medium is agitated at room temperature then left to stand. The solvent are evaporated under vacuum and the residue is dissolved in 100ml of water and 20ml of hydrochloric acid (sp. gr. 1.18). The organic phase is extracted 3 times with 50ml of methylene chloride, dried over magnesium sulphate, filtered and evaporated to dryness under vacuum. The residue is dissolved in 100ml of water. The solution is filtered in the presence of carbon black and the filtrate made alkaline with 10ml of ammonia. A gum is precipitated. This is extracted 3 times with 50ml of methylene chloride, and the organic solution is washed twice with 50ml of water and dried over magnesium sulphate. It is filtered, then the solvent is evaporated under vacuum and the residue re-crystallised in 200ml of isopropanol. The crystals are filtered off, washed twice with a little iced isopropanol and dried in an oven at 50°C.

Yield 14.2g (63%). The product melts at 158—159°C.

EXAMPLE 55

N-(1-cyclopentyl-2-pyrrolidinyl methyl)-2,4-dimethoxy-5-methylsulphonyl benzamide.

91g of 2,4-dimethoxy-5-methylsulphonyl benzoic acid, 400ml of acetone, 130ml of water and 48.6ml of triethylamine are placed in a litre flask fitted with an agitator, a thermometer and a dropping

funnel. 47.6g of isobutyl chloroformate is dripped into the solution obtained, at about 10°C. It is agitated for 40 minutes, then 58.8g of 1-cyclopentyl-2-aminomethyl-pyrrolidine is poured in drop by drop at about 0°C. A precipitate appears after 30 minutes of agitation at room temperature. It is allowed to react then the precipitate is filtered off, washed with water and dried. 74g of a crude version of the product is obtained, melting at 198°C.

The filtrate is evaporated to dryness under vacuum. The residue is dissolved in 200ml of water and 20ml of soda lye. The insoluble product is filtered off, washed with water and dried in an oven. This final version weighs 47g.

The mixture of the first and second versions is dissolved in 1,300ml of water containing 40ml of hydrochloric acid (sp. gr. 1.18). The solution is filtered in the presence of 5g of charcoal and the product is re-precipitated by adding 45ml of soda lye. A gum is formed and crystallises slowly. The product is filtered off, washed with water and dried in an oven at 60°C.

95g of amide is obtained.

The crystals are dissolved in 2,500ml of boiling acetonitrile. The solution is filtered and cooled in a refrigerator. The precipitate is drained, washed with a little acetonitriie then with water and dried in an oven at 50°C.

73g (51%) of product is obtained, with a melting point of 212°C.

The products of the invention are used in the form of capsules, tablets, pills, in granulated form or as an injectable solution; the preparation of these is known *per se*. Substances which are inert relative to the compounds of the invention can be used, such as lactose, magnesium stearate, starch, talc, cellulose, levilite, alkali metal lauryl-sulphates, saccharose and the vehicles commonly employed in medicinal preparations.

The compounds may be administered in doses of 50—750mg per day taken in 1 or more stages.

The examples which follow concern pharmaceutical preparations made in conventional manner from the compounds of the invention.

EXAMPLE 56
Tablets
N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)

2,3-dimethoxy-5-sulphamoyl benzamide	100 mg
dried starch	20 mg
lactose	100 mg
methylcellulose 1500 cps	1.5 mg
levilite	10 mg
magnesium stearate	4 mg
	for 1 tablet.

EXAMPLE 57
Capsules
N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)

2-methoxy-4-amino-5-ethylsulphonyl benzamide	50 mg
microcrystalline cellulose	50 mg
methylcellulose 1500 cps	1 mg
magnesium stearate	5 mg
talc	2 mg
	for 1 capsule.

EXAMPLE 58
Injectable solution
N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)

2,3-dimethoxy-5-sulphamoyl benzamide	40 mg
N-hydrochloric acid	0.10 mg
sodium chloride	14 mg
	for 2 ml.

EXAMPLE 59
Injectable solution
N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)

2-methoxy-4-amino-5-ethylsulphonyl benzamide	100 mg
N-hydrochloric acid	0.250 mg
sodium chloride	8 mg
	for 2 ml.

To prepare the tablets, the selected compound is mixed with the starch and lactose by the method of successive dilutions; the mixture is granulated with methylcellulose. The levilite, magnesium stearate

and talc are added to the granules before proceeding with compression.

It is possible to replace the methylcellulose with any other appropriate granulating agent, such as ethylcellulose, polyvinylpyrrolidone or starch paste. The magnesium stearate may be replaced by stearic acid.

When preparing injectable solutions, it is possible to dissolve the compound of the invention in the following acids: hydrochloric or levulinic acid, gluconic acid, or glucoheptonic acid.

The solution is prepared under sterile conditions and made isotonic with an alkali metal chloride such as sodium chloride, then preservatives are added. It is also possible to prepare the same solution without adding any preservatives: the ampoule is then filled under nitrogen and sterilised for $\frac{1}{2}$ hour at 100°C.

The pharmacodynamic tests on the compounds of the invention, and particularly a study of their antiemetic power (antagonism to apomorphine administered subcutaneously to the dog is 5 to 20 times greater than that of known compounds of the same series) have led us to think that they have strong properties of acting on the central nervous system.

Their low toxicity and the absence of any undesirable side-effects such as catalepsy, which normally accompany this type of product, make these compounds particularly important.

The acute toxicity of the compounds of the invention has been studied in the mouse. The lethal doses 50 are set out in the following table:

LD_{50} IN THE MALE MOUSE – EXPRESSED IN mg/kg

Compound	I.V.	I.P.	S.C.	Oral
1	60 – 64,5	372 – 403	930	2280
2	52,5 – 54,6	203,5 – 220	380 – 396	1260 – 1325
3	152 – 155		555	
4	48		725	
5	48 – 52,5	264 – 280	924	3600 – 3630
6	51 – 51,75	96 – 108	170 – 186	
7	72 – 73,8	159,5 – 172	290 – 319	600 – 682
8	23,5 – 25,8	70 – 72,5	90 – 93	256
9	84 – 87,5	172,5 – 188,5	450	1020 – 1080
10	26,4 – 28.7	77.5 – 78	85 – 86	198 – 210
11	15,3 – 15,6	79,2 – 81,6	180 – 184	300 – 320
12	55,9 – 56,4	132 – 133	407 – 420	510 – 546
13	40,8 – 41			
14	31,2 – 32	82 – 87	128 – 138	259 – 270
15	28,8 – 29			
16	61,5 – 62	175 – 180	430 – 444	400 – 414
17	96 – 105	159,5 – 162		
18	26,4 – 27	103 – 106	120 – 126	599 – 626
19	62,5 – 68,2	253 – 280	703	
20	64,5 – 70	221	590 – 614	514 – 516
21	41,8 – 45,6	147 – 152		
22	37 – 40,8	133 – 145,2	336 – 342	348 – 380
23	51,8 – 52,8	185		560 – 572

Compound 1: N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl benzamide
Compound 2: N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2-methoxy 4-amino-5-ethylsulphonyl benzamide
Compound 3: N-(1-cyclopropyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl benzamide
Compound 4: N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl benzamide
Compound 5: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl benzamide
Compound 6: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino 5-ethylsulphonyl benzamide
Compound 7: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl benzamide
Compound 8: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino 5-chloro benzamide
Compound 9: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphamoyl benzamide
Compound 10: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4,5-azimido benzamide
Compound 11: N-(1-cyclohexyl-2-pyrrolidinylmethyl)2-propargyloxy-3,5-dichlorobenzamide
Compound 12: N-(1-(1'-adamantyl)-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphonyl benzamide
Compound 13: N-(1-(1'-adamantyl)-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl benzamide
Compound 14: N-(1-(1'-adamantyl)-2-pyrrolidinylmethyl)-2-methoxy-5-ethylsulphonyl benzamide
Compound 15: N-(1-(1'-adamantyl)-2-pyrrolidinylmethyl)-2-methoxy-4,5-azimido benzamide
Compound 16: N-(1-cycloheptyl-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphonyl benzamide
Compound 17: N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-5-methylsulphonyl benzamide
Compound 18: N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-methylsulphamoyl benzamide
Compound 19: N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-5-sulphamoyl benzamide
Compound 20: N-(1-cyclopentyl 2-pyrrolidinylmethyl)-2-methoxy-4-chloro-5-ethylsulphonyl benzamide
Compound 21: N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino 5-ethylsulphinyl benzamide
Compound 22: N-(1-cyclohexylmethyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl benzamide
Compound 23: N-(1-(2'-norbornyl)-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl benzamide

The antiemetic power relative to apomorphine has been measured on the dog by the method of Chen and Ensor.

The compounds of the invention were administed subcutaneously 30 minutes before the apomorphine, which was administed subcutaneously in a dose of 100μg/kg.

The following results were obtained:

ED_{50} subcutaneously in the dog — expressed in μg/kg.							
COMPOUND	1	2	3	12	16	17	22
ED_{50}	2.2	0.4	8	9.5	2	1.75	Effect of 89% at 10 g/kg

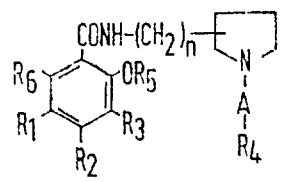
The compounds of the invention have virtually no cataleptic action.

The benzamides were administered subcutaneously to male rats. The criterion for the cataleptic state was that the animal should be immobile for 30 seconds with its rear limbs apart, arranged carefully on wooden cubes four cm high, thus putting the animal in an unaccustomed and uncomfortable position. The cataleptic action was measured when the effect was at its maximum, i.e. 5—6 hours after the product had been administered.

It was found that a dose of 100 mg/kg compounds 2, 5, 6, 9, 10, 13, 15, 18, 19, 20, 21 and 23 were completely free from any cataleptic action and that at a dose of 200 mg/kg compounds 1, 7, 12 and 14 produced a cataleptic state in 10% of the animals.

CLAIMS

1. Substituted heterocyclic benzamides of the general formula:



in which R_4 is a cycloalkyl, cycloalkenyl, bicyloalkyl or tricycloalkyl group; A is a single bond or a

saturated or unsaturated hydrocarbon chain containing 1 to 3 carbon atoms; *n* is 0, 1, 2 or 3; R_5 is a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an alkenyl or alkynyl group; and each of R_1, R_2, R_3 and R_6, which are the same or different, is a hydrogen or halogen atom or an alkyl, alkoxy, amino, acetamido, sulphamoyl, alkylsulphamoyl, dialkylsulphamoyl, alkylsulphonyl or alkylsulphinyl group, or any two of them are bonded together to form an azimido group; with the following provisos (a) that when R_4 is a cycloalkyl group, R_5 a hydrogen atom or an alkyl group, A a single bond and *n* equal to 0, at least one of R_1, R_2, R_3 and R_6 is an alkylsulphonyl or alkylsulphinyl group or two of them are bonded together to form an azimido group; and (b) that when R_4 is a cycloalkyl group, R_5 is a methyl group, A is an alkylene group with one to three carbon atoms, *n* is 1 and the amide chain is bonded at the 2-position of the pyrrolidine, R_1 can be a halogen atom or a sulphamoyl, alkylsulphamoyl, dialkylsulphamoyl or alkylsulphonyl group only when R_2, R_3, R_6 are not all hydrogen atoms; and their salts of addition with pharmacologically acceptable acids, their quaternary ammonium salts, and their oxides, including laevorotatory and dextrorotatory isomers of such compounds.

2. N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl-benzamide.

3. N-(1-cyclopropyl-methyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

4. N-(1-cyclopropyl-2-pyrrolidinyl-methyl)-2-methoxy-5-sulphamoyl-benzamide.

5. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl-benzamide.

6. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl-benzamide.

7. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

8. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-methylsulphamoyl-benzamide.

9. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-chlorobenzamide.

10. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphamoyl-benzamide.

11. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4,5-azimido-benzamide.

12. N-(1-cyclopropyl-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphinyl-benzamide.

13. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-sulphamoyl-benzamide.

14. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-methylsulphamoyl-benzamide.

15. N-(1-cyclohexylmethyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

16. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-methylsulphinyl-benzamide.

17. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphinyl-benzamide.

18. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2,4-dimethoxy-5-methylsulphonyl-benzamide.

19. N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2,4-dimethoxy-5-methylsulphonyl-benzamide.

20. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2,4-dimethoxy-5-ethylsulphonyl-benzamide.

21. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-4-chloro-5-ethylsulphonyl-benzamide.

22. N-(1-cyclopropyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-dimethylsulphamoyl-benzamide.

23. N-(1-cyclopropylmethyl-2-pyrrolidinylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

24. N-(1-cyclopentyl-2-pyrrolidinylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

25. N-(1-cyclohexylmethyl-2-pyrrolidinylmethyl)-2-methoxy-3-isopropyl-5-sulphamoyl-6-methylbenzamide.

26. N-(1-cycloheptyl-2-pyrrolidinylmethyl)-2-methoxy-5-methylsulphonyl-benzamide.

27. N-(1-norbornyl-2-pyrrolidinylmethyl)-2-methoxy-5-methysulphonyl-benzamide.

28. N-(1-cycloheptylmethyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-methylsulphamoyl-benzamide.

29. N-[1-(2′-norbornyl)-2-pyrrolidinylmethyl]-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

30. N-(1-cyclohexenylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl-benzamide.

31. N-(1-cycloheptylmethyl-2-pyrrolidinylmethyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

32. N-(1-cyclooctyl-2-pyrrolidinylmethyl)-2,4-dimethoxy-5-methylsulphonyl-benzamide.

33. N-(1-cyclooctyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl-benzamide.

34. N-(1-cycloheptylmethyl-2-pyrrolidinylmethyl)-2,3-dimethoxy-5-sulphamoyl-benzamide.

35. N-(1-norbornyl-2-pyrrolidinylmethyl)-2-methoxy-4-bromo-5-sulphamoyl-benzamide.

36. N-(1-cycloheptyl-2-pyrrolidinylmethyl)-2-methoxy-4-chloro-5-ethylsulphonyl-benzamide.

37. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-5-sulphamoyl-benzamide.

38. N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-5-methylsulphonyl-benzamide.

39. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-methylsulphamoyl-benzamide.

40. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

41. N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-ethylsulphonyl-benzamide.

42. N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-ethylsulphinyl-benzamide.

43. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2,4-dimethoxy-5-ethylsulphonyl-benzamide.

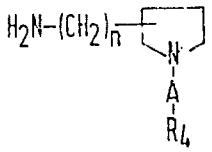
44. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2,3-dimethoxy-5-sulphamoyl-benzamide.

45. N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2,3-dimethoxy-5-sulphamoyl-benzamide.

46. N-(1-cyclohexylmethyl-3-pyrrolidinyl)-2-methoxy-4-amino-5-chlorobenzamide.
47. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-4-bromo-5-methylsulphonyl-benzamide.
48. N-(1-cyclopropylmethyl-3-pyrrolidinyl)-2-methoxy-5-ethylsulphonyl-benzamide.
49. N-(1-cyclopropylmethyl-3-pyrrolidinylmethyl-2-methoxy-5-sulphamoyl-benzamide.
50. N-(1-cyclohexyl-2-pyrrolidinylmethyl)-2-propargyloxy-3,5-dichlorobenzamide.
51. N-(1-adamantyl-2-pyrrolidinylmethyl)-2-methoxy-5-sulphamoyl-benzamide.
52. N-(1-adamantyl-2-pyrrolidinylmethyl)-2-methoxy-5-methyl-sulphonyl-benzamide.
53. N-(1-adamantyl-2-pyrrolidinylmethyl)-2-methoxy-4,5-azimidobenzamide.
54. N-(1-adamantyl-2-pyrrolidinylmethyl)-2-methoxy-5-ethylsulphonyl-benzamide.
55. N-(1-cyclohexylmethyl-2-pyrrolidinylmethyl0-2,3-dimethoxy-5-sulphamoyl-benzamide.
56. A method of preparing a compound of formula (I) in Claim 1, comprising reacting an acid of formula (II):

(II)

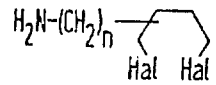
where R_1, R_2, R_3, R_5, R_6 are as defined in Claim 1 or one of its reactive derivatives, with a primary amine of the general formula (III):



(III)

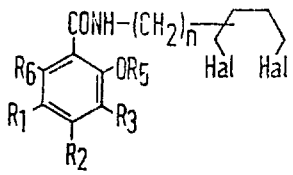
where *n*, A, R_4 have the above meaning, or one of its reactive derivatives, with or without a condensing agent present, or on an ion-exchange column.

57. A method of preparing a compound of formula (I) in Claim 1 comprising reacting a reactive derivative of an acid of formula (II) with a primary amine of formula (IV):



(IV)

where *n* is 0, 1,2 or 3 and Hal represents a chlorine, bromine or iodine atom, to obtain a compound of formula (V):



(V)

where R_1, R_2, R_3, R_5 and R_6 are as defined in Claim 1 and Hal and *n*, are as defined above, and reacting the latter with an amine of formula $H_2N—A—R_4$ where A and R_4 are as defined in Claim 1.

58. A method as claimed in Claim 56, as applied to the preparation of a compound as claimed in any one of Claims 2 to 55.

59. A method as claimed in Claim 57, as applied to the preparation of a compound as claimed in any one of Claims 2 to 55.

60. A method of preparing a compound as claimed in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 55.

61. A compound as claimed in Claim 1 when prepared by a method as claimed in any one of Claims 56 to 60.

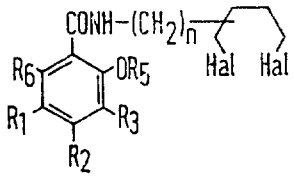
62. The use as a medicine, characterised by therapeutic properties particularly in the psychiatric field, of a compound as claimed in any one of Claims 1 to 55 and 61.

63. A pharmaceutical composition containing as active ingredient a compound as claimed in Claim 1 mixed with a pharmaceutically acceptable excipient and possibly other active ingredients.

64. A composition as claimed in Claim 63 in which the said compound is a compound as claimed in any one of Claims 2 to 55 and 61.

65. A composition as claimed in Claim 63 substantially as hereinbefore described in any one of Examples 56 to 59.

66. Substituted benzamides of the general formula:



where R_1, R_2, R_3, R_5, R_6 and *n* are as defined in Claim 1 and Hal is as defined in Claim 57.

67. N-(2,5-Dichloropentyl)-2-methoxy-5-sulphamoylbenzamide.

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