PATENT SPECIFICATION

NO DRAWINGS

Inventors: JOHN MERVYN OSBOND, GRAHAM ALWYN FOTHERGILL and JAMES CHARLES WICKENS

1,106,058

1,106,058

Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949): Sept. 21, 1966.

Application Date: Dec. 15, 1965. *No. 53209/65.*

Application Date: Feb. 4, 1966. *No. 4931/66.*

Complete Specification Published: March 13, 1968.

© Crown Copyright 1968.

Index at acceptance: —C2 C(1E5K4, 1E6K4, 3A2, 3A14A3D, 3A14A8C, LJ29X, LJ29Y, LJ32Y, LJ36Y, LJ45Y, LJ50Y, LJ200, LJ213, LJ246, LJ253, LJ322, LJ360, LJ362, LJ456, LJ502, LJ620, LJ623)

Int. Cl.: —C 07 d 5/42

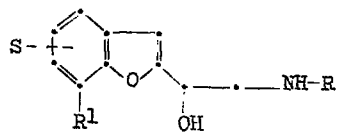
COMPLETE SPECIFICATION

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 general formula

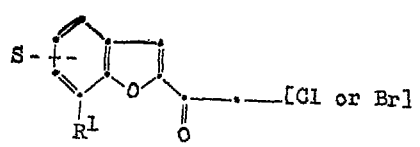


(I)

wherein R stands for a lower-alkyl group, R^1 stands for an allyl group and S stands for 5- or 6-(lower alkyl), 5-allyl or 4,6- or 5,6-di(lower alkyl) substitution and wherein the broken line denotes that the S-substitution is optional, 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 R^1 (and any allyl value for S) becomes a propyl group and 2,3-dihydro derivatives thereof [see the specification of our copending Application for Letters Patent No: 19823/65 (now Serial No: 1106057) where the last-mentioned compounds and their 2,3-dihydro derivatives are claimed *per se*].

It will be appreciated that the term 'lower alkyl' is used in this specification to mean straight-chain and branched-chain alkyl groups containing from one to four carbon atoms (e.g. methyl, ethyl, propyl, *iso*propyl, butyl, secondary butyl and tertiary butyl). An interesting class of derivatives provided by the invention comprises those compounds of formula I in which S (when present) stands for 5- or 6-(lower alkyl) or 4,6- or 5,6-di-(lower alkyl) [especially 5-(lower alkyl)] substitution and their acid addition salts. Yet another interesting class of derivatives provided by the invention comprises those compounds of formula I in which S is present and stands for 5-allyl substitution and acid addition salts thereof. An especially interesting class of derivatives provided by the invention comprises those compounds of formula I in which R represents the *iso*propyl group, and acid addition salts thereof.

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 R^1, S and the broken line have the

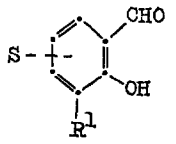
significance given earlier, with an alkali-metal borohydride or with aluminium *iso*propoxide in *iso*propanol and reacting the resulting halohydrin with an amine of the general formula

$$R—NH_2 \quad (III)$$

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 provided by the invention, the halohydrin aforesaid is dehydrohalogenated to the corresponding epoxide which is then reacted with an amine of formula III.

The halo-ketone starting materials of formula II can be obtained, for example, by converting a substituted salicylaldehyde of the formula



(IV)

wherein R^1, S and the broken line have the significance given earlier, into an alkali-metal salt, reacting this salt with chloro-acetone and chlorinating or brominating the resulting substituted 2-acetyl-benzofuran. The conversion into an alkali-metal salt can conveniently be carried out by treatment with an alkali-metal hydroxide in an alkanol containing from one to four carbon atoms (e.g. ethanolic potassium hydroxide). The reaction of the salt with chloroacetone can conveniently be carried out in the presence of an inert organic solvent (e.g. an alkanol containing from one to four carbon atoms such as ethanol). The chlorination is conveniently carried out by treatment with sulphuryl chloride in an inert organic solvent (preferably chloroform) and the bromination is conveniently carried out using cupric bromide in a mixture of ethyl acetate and chloroform. The substituted salicylaldehydes of formula IV hereinbefore in which S (when present) represents lower-alkyl substitution can be obtained, for example, *either* by converting the corresponding salicylaldehyde in which R^1 is absent into its allyl ether and subjecting this ether to a CLAISEN rearrangement *or* by reacting the appropriately substituted phenol with dichloromethyl methyl ether and titanium tetrachloride in methylene chloride or using hexamethylenetetramine under the conditions of a DUFF reaction. The 3,5-diallyl-salicylaldehyde of formula IV can be obtained, for example, by converting salicylaldehyde into its allyl ether, subjecting this ether to a CLAISEN rearrangement, converting the resulting 3-allyl-salicylaldehyde into its allyl ether and subjecting the resulting ether to a CLAISEN rearrangement. An interesting class of halo-ketone starting materials comprises those in which S (when present) stands for 5- or 6-(lower alkyl) or 4,6- or 5,6-di-(lower alkyl) [especially 5-(lower alkyl)] substitution. Another interesting class of halo-ketone starting materials are those in which S is present and stands for 5-allyl substitution. Especially interesting halo-ketone starting materials are 2 - chloroacetyl - 7 - allyl - benzofuran, 2 - chloroacetyl - 7 - allyl - 5 - methyl - benzofuran and 2 - chloroacetyl - 5,7 - diallyl - benzofuran.

The reduction of the halo-ketone starting material of formula II with an alkali-metal borohydride (suitably sodium borohydride) can conveniently be 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 can also be carried out using aluminium *iso*propoxide in *iso*propanol (preferably at elevated temperature).

The reaction of the halohydrin with the amine of formula III can conveniently be carried out by heating the halohydrin with at least one 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 itself. The reaction is accordingly preferably carried out using at least two molecular proportions of amine for each molecular proportion of halohydrin. The heating can be carried out in the presence of an inert organic solvent (e.g. an alkanol containing from one to four carbon atoms such as ethanol or *iso*propanol) but, except where solution of the acid-binding agent is necessary, this is not essential. The heating can also be carried out in an autoclave, and this procedure is advantageous when readily volatile amines are used. *Iso*propyl amine is an especially interesting amine of formula III.

The dehydrohalogenation of the halohydrin to the epoxide in accordance with the variant process provided by the invention can conveniently be 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 such as 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.

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 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 toluenesulphonic acids).

The novel derivatives provided by the invention may be used as medicaments in the form of pharmaceutical preparations which contain them in admixture 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 provided by the invention:—

EXAMPLE 1

i) The preparation of the starting material:

A solution of 243 g (1.5 mol) of 3-allylsalicylaldehyde in 1000 ml of ethanol was treated at 20°C with stirring with a solution of 91.5 g of potassium hydroxide in 500 ml of ethanol. 146 g of chloro-acetone were added in the course of 0.5 hour with stirring to the resulting yellow potassium salt. The temperature of the mixture rose to 40°C. The mixture was subsequently stirred at 20°C for 20 hours, after which time water was added and most of the ethanol was removed under reduced pressure. The residue was extracted three times with ether and the combined extracts were washed with water and dried over sodium sulphate. Distillation of the dried solution gave 184 g of 2-acetyl-7-allyl-benzofuran of boiling point 110°—140°C/0.3 mm. Crystallization from *iso*propanol gave 144 g of colourless plates of melting point 45°—47°C.

115 g of 2-acetyl-7-allyl-benzofuran were dissolved in 690 ml of chloroform and the solution was treated dropwise with stirring in the course of 0.5 hour with 55.2 ml of sulphuryl chloride. The mixture was slowly heated to the reflux temperature (over the course of 20 minutes) and heated under gentle reflux for 2.5 hours. After cooling, the mixture was poured on to ice and the aqueous layer was extracted several times with chloroform. The combined extracts were washed with sodium carbonate solution and water and dried over sodium sulphate. The dried solution was filtered and evaporated to give 61 g of 2-chloroacetyl-7-allyl-benzofuran which melted at 59°—62°C after crystallization from a small volume of ethanol. Recrystallization from petroleum ether (boiling range 40°—60°C) gave 40.2 g of pure material of melting point 66°—67°C.

ii) The process:

39.1 g of 2-chloroacetyl-7-allyl-benzofuran in 167 ml of dioxan and 42 ml of water were treated portionwise with stirring over the course of 0.5 hour at 0°C with 4 g of sodium borohydride. After several hours at 20°C, the solvent was removed under reduced pressure, water was added to the residue and the mixture was extracted three times with ether. There resulted 51.6 g of crude 2 - (2 - chloro - 1 - hydroxy - ethyl) - 7 - allyl - benzofuran which did not crystallize.

25 g of crude 2 - (2 - chloro - 1 - hydroxy - ethyl) - 7 - allyl - benzofuran in 60 ml of ethanol were heated at reflux for 24 hours with 17.7 g of *iso*propyl amine. The solvent was then removed and the residue was dissolved in dilute hydrochloric acid. The solution was washed three times with ether and made basic with 2-*N* sodium hydroxide solution. 2 - (2 - *Iso*propylamino - 1 - hydroxy - ethyl) - 7 - allyl - benzofuran was extracted with ether and converted into the hydrochloride by means of ethereal hydrochloric acid. 2 - (2 - *Iso*propylamino - 1 - hydroxy - ethyl) - 7 - allyl - benzofuran hydrochloride crystallized from *iso*propanol in the form of colourless needles of melting point 118°—119°C.

EXAMPLE 2

i) The preparation of the starting material:

7.4 g (0.05 mol) of 2-allyl-4-hydroxytoluene, 3.75 g of hexamethylenetetramine and

3.75 g of paraformaldehyde were melted together at 100°C. 15 ml of glacial acetic acid were added with stirring over 1 hour to the melt and the temperature of the mixture was raised to 118°—120°C. 4 ml of concentrated sulphuric acid were added over a period of 1.5 hours, then the mixture was poured into 200 ml of hot water and steam distilled until no more oil came over in the distillate. The distillate was extracted twice with chloroform and the extracts were washed with water and dried over anhydrous sodium sulphate. The dried solution was filtered and the chloroform was removed from the filtrate under reduced pressure. The residual oil was distilled to give 5.2 g of 3-allyl-5-methyl-salicylaldehyde as a pale yellow oil of boiling point 98°C/2 mm; $n_D^{20}=1.5602$.

A solution of 21.3 g of potassium hydroxide in 250 ml of ethanol was added dropwise at room temperature to a stirred solution of 52.8 g (0.3 mol) of 3-allyl-5-methyl-salicylaldehyde in 350 ml of ethanol to give a yellow solution of the corresponding potassium salt. 32.4 g (0.3 mol) of chloro-acetone were added dropwise over 0.5 hour and the mixture obtained was stirred at room temperature for 24 hours, then poured into 2 litres of water and extracted three times with chloroform. The combined extracts were washed successively with water, dilute sodium hydroxide solution and water and dried over anhydrous sodium sulphate. The dried solution was filtered and the chloroform was removed from the filtrate under reduced pressure. The residual dark, viscous oil was distilled to give a yellow oil of boiling point 120°—145°C/2 mm which solidified on cooling. Crystallization from ethanol gave 28.9 g of 2-acetyl-7-allyl-5-methyl-benzofuran as white prisms of melting point 71°—72°C.

71 g (0.525 mol) of sulphuryl chloride were added with stirring over 20 minutes to 105.8 g (0.5 mol) of 2 - acetyl - 7 - allyl - 5 - methyl-benzofuran in 500 ml of chloroform. The mixture was then heated under reflux for 3 hours, cooled and poured on to ice-water. The layers were separated and the aqueous layer was washed with chloroform. The combined washings and chloroform layer were washed with sodium bicarbonate solution and then with water and dried over anhydrous sodium sulphate. The dried solution was filtered and the chloroform was removed from the filtrate under reduced pressure. The solid residue was crystallized from ethanol to give 73.5 g of 2 - chloroacetyl - 7 - allyl - 5 - methyl - benzofuran as off-white crystals of melting point 75°—77°C.

ii) The process:

12.4 g (0.02 mol) of 2-chloroacetyl - 7 - allyl - 5 - methyl - benzofuran were dissolved in a mixture of 120 ml of dioxan and 30 ml of water and the solution was cooled to 0°C in ice-water. 1.2 g of sodium borohydride were added in portions with stirring over 0.5 hour and the mixture was stirred at room temperature for 3 hours. The dioxan was then removed under reduced pressure and the residue was diluted with water and extracted three times with ether. The combined extracts were washed with water and with brine and dried over sodium sulphate. The dried solution was filtered and the filtrate was evaporated under reduced pressure to give 12 g of 7 - allyl - 2 - (2 - chloro - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran as a pale yellow viscous oil.

This crude 7 - allyl - 2 (2 - chloro - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran (*ca.* 0.02 mol) was heated under reflux for 24 hours in ethanol with 18 g (0.3 mol) of *iso*propyl amine. The mixture was then cooled and the ethanol and excess *iso*propyl amine were removed under reduced pressure. The residual oil was dissolved in dilute hydrochloric acid and the solution was washed twice with ether and made basic with 2-*N* sodium hydroxide solution. The liberated oil was extracted with two portions of ether. The combined extracts were washed with water and with brine and dried over sodium sulphate. The dried solution was filtered and the ether was evaporated from the filtrate under reduced pressure. On cooling to 0°C, the residual oil became crystalline. Recrystallization from *cyclo*hexane gave 3.5 g of 7 - allyl - 2 (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran as a white powder of melting point 66°—67°C. This was shown by thin-layer chromatography to be a single substance and by nuclear magnetic resonance spectroscopy to be the desired product. The free base was converted into the hydrochloride which crystallized, with difficulty, from (ethyl acetate)/ether; melting point=88°—90°C.

Example 3

i) The preparation of the starting material:

A solution of 53.7 g of potassium hydroxide in 300 ml of ethanol was added to a solution of 176 g (0.871 mol) of 3,5-diallyl-salicylaldehyde in 700 ml of ethanol. After stirring the mixture at 20°C for 0.5 hour, 92.7 g (0.871 mol+15% excess) of chloroacetone were added dropwise with stirring over 0.5 hour, the temperature rising to 55°C. The mixture was stirred at 20°C for 20 hours, after which time part of the ethanol was removed under reduced pressure and *ca* 300 ml of water were added. The mixture obtained was extracted with ether and the extracts were washed twice with water and dried over anhydrous sodium sulphate. The dried solution was evaporated to a syrup which was distilled to give a main fraction boiling at 155°—160°C/0.8—1.0 mm. The 2-acetyl-5,7-diallyl-benzofuran thus obtained was re-

distilled and boiled at 150°—153°C/1.0 mm.

A solution of 12 g (0.05 mol) of 2-acetyl-5,7-diallyl-benzofuran in 60 ml of chloroform was cooled to 0°C and 4.25 ml (0.0525 mol) of sulphuryl chloride were added dropwise thereto over a period of 10 minutes with stirring. The temperature of the mixture obtained was gently raised to reflux temperature over a period of 0.5 hour and kept there for 2.5 hours. After this time, the mixture was poured on to ice and extracted three times with chloroform. The extracts were washed twice with 2-*N* sodium carbonate solution and once with water, dried over anhydrous sodium sulphate, filtered and evaporated to a syrup which was first crystallized from 95% *iso*propanol and then from petroleum ether (boiling range=40°—60°C) to give 5,7 - diallyl - 2 - chloroacetyl - benzofuran as creamy prisms of melting point 68°—71°C. Analysis indicated attack on the allyl double bonds by chlorine and the several recrystallizations required to remove resulting impurity caused some decrease in yield.

ii) The Process:

A solution of 8.24 g (0.033 mol) of 5,7-diallyl-2-chloroacetyl-benzofuran in 50 ml of dioxan and 8 ml of water was cooled to 0°C. At this temperature, 0.8 g (0.017 mol+25%) of sodium borohydride was added portionwise with stirring over 0.25 hours. The mixture was stirred for a further 0.5 hour at 0°—5°C and for 3.5 hours at 20°C. The solvent was then removed under reduced pressure and 50 ml of water were added. The mixture was extracted three times with ether and the extracts were washed once with water and dried over anhydrous sodium sulphate. The dried extracts were evaporated to yield 5,7-diallyl - 2 - (2 - chloro - 1 - hydroxy - ethyl) - benzofuran in the form of a yellow syrup.

0.033 mol of 5,7 - diallyl - 2 - (2 - chloro - 1 - hydroxy - ethyl) - benzofuran and 12 g (0.2 mol) of *iso*propyl amine in 50 mol of *iso*propanol were boiled under reflux for 17 hours. The solvent and excess *iso*propyl amine were then removed under reduced pressure and the residue was acidified with dilute hydrochloric acid. Water was added until the oily hydrochloride which had separated out dissolved. Any neutral material remaining was removed by extracting three times with ether, then the aqueous solution was made basic with 2-*N* sodium hydroxide solution and extracted three times with ether. The extracts were washed twice with water, dried over anhydrous sodium sulphate, filtered and evaporated to give 7.5 g of a basic syrup. This was not crystallized; thin layer chromatography indicated the presence of both 5,7 - diallyl - 2 (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran and 5,7 - diallyl - 2 - (1 - *iso*propylamino - 2 - hydroxy - ethyl)-benzofuran. The syrup was chromatographed on alumina to yield 4.3 g of material shown by thin layer chromatography to consist solely of 5,7 - diallyl - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran. Recrystallization from petroleum ether (boiling range=40°—60°C) at 0°C gave material of melting point 55°—58°C. The crystalline base was converted into the hydrochloride which was crystallized from a large volume of (ethyl acetate)/ether as colourless prisms of melting point 94°—97°C.

The following Examples illustrate the manner in which the novel derivatives provided by the invention may be made up into pharmaceutical preparations.

EXAMPLE A

Tablets each containing 25 mg of 2-(2-*iso*propylamino - 1 - hydroxy - ethyl) - 7 - allyl-benzofuran hydrochloride, 114 mg of lactose, 50.0 mg of corn starch, 8.0 mg of pregelatinized corn starch and 3.0 mg of calcium stearate and having a total weight of 200.0 mg were prepared by mixing the active material with the lactose, corn starch and pregelatinized corn starch in a suitable mixer, passing the mix through a comminuting machine, returning the mixture to the mixer, moistening it with water so as to form a thick paste, passing the moist mass through a screen, drying the moist granules on paper-lined trays at 45°C, returning the dried granules to the mixer, adding the calcium stearate, mixing well and compressing the granulate at a tablet weight of 200 mg using standard 8 mm diameter concave punches.

EXAMPLE B

Capsules each containing 15.0 mg of 2-(2-*iso*propylamino - 1 - hydroxy - ethyl) - 7 - allyl-benzofuran hydrochloride, 170.0 mg of lactose, 30.0 mg of corn starch and 5.0 mg of talc and having a total net weight of 220.0 mg were prepared by mixing the active material with the lactose and corn starch in a suitable mixer, passing the mix through a comminuting machine, returning the mixture to the mixer, adding the talc, blending thoroughly and filling the resulting powder into hard shell gelatin capsules on a capsulating machine.

EXAMPLE C

Tablets each containing 25 mg of 5,7-diallyl - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran hydrochloride, 114 mg of lactose, 50.0 mg of corn starch, 8.0 mg of pregelatinized corn starch and 3.0 mg of calcium stearate and having a total weight of 200.0 mg were prepared by mixing the active material with the lactose, corn starch and pregelatinized corn starch in a suitable mixer, passing the mix through a comminuting machine, returning the mixture to the mixer, moistening it with water so as

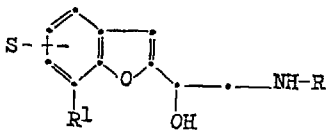
to form a thick paste, passing the moist mass through a screen, drying the moist granules on paper-lined trays at 45°C, returning the dried granules to the mixer, adding the calcium stearate, mixing well and compressing the granulate at a tablet weight of 200 mg using standard 8 mm diameter concave punches.

EXAMPLE D

Capsules each containing 15.0 mg of 5,7-diallyl - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran hydrochloride, 170.0 mg of lactose, 30.0 mg of corn starch and 5.0 mg of talc and having a total net weight of 220.0 mg were prepared by mixing the active material with the lactose and corn starch in a suitable mixer, passing the mix through a comminuting machine, returning the mixture to the mixer, adding the talc, blending thoroughly and filling the resulting powder into hard shell gelatin capsules on a capsulating machine.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein R stands for a lower-alkyl group, R^1 stands for an allyl group and S stands for 5- or 6-(lower alkyl), 5-allyl or 4,6- or 5,6-di-(lower alkyl) substitution and wherein the broken line denotes that the S-substitution is optional, and acid addition salts thereof.

2) Compounds as formulated in claim 1, wherein S (when present) stands for 5- or 6-(lower alkyl) or 4,6- or 5,6-di-(lower alkyl) substitution, and acid addition salts thereof.

3) Compounds as set forth in claim 2, wherein S (when present) stands for 5-(lower alkyl) substitution, and acid addition salts thereof.

4) Compounds as formulated in claim 1, wherein S is present and stands for 5-allyl substitution, and acid addition salts thereof.

5) Compounds as set forth in any one of the preceding claims, wherein R stands for the *iso*propyl group, and acid addition salts thereof.

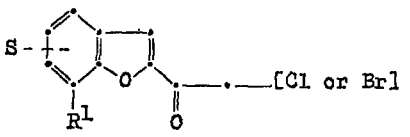
6) 2 - (2 - *Iso*propylamino - 1 - hydroxy - ethyl) - 7 - allyl - benzofuran or its hydrochloride.

7) 7 - Allyl - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran or its hydrochloride.

8) 5,7 - Diallyl - 2 (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran or its hydrochloride.

9) A pharmaceutical preparation comprising a compound or salt as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

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



wherein R^1, S and the broken line 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 general 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.

11) A process as set forth in claim 10, wherein a halo-ketone in which S (when present) stands for 5- or 6-(lower alkyl) or 4,6- or 5,6-di(lower alkyl) substitution is used as the starting material.

12) A process as set forth in claim 11, wherein a halo-ketone in which S (when present) stands for 5-(lower alkyl) substitution is used as the starting material.

13) A process as set forth in claim 12, wherein 2 - chloroacetyl - 7 - allyl - benzofuran or 2 - chloroacetyl - 7 - allyl - 5 - methyl - benzofuran is used as the starting material.

14) A process as set forth in claim 10, wherein a halo-ketone in which S is present and stands for 5-allyl substitution is used as the starting material.

15) A process as set forth in claim 14, wherein 2 - chloroacetyl - 5,7 - diallyl - benzofuran is used as the halo-ketone starting material.

16) A process as set forth in any one of claims 10 to 15 inclusive, wherein the reduction of the halo-ketone starting material is carried out using an alkali-metal borohydride.

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

18) A process as set forth on any one of claims 10 to 17 inclusive, wherein *iso*propyl amine is the amine used.

19) A process as set forth in any one of claims 10 to 18 inclusive, wherein the reaction between the halohydrin and the amine is carried out using at least two molecular proportions of amine for each molecular proportion of halohydrin.

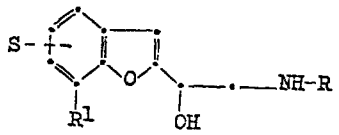
to form a thick paste, passing the moist mass through a screen, drying the moist granules on paper-lined trays at 45°C, returning the dried granules to the mixer, adding the calcium stearate, mixing well and compressing the granulate at a tablet weight of 200 mg using standard 8 mm diameter concave punches.

EXAMPLE D

Capsules each containing 15.0 mg of 5,7-diallyl - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran hydrochloride, 170.0 mg of lactose, 30.0 mg of corn starch and 5.0 mg of talc and having a total net weight of 220.0 mg were prepared by mixing the active material with the lactose and corn starch in a suitable mixer, passing the mix through a comminuting machine, returning the mixture to the mixer, adding the talc, blending thoroughly and filling the resulting powder into hard shell gelatin capsules on a capsulating machine.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein R stands for a lower-alkyl group, R^1 stands for an allyl group and S stands for 5- or 6-(lower alkyl), 5-allyl or 4,6- or 5,6-di-(lower alkyl) substitution and wherein the broken line denotes that the S-substitution is optional, and acid addition salts thereof.

2) Compounds as formulated in claim 1, wherein S (when present) stands for 5- or 6-(lower alkyl) or 4,6- or 5,6-di-(lower alkyl) substitution, and acid addition salts thereof.

3) Compounds as set forth in claim 2, wherein S (when present) stands for 5-(lower alkyl) substitution, and acid addition salts thereof.

4) Compounds as formulated in claim 1, wherein S is present and stands for 5-allyl substitution, and acid addition salts thereof.

5) Compounds as set forth in any one of the preceding claims, wherein R stands for the *iso*propyl group, and acid addition salts thereof.

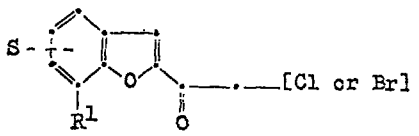
6) 2 - (2 - *Iso*propylamino - 1 - hydroxy - ethyl) - 7 - allyl - benzofuran or its hydrochloride.

7) 7 - Allyl - 2 - (2 - *iso*propylamino - 1 - hydroxy - ethyl) - 5 - methyl - benzofuran or its hydrochloride.

8) 5,7 - Diallyl - 2 (2 - *iso*propylamino - 1 - hydroxy - ethyl) - benzofuran or its hydrochloride.

9) A pharmaceutical preparation comprising a compound or salt as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

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



wherein R^1, S and the broken line 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 general 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.

11) A process as set forth in claim 10, wherein a halo-ketone in which S (when present) stands for 5- or 6-(lower alkyl) or 4,6- or 5,6-di(lower alkyl) substitution is used as the starting material.

12) A process as set forth in claim 11, wherein a halo-ketone in which S (when present) stands for 5-(lower alkyl) substitution is used as the starting material.

13) A process as set forth in claim 12, wherein 2 - chloroacetyl - 7 - allyl - benzofuran or 2 - chloroacetyl - 7 - allyl - 5 - methyl - benzofuran is used as the starting material.

14) A process as set forth in claim 10, wherein a halo-ketone in which S is present and stands for 5-allyl substitution is used as the starting material.

15) A process as set forth in claim 14, wherein 2 - chloroacetyl - 5,7 - diallyl - benzofuran is used as the halo-ketone starting material.

16) A process as set forth in any one of claims 10 to 15 inclusive, wherein the reduction of the halo-ketone starting material is carried out using an alkali-metal borohydride.

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

18) A process as set forth on any one of claims 10 to 17 inclusive, wherein *iso*propyl amine is the amine used.

19) A process as set forth in any one of claims 10 to 18 inclusive, wherein the reaction between the halohydrin and the amine is carried out using at least two molecular proportions of amine for each molecular proportion of halohydrin.

20) A variation of the process set forth in any one of claims 10 to 18 inclusive which comprises dehydrohalogenating the halohydrin to the corresponding epoxide prior to the reaction with the amine.

21) A process for the manufacture of the derivatives claimed in claim 1, substantially as described with reference to part ii of Examples 1 to 3.

22) Compounds as formulated in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 10 to 21 inclusive.

W. D. WHITTAKER,
Patent Agent
for Roche Products Limited.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

