1,106,059

PATENT SPECIFICATION

NO DRAWINGS

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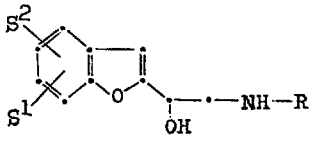
COMPLETE SPECIFICATION

Novel Benzofuran Derivatives and a Process for the Manufacture thereof

We, ROCHE PRODUCTS LIMITED, a British Company of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

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

The novel benzofuran derivatives provided by the invention are compounds of the formula

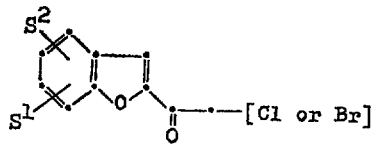


I

wherein R represents a lower-alkyl group, S^1 represents 5- or 7-(chloro or bromo) or 5,7-di(chloro or bromo) substitution and S^2 represents mono- di- or tri(lower alkyl) substitution according to the availability of position or positions, and acid addition salts thereof. They are useful as adrenergic blocking agents [*beta*-type effects]. The compounds of formula I are also useful in that they can be readily converted into the corresponding compounds in which S^1 is absent and 2,3-dihydro derivatives thereof. These latter compounds and derivatives are claimed *per se* in the specification of our copending Application for Letters Patent No. 19823/65 (now Serial No: 1,106,057).

It will be appreciated that the term 'lower alkyl' is used in this description and in the claims appended hereto to mean alkyl groups containing from one to four carbon atoms. One interesting class of derivatives provided by the invention comprises those compounds of formula I in which S^2 represents mono- or di(lower alkyl) substitution (especially mono- or dimethyl or ethyl substitution), and acid addition salts thereof. Another interesting class of derivatives provided by the invention comprises those compounds of formula I in which S^1 represents bromo substitution, and acid addition salts thereof. An interesting lower-alkyl value for R is the *iso*propyl group.

According to the process provided by the invention, the novel derivatives aforesaid are manufactured by reducing a halo-ketone of the general formula



II

(wherein S^1 and S^2 have the significance given earlier) with an alkali-metal borohydride or with aluminium *iso*peroxide in *iso*propanol and reacting the resulting halohydrin with an amine of the formula

$$R—NH_2$$

(III)

(wherein R has the significance given earlier) in the presence of an acid-binding agent and, if desired, converting the reaction product into an acid addition salt.

According to a variant process, also in accordance with the present invention, the halohydrin aforesaid is dehydrohalogenated to the corresponding epoxide and this epoxide is then reacted with the amine of formula III.

The halo-ketone starting materials of formula II can be obtained, for example, by chlorinating or brominating the appropriate lower alkyl-substituted phenol, transforming the chlorination or bromination product into the corresponding substituted-salicylaldehyde, converting this substituted-salicylaldehyde into an alkali-metal salt, condensing this salt with chloro-acetone and chlorinating or brominating the resulting substituted 2-acetyl-benzofuran. The chlorination and bromination of the lower alkyl-substituted phenol can suitably be carried out by passing gaseous chlorine or bromine through a solution of the phenol in an inert organic solvent (e.g. chloroform or acetic acid) at a temperature of from about 0°C to 20°C. The transformation of the chlorination or bromination product into the corresponding substituted-salicylaldehyde can be carried out in accordance with methods known *per se;* for example, using dichloromethyl methyl ether and titanium tetrachloride in methylene chloride or using hexamethylene-tetramine under the conditions of a DUFF reaction. The conversion of the substituted - salicylaldehyde into an alkali-metal salt can conveniently be carried out using an alkali-metal hydroxide in an alkanol containing from one to four carbon atoms (e.g. ethanolic potassium hydroxide). The reaction of the alkali-metal salt with chloro-acetone is conveniently carried out in an inert organic solvent (e.g. an alkanol containing from one to four carbon atoms such as ethanol). The chlorination of the reaction product is conveniently carried out by treatment with sulphuryl chloride and the bromination is conveniently carried out by treatment with bromine in an inert organic solvent such as ether or with cupric bromide in a mixture of ethyl acetate and chloroform. One interesting class of halo-ketone starting materials of formula II comprises those in which S^2 represents mono- or di(lower alkyl) substitution (especially mono- or dimethyl or ethyl substitution). Another interesting class of halo-ketone starting materials of formula II comprises those in which S^1 represents bromo substitution, particularly 2 - chloroacetyl - 5 - bromo - 6,7 - dimethyl - benzofuran, 2 - chloroacetyl - 5 - bromo - 7 - methyl - benzofuran, 2 - chloroacetyl - 7 - bromo - 5 - methyl - benzofuran, 2 - chloroacetyl - 5,7 - dibromo - 4 - methyl - benzofuran and 2 - chloroacetyl - 5 - bromo - 7 - ethyl - benzofuran.

The reduction of the halo-ketone starting materials of formula II with an alkali-metal borohydride (suitably sodium borohydride) is conveniently carried out at a temperature of 20°C or below (preferably at 0°—20°C). The reduction is conveniently carried out in the presence of a solvent which is inert under the conditions of the reduction. Alkanols containing from one to four carbon atoms (e.g. ethanol) and aqueous dioxan have been found to be suitable for this purpose. The reduction of the halo-ketone starting materials of formula II with aluminium *iso*propoxide in *iso*propanol is preferably carried out at an elevated temperature.

The reaction of the halohydrin with the amine of formula III is conveniently carried out by heating the halohydrin with at least 1 molecular proportion of the amine at an elevated temperature (e.g. 50°—100°C) in the presence of a suitable acid-binding agent. Suitable acid-binding agents are, for example, alkali-metal carbonates, pyridine or, preferably, an excess of the amine. The reaction is accordingly preferably carried out using at least 2 molecular proportions of the amine for each molecular proportion of halohydrin. The heating can be carried out in the presence of an inert organic solvent such as ethanol but, except where solution of the acid-binding agent is necessary, this is not essential. The heating can also be carried out in a closed vessel and this procedure is especially advantageous when readily volatile amines are used. *Iso*propyl amine is a particularly useful amine of formula III.

The dehydrohalogenation of the halohydrin to the epoxide in accordance with the variant process provided by the invention is conveniently carried out by treatment at room temperature with an alkali-metal hydroxide (e.g. potassium hydroxide) dissolved in an alkanol containing from one to four carbon atoms (especially methanol) or suspended in a non-polar organic solvent (e.g. benzene).

The reaction of the epoxide with the amine can be carried out by heating the epoxide with the amine at an elevated temperature (e.g. 50°—100°C). It is preferred to use an excess of the amine in this reaction. Alternatively, the reaction can be carried out in an inert organic solvent (e.g. benzene) at room temperature in the presence of boron trifluoride etherate.

It will be appreciated that the compounds of formula I contain an asymmetric carbon atom and occur in the form of a stereoisomeric racemate. This racemate can be separated into its optical isomers in accordance with methods known *per se;* for example, by fractional crystallization of the salts.

The acid addition salts provided by the invention are those formed with inorganic

acids (e.g. hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid) and with organic acids (e.g. acetic acid, tartaric acid, maleic acid, citric acid and toluene-sulphonic acids).

The novel derivatives provided by the invention may be used as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. The pharmaceutical preparations may be made up for enteral (e.g. oral or parenteral administration. Solid preparations for oral administration include tablets, pills, powders, capsules and granulates, the carrier being inorganic (e.g. talc) or organic (e.g. lactose or starch). Additives such as magnesium stearate (a lubricant) may also be present. Liquid preparations for oral administration include emulsions, solutions and suspensions and the diluents commonly used in pharmacy (e.g. water and petroleum jelly) may be present in such preparations. The liquid preparations may take the form of sterile aqueous or non-aqueous solutions, suspensions or emulsions. Polyoxyethyleneglycols and vegetable oils are useful suspending media. Emulsifying agents, dispersing agents and other adjuvants may also be present. The pharmaceutical preparations may be submitted to the usual pharmaceutical operations such as sterilization and may be compounded with other therapeutically valuable materials.

The following Examples illustrate the process of the invention:

EXAMPLE 1

i) The preparation of the starting material:

A mixture of 50.25 g (0.25 mol) of 4-bromo - 2,3 - xylenol, 18.75 g of paraformaldehyde and 18.75 g of hexamethylenetetramine was melted to a paste. 75 ml of glacial acetic acid were added to the stirred mixture over a period of 1 hour, the internal temperature being maintained at 100°C (bath temperature 125°C). 20.4 ml of concentrated sulphuric acid were then added dropwise over a period of 2 hours, the internal temperature being maintained at 118—120°C (bath temperature 140°C). After addition was complete, the mixture was stirred for a further 0.25 hour at 118°C. The mixture was then poured into hot water and steam distilled. The aqueous distillate was extracted with chloroform and the extract was washed with water and dried over sodium sulphate. Evaporation of the chloroform under reduced pressure yielded *ca* 43 g of a yellow solid. This crude material was crystallized from ethanol to give 35.2 g of 5 - bromo - 3,4 - dimethyl - salicylaldehyde of melting point 73°—74°C.

22.9 g (0.1 mol) of 5 - bromo - 3,4 - dimethyl - salicylaldehyde were suspended in 100 ml of ethanol and a solution of 6.1 g (*ca* 0.1 mol) of potassium hydroxide in 75 ml of ethanol was added dropwise with stirring over a period of 0.25 hour (the 5 - bromo - 3,4 - dimethyl - salicylaldehyde initially dissolved, but towards the end of the addition its potassium salt was precipitated). 8.5 ml (0.1 mol + 5%) of chloro-acetone were then added dropwise with stirring over a period of 0.25 hour. The internal temperature rose to 42°C. Stirring was continued a further 2 hours, after which time the solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted three times with chloroform. The extract was washed once with water and dried over sodium sulphate. The dried solution was filtered and the filtrate was evaporated. The residue was crystallized from ethanol to give 16 g of 2 - acetyl - 5 - bromo - 6,7 - dimethyl - benzofuran in the form of a crystalline solid of melting point 137.5°—139.5°C.

4.3 ml (0.05 mol + 5%) of sulphuryl chloride were added over a period of 10 minutes to a stirred solution of 13.36 g (0.05 mol) of 2 - acetyl - 5 - bromo - 6,7 - dimethyl - benzofuran in 75 ml of chloroform. The mixture was slowly brought to boiling (0.5 hour) and then kept at reflux for 2 hours. The mixture was then cooled, poured on to ice/water and extracted three times with chloroform. The extracts were washed once with 2-*N* sodium carbonate solution then once with water and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue was crystallized from ethanol/methanol to give 9.2 g of 2-chloroacetyl - 5 - bromo - 6,7 - dimethyl - benzofuran of melting point 135°—140°C. Recrystallization from ethanol gave 7.0 g of material of melting point 141°—144°C. When the chlorination was repeated using 60.12 g of 2 - acetyl - 5 - bromo - 6,7 - dimethyl - benzofuran, a first crop of 43 g of 2-chloroacetyl - 5 - bromo - 6,7 - dimethyl - benzofuran of melting point 139°—143°C was obtained.

ii) The process:

42.2 g (0.143 mol) of 2 - chloroacetyl - 5 - bromo - 6,7 - dimethyl - benzofuran were suspended in a mixture of 210 ml of dioxan and 35 ml of water and the suspension was cooled to 0°C. 3.99 g (0.072 mol+25%) of sodium borohydride were added portionwise at 0°—5°C over a period of 0.5 hour and the mixture was stirred at 20°C for 3 hours. The solvent was then removed under reduced pressure and the residue was treated with water and extracted three times with ether. The extracts were washed once with water and dried over anhydrous sodium sulphate. The dried solution was filtered and the filtrate was evaporated to give a buff solid which was crystallized from benzene/(60°—80°C

petroleum ether) to yield 35.3 g of 5 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 6,7 - dimethyl - benzofuran in the form of colourless needles of melting point 100°—102°C.

A solution of 27.27 g (0.09 mol) of 5 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 6,7 - dimethyl - benzofuran and 47 ml (0.54 mol) of *iso*propyl amine in 180 ml of *iso*propanol was heated under reflux for 24 hours (thin layer chromatography of the reaction mixture showed the reaction product to be virtually uniform). The *iso*propanol and excess *iso*propyl amine were removed under reduced pressure and the solid residue vigorously shaken with excess 2-*N* aqueous sodium carbonate solution and filtered. The filter cake was shaken with water and again filtered, then shaken again with water, filtered once more, sucked dry and crystallized from ethanol to give a first crop of 16.6 g of 5 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 6,7 - dimethyl - benzofuran of melting point 135°—138°C.

Example 2

i) The preparation of the starting material:

A solution of 3.1 g (*ca* 0.05 mol) of potassium hydroxide in 30 ml of ethanol was added dropwise with stirring at room temperature over a period of 10 minutes to a solution of 10.8 g (0.05 mol) of 5 - bromo - 3 - methyl - salicylaldehyde in 100 ml of ethanol. 4.8 g (0.05 mol + 5%) of chloroacetone were added dropwise over a period of 0.25 hour to the resulting yellow solution. The mixture was stirred at room temperature for 20 hours, then poured into 500 ml of water and extracted twice with chloroform. The combined extracts were washed with dilute sodium hydroxide solution and then with water and dried over sodium sulphate. The solvent was removed to give a yellow solid which was recrystallized from ethanol to yield 9.3 g of 2 - acetyl - 5 - bromo - 7 - methyl - benzofuran as fine yellow needles of melting point 122°—123°C.

4.9 g (0.03 mol + 20%) of sulphuryl chloride were added dropwise with stirring over 10 minutes to 7.6 g (0.03 mol) of 2-acetyl - 5 - bromo - 7 - methyl - benzofuran in 30 ml of chloroform. The mixture was heated at gentle reflux for 3 hours, cooled and poured on to ice. The layers were separated and the aqueous layer was extracted with chloroform. The extract was combined with the organic layer, washed with 2-*N* sodium carbonate solution and then with water and dried over sodium sulphate. The dried solution was filtered and the filtrate was evaporated under reduced pressure. The solid residue was recrystallized from ethanol to yield 7.1 g of 2 - chloroacetyl - 5 - bromo - 7 - methyl - benzofuran as fine yellow needles of melting point 134°—137°C.

ii) The process:

14.4 g (0.05 mol) of 2 - chloroacetyl - 5 - bromo - 7 - methyl - benzofuran were dissolved in a mixture of 100 ml of dioxan and 20 ml of water and the solution was cooled to 0°C. 1.2 g (0.025 mol + 20%) of sodium borohydride were added portionwise over a period of 0.5 hour and the mixture was stirred at room temperature for 2 hours. The dioxan was removed under reduced pressure and the residue was diluted with *ca* 200 ml of water and extracted twice with ether. The combined extracts were washed with water and with brine and dried over sodium sulphate. Removal of the solvent gave crude 5 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 7 - methyl - benzofuran, in almost quantitative yield, as a pale yellow oil.

The crude 5 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 7 - methyl - benzofuran (*ca* 0.05 mol) and 12 g (0.2 mol) of *iso*propyl amine were heated at reflux for 24 hours in 50 ml of ethanol. The solvent and excess *iso*propyl amine were then removed under reduced pressure and the residual solid was partitioned between ether and dilute hydrochloric acid. The aqueous acidic layer was washed with ether, made basic with dilute sodium hydroxide solution and extracted three times with ether. The combined extracts were washed with water and with brine and dried over sodium sulphate. Removal of the solvent left a brown solid which was crystallized from petroleum ether (boiling range 60°—80°C) to give 9.0 g of 5 - bromo - 2 - (2 - isopropylamino - 1 - hydroxy - ethyl) - 7 - methyl - benzofuran as buff crystals of melting point 120°—130°C. Thin layer chromatography showed the product to be a single substance and its structure was verified by nuclear magnetic resonance spectroscopy 5 - Bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - methyl - benzofuran hydrochloride melted at 158°—159°C after recrystallization from ethanol/ether.

Example 3

i) The preparation of the starting material:

In a manner analogous to that described in the first paragraph of Example 2(i), 3-bromo - 5 - methyl - salicylaldehyde was reacted with chloro-acetone to give 2 - acetyl - 7 - bromo - 5 - methyl - benzofuran as cream-coloured crystals of melting point 85°C (after recrystallization from ethanol).

In a manner analogous to that described in the second paragraph of Example 2(i), from 2 - acetyl - 7 - bromo - 5 - methyl - benzofuran there was obtained 2 - chloroacetyl - 7 - bromo - 5 - methyl - benzofuran as yellow prisms of melting point 131°—133°C (after recrystallization from ethanol).

ii) The process:

2 - Chloroacetyl - 7 - bromo - 5 - methyl -

benzofuran was reduced in a manner analogous to that described in the first paragraph of Example 2(ii) to give 7 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran as a pale yellow oil. Without further purification, this oil was reacted with *iso*propyl amine in accordance with the second paragraph of Example 2(ii) to give 7 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran which melted at 107°C after crystallization from petroleum ether (boiling range 60°—80°C). 7 - Bromo - 2 -(2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran hydrochloride melted at 136°—138°C after recrystallization from ethanol/ether.

EXAMPLE 4

i) The preparation of the starting material:

In a manner analogous to that described in the first paragraph of Example 2(i), 3,5-dibromo - 6 - methyl - salicylaldehyde was reacted with chloro-acetone to give 2-acetyl-5,7 - dibromo - 4 - methyl - benzofuran in the form of white prisms of melting point 162°—163°C (after recrystallization from ethanol).

In a manner analogous to that described in the second paragraph of Example 2(i), from 2 - acetyl - 5,7 - dibromo - 4 - methyl - benzofuran there was obtained 2 - chloroacetyl - 5,7 - dibromo - 4 - methyl - benzofuran as fine white needles of melting point 187°—188°C (after crystallization from ethanol).

ii) The process:

2 - Chloroacetyl - 5,7 - dibromo - 4 - methyl - benzofuran was reduced in a manner analogous to that described in the first paragraph of Example 2(ii) to give 5,7 - dibromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran. Without further purification, this was reacted with *iso*propyl amine in accordance with the second paragraph of Example 2(ii) to give 5,7-dibromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran as grey crystals of melting point 123°—125°C. 5,7 - Dibromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran hydrochloride was obtained as white crystals of melting point 200°—201°C after crystallization from ethanol/ether.

EXAMPLE 5

i) The preparation of the starting material:

In a manner analogous to that described in the first paragraph of Example 2(i), 5-bromo - 3 - ethyl - salicylaldehyde was reacted with chloro-acetone to give 2 - acetyl - 5 - bromo - 7 - ethyl - benzofuran as yellow crystals of melting point 68°—70°C.

In a manner analogous to that described in the second paragraph of Example 2(i), from 2 - acetyl - 5 - bromo - 7 - ethyl - benzofuran there was obtained 2 - chloroacetyl - 5 - bromo - 7 - ethyl - benzofuran as cream plates of melting point 108°—110°C (after recrystallization from ethanol).

ii) The process:

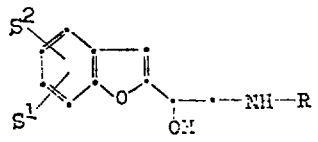
2 - Chloroacetyl - 5 - bromo - 7 - ethyl - benzofuran was reduced in a manner analogous to that described in the first paragraph of Example 2(ii) to give 5 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran as a yellow oil. Without further purification, this oil was reacted with *iso*propyl amine in accordance with the second paragraph of Example 2(ii) to give 5 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran. This low-melting free base was treated with ethereal hydrogen chloride to give 5 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran hydrochloride which melted at 102°—104°C after recrystallization from ethanol/ether.

The following Example illustrates the manner in which the novel derivatives provided by the invention may be made up into pharmaceutical preparations:

10 g of 7 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran hydrochloride were mixed with 10 g of lactose. The mixture was granulated using 0.5 g of 10% aqueous gelatin and the granulate was mixed with 2.5 g of maize starch. 0.25 g of stearic acid were added and the mixture was compressed according to known methods to give tablets each containing 100 mg of active material.

WHAT WE CLAIM IS:—

1) Compounds of the formula



I

wherein R represents a lower-alkyl group, S^1 represents 5- or 7-(chloro or bromo) or 5,7-di(chloro or bromo) substitution and S^2 represents mono-, di- or tri(lower alkyl)substitution according to the availability of position or positions, and acid addition salts thereof.

2) Compounds as formulated in claim 1, wherein S^2 represents mono- or di(lower alkyl) substitution, and acid addition salts thereof.

3) Compounds as formulated in claim 1 or as set forth in claim 2, wherein S^1 represents

benzofuran was reduced in a manner analogous to that described in the first paragraph of Example 2(ii) to give 7 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran as a pale yellow oil. Without further purification, this oil was reacted with *iso*propyl amine in accordance with the second paragraph of Example 2(ii) to give 7 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran which melted at 107°C after crystallization from petroleum ether (boiling range 60°—80°C). 7 - Bromo - 2 -(2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran hydrochloride melted at 136°—138°C after recrystallization from ethanol/ether.

EXAMPLE 4

i) The preparation of the starting material:

In a manner analogous to that described in the first paragraph of Example 2(i), 3,5-dibromo - 6 - methyl - salicylaldehyde was reacted with chloro-acetone to give 2-acetyl-5,7 - dibromo - 4 - methyl - benzofuran in the form of white prisms of melting point 162°—163°C (after recrystallization from ethanol).

In a manner analogous to that described in the second paragraph of Example 2(i), from 2 - acetyl - 5,7 - dibromo - 4 - methyl - benzofuran there was obtained 2 - chloroacetyl - 5,7 - dibromo - 4 - methyl - benzofuran as fine white needles of melting point 187°—188°C (after crystallization from ethanol).

ii) The process:

2 - Chloroacetyl - 5,7 - dibromo - 4 - methyl - benzofuran was reduced in a manner analogous to that described in the first paragraph of Example 2(ii) to give 5,7 - dibromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran. Without further purification, this was reacted with *iso*propyl amine in accordance with the second paragraph of Example 2(ii) to give 5,7-dibromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran as grey crystals of melting point 123°—125°C. 5,7 - Dibromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran hydrochloride was obtained as white crystals of melting point 200°—201°C after crystallization from ethanol/ether.

EXAMPLE 5

i) The preparation of the starting material:

In a manner analogous to that described in the first paragraph of Example 2(i), 5-bromo - 3 - ethyl - salicylaldehyde was reacted with chloro-acetone to give 2 - acetyl - 5 - bromo - 7 - ethyl - benzofuran as yellow crystals of melting point 68°—70°C.

In a manner analogous to that described in the second paragraph of Example 2(i), from 2 - acetyl - 5 - bromo - 7 - ethyl - benzofuran there was obtained 2 - chloroacetyl - 5 - bromo - 7 - ethyl - benzofuran as cream plates of melting point 108°—110°C (after recrystallization from ethanol).

ii) The process:

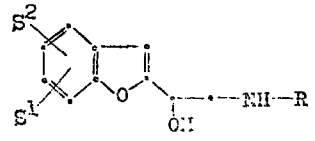
2 - Chloroacetyl - 5 - bromo - 7 - ethyl - benzofuran was reduced in a manner analogous to that described in the first paragraph of Example 2(ii) to give 5 - bromo - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran as a yellow oil. Without further purification, this oil was reacted with *iso*propyl amine in accordance with the second paragraph of Example 2(ii) to give 5 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran. This low-melting free base was treated with ethereal hydrogen chloride to give 5 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran hydrochloride which melted at 102°—104°C after recrystallization from ethanol/ether.

The following Example illustrates the manner in which the novel derivatives provided by the invention may be made up into pharmaceutical preparations:

10 g of 7 - bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran hydrochloride were mixed with 10 g of lactose. The mixture was granulated using 0.5 g of 10% aqueous gelatin and the granulate was mixed with 2.5 g of maize starch. 0.25 g of stearic acid were added and the mixture was compressed according to known methods to give tablets each containing 100 mg of active material.

WHAT WE CLAIM IS:—

1) Compounds of the formula



I

wherein R represents a lower-alkyl group, S^1 represents 5- or 7-(chloro or bromo) or 5,7-di(chloro or bromo) substitution and S^2 represents mono-, di- or tri(lower alkyl)substitution according to the availability of position or positions, and acid addition salts thereof.

2) Compounds as formulated in claim 1, wherein S^2 represents mono- or di(lower alkyl) substitution, and acid addition salts thereof.

3) Compounds as formulated in claim 1 or as set forth in claim 2, wherein S^1 represents

bromo substitution, and acid addition salts thereof.

4) Compounds as formulated in claim 1 or as set forth in claim 2 or in claim 3, wherein R represents the *iso*propyl groups, and acid addition salts thereof.

5) 5 - Bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 6,7 - dimethyl - benzofuran.

6) 5 - Bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - methyl - benzofuran or the hydrochloride thereof.

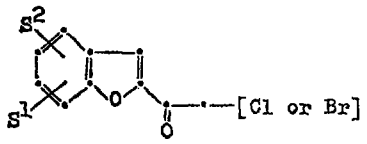
7) 7 - Bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran or the hydrochloride thereof.

8) 5,7 - Dibromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 4 - methyl - benzofuran or the hydrochloride thereof.

9) 5 - Bromo - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 7 - ethyl - benzofuran or the hydrochloride thereof.

10) A pharmaceutical preparation comprising a compound or acid addition salt as claimed in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

11) A process for the manufacture of the derivatives claimed in claim 1, which process comprises reducing a halo-ketone of the general formula



II

wherein S^1 and S^2 have the significance given in claim 1, with an alkali-metal borohydride or with aluminium *iso*propoxide in *iso*propanol and reacting the resulting halohydrin with an amine of the formula

$$R—NH_2$$

wherein R has the significance given in claim 1, in the presence of an acid-binding agent and, if desired, converting the reaction product into an acid addition salt.

12) A process as set forth in claim 11, wherein a halo-ketone in which S^2 represents mono- or di(lower alkyl) substitution is used as the starting material.

13) A process as set forth in claim 11 or in claim 12, wherein a halo-ketone in which S^1 represents bromo substitution is used as the starting material.

14) A process as set forth in claim 11, claim 12 or claim 13, wherein 2-chloroacetyl - 5 - bromo - 6,7 - dimethyl - benzofuran, 2 - chloroacetyl - 5 - bromo - 7 - methyl - benzofuran, 2 - chloroacetyl - 7 - bromo - 5 - methyl - benzofuran, 2 - chloroacetyl - 5,7 - dibromo - 4 - methyl - benzofuran or 2 - chloroacetyl - 5 - bromo - 7 - ethyl - benzofuran is used as the halo-ketone starting material.

15) A process as set forth in any one of claims 11 to 14 inclusive, wherein the reduction of the halo-ketone starting material is carried out using an alkali-metal borohydride.

16) A process as set forth in claim 15, wherein sodium borohydride is used as the alkali-metal borohydride.

17) A process as set forth in any one of claims 11 to 16 inclusive, wherein *iso*propyl amine is the amine used.

18) A process as set forth in any one of claims 11 to 17 inclusive, wherein the reaction of the halohydrin with the amine is carried out using at least two molecular proportions of the amine for each molecular proportion of halohydrin.

19) A variation of the process set forth in any one of claims 11 to 17 inclusive which comprises dehydrohalogenating the halohydrin to the corresponding epoxide prior to the reaction with the amine.

20) A process for the manufacture of the derivatives set forth in claim 1, substantially as described with reference to part ii of Examples 1 to 5.

21) Derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 11 to 20 inclusive.

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