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PATENT SPECIFICATION

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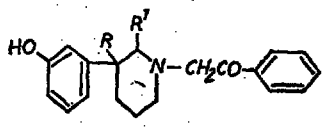
COMPLETE SPECIFICATION

3-(3-Hydroxyphenyl)-1-Phenacyl-Piperidine Compounds and their preparation

We, TANABE SEIYAKU CO., LTD., a corporation organized under the laws of Japan, of 21, Doshomachi 3-chome, Higashi-ku, Osaka, Japan, 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:—

This invention relates to derivatives of 3-(3 - hydroxyphenyl) - 1 - phenacylpiperidine and to a process for preparing these compounds.

The compounds of the present invention are represented by the following formula:



(I)

wherein R is a lower alkyl group containing up to 4 carbon atoms or a benzyl group and R^1 is a hydrogen atom or a lower alkyl group containing up to 4 carbon atoms. The invention also provides the acid addition salts of these compounds.

We have found that the 3 - (3 - hydroxyphenyl) - 1 - phenacyl - piperidine compounds of this invention are useful as analgesics. Among them, 3 - (3 - hydroxyphenyl) - 3-methyl - 1 - phenacyl - piperidine possesses an analgesic effect comparable to meperidine and is less toxic than meperidine. The analgesic effect and the toxicity in mice are indicated in Table 1 where they are compared to those of meperidine and codeine.

TABLE 1

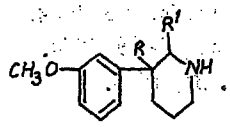
	Analgesic ED_{50}* (mg./kg.)	Toxicity LD_{50}** (mg./kg.)	LD_{50}/ED_{50}
3-(3-hydroxyphenyl)-3-methyl-1-phenacyl-piperidine	12.1	368.0	30.4
Meperidine	12.5	273.5	21.9
Codeine	24.3	231.2	9.5

* Calculated from the pain reaction time of groups of ten mice on a hot plate at 55 °C.

** Calculated from the mortality of groups of five mice for 24 hours after subcutaneous administration.

[*Price 4s. 6d.*]

According to the present invention, the compounds of formula (I) above can be prepared by reacting a phenacyl halide, such as phenacyl bromide or phenacyl chloride, with a 3-(3-methoxyphenyl) - piperidine compound of the formula:



(II)

in which R and R^1 have the same meaning as given above, in the presence of an acid acceptor, such as potassium carbonate, to obtain the corresponding N-phenacyl compound and hydrolysing the product with a hydrohalic acid.

The reaction may be preferably carried out in an organic solvent such as acetone, methanol, ethanol, propanol, or aqueous mixtures thereof. The reaction is advantageously carried out at the boiling point of the reaction mixture. Potassium carbonate may be replaced by another acid acceptor such as sodium carbonate, an alkali metal bicarbonate, an alkali metal hydroxide or an organic base, such as pyridine. An excess of the starting amine may be also used for this purpose. Thereafter the remaining part of the starting compound may be removed from the reaction mixture in the form of its N-acetyl derivative.

The 3 - (3 - methoxyphenyl) - 1 - phenacyl - piperidine compounds which are obtained by the above mentioned procedure are then hydrolysed with a hydrohalic acid, such as hydrochloric acid or hydrobromic acid to obtain the final products by the cleavage of the ethereal linkage. The compounds of this invention may form acid addition salts with various inorganic or organic acids, such as hydrochloric, hydrobromic, sulphuric, acetic or oxalic acid. Examples of the starting piperidine compounds represented by the formula (II) are: 3 - (3 - methoxyphenyl) - 3-methyl-piperidine, 3 - ethyl - 3 - (3 - methoxyphenyl) - piperidine, 2,3 - dimethyl - 3 - (3-methoxyphenyl) - piperidine, 3 - (3 - methoxyphenyl) - 2 - methyl - 3 - propyl - piperidine and 3 - benzyl - 3 - (3 - methoxyphenyl) - 2 - methyl - piperidine. Among them, the compound wherein R^1 is a hydrogen atom can be prepared by the process described in "Chemical and Pharmaceutical Bulletine Vol. 11, pages 253—257."

The compounds having a lower alkyl substituent at the 2-position of the piperidine ring may be prepared by hydrolysing 2-benzyl- or 2 - lower alkyl - 2 - (3 - methoxyphenyl) - acetonitrile to yield the corresponding carboxylic acid, reacting the carboxylic acid with alkyl-lithium to obtain the corresponding ketone, reacting the ketone with acrylonitrile in the presence of a basic catalyst such as "Triton" B, and reducing the addition product in the presence of Raney nickel under pressure to form the piperidine nucleus The word "Triton" is a registered Trade Mark. The following preparations A and B illustrate the preparation of 2,3-dimethyl - 3 - (3 - methoxyphenyl) - piperidine and 3 - benzyl - 3 - (3 - methoxyphenyl) - 2-methyl - piperidine.

PREPARATION A.

50 g. of 2 - (3 - methoxyphenyl) - propionitrile was added to a mixture of 33 ml. of glacial acetic acid, 36 ml. of concentrated sulphuric acid and 28 ml. of water. The mixture was stirred for 3.5 hours at 90° to 100°C and refluxed for an additional 30 minutes at 130°C. Water was added to the reaction mixture and the oil which separated was extracted with ether. The ethereal layer was washed with water and extracted with 10% sodium carbonate solution. The aqueous layer was acidified with concentrated hydrochloric acid and re-extracted with ether. After evaporating the ether, the residue was distilled under reduced pressure, whereby 45 g. of 2 - (3 - methoxyphenyl) - propionic acid was obtained (B.P. 156° to 157°C./2 mm Hg.)

30 ml. of absolute ether solution containing 15 g. of the product was dropped into 200 ml. of absolute ether solution containing 0.33 mol of methyl-lithium with stirring at 0° to 5°C over a period of 25 minutes. The reaction mixture was stirred at the same temperature for an additional 30 minutes and poured into iced water containing ammonium chloride. The ethereal layer was separated, washed successively with 10% sodium carbonate solution and water, dried with anhydrous sodium sulphate and evaporated to remove ether. The residue was distilled under reduced pressure, whereby 14.2 g of 3 - (3 - methoxyphenyl)-butane-2-one was obtained as an oily product. (B.P. 135° to 140°C/15 mm Hg). To 30 ml. of a solution containing 15.8 g. of the product in dioxane, 1.5 ml. of Triton B (40% aqueous solution of benzyl-trimethyl-ammonium hydroxide) was added. 6.1 g. of acrylonitrile was added with stirring to the mixture over a period of 30 minutes.

The reaction mixture was stirred for an additional 30 minutes at 45° to 50°C and cooled. Dioxane was removed by evaporation, the residue was extracted with ether after the addition of water to the residue. The extract was dried, evaporated to remove ether, and the residue was distilled under reduced pressure, whereby 16.6 g. of an oil, 4-acetyl-4-(3-methoxyphenyl) - *n* - valeronitrile was obtained. (B.P. 145° to 150°C/0.1 mm Hg). 15 g. of the product and 15 ml of Raney nickel were added to 80 ml. of methanol and the mixture was placed in an autoclave. Hydrogen gas was introduced into the autoclave

until the pressure reached 90 kg/cm², then the autoclave was shaken for 2 hours at 120° to 130°C. The reaction mixture was filtered and the filtrate was evaporated to remove methanol. The residue was extracted with ether after addition of water to the residue. The ethereal extract was extracted with 10% hydrochloric acid. The extract was made alkaline with potassium carbonate and the separated oil was extracted with ether. The ethereal extract was dried and evaporated to remove ether. The residue was distilled under reduced pressure, whereby 12.0 g. of colourless oil, 2,3-dimethyl-3-(3-methoxyphenyl) - piperidine was obtained. (B.P. 138° to 140°C/4 mm Hg). Gas chromatography of the product provided a single peak. The hydrochloride in the form of colourless prisms melting at 226° to 228°C was obtained after recrystallisation from ethanol.

Analysis: Calculated for $C_{14}H_{21}NO.HCl$
C, 65.74; H, 8.67; N, 5.48
Found: C, 65.84; H, 8.30; N, 5.42.

PREPARATION B.

41 g. of 2 - (3 - methoxyphenyl) - 3-phenyl - propionitrile was added to a mixture consisting of 30 ml. of water, 42 ml. of glacial acetic acid and 42 ml. of concentrated sulphuric acid, and the mixture was refluxed for one hour. The reaction mixture was treated as in Preparation A. 37 g. of 2 - (3 - methoxyphenyl) - 3 - phenyl - propionic acid was obtained. (B.P. 175° to 185°C/0.4 mm Hg). 50 ml. of absolute ether solution containing 37 g of the product was dropped into a solution of 8.0 g. of lithium and 82 g. of methyl iodide in 350 ml. of absolute ether at 2° to 3°C. with stirring over a period of 30 minutes. The reaction mixture was stirred for an additional 30 minutes at 5° to 10°C and was treated as in Preparation A. 34.5 g. of 3-(3-methoxyphenyl) - 4 - phenyl - butane - 2 - one was thereby obtained. (B.P. 136° to 137°C/0.3 mm Hg).

1.2 ml. of "Triton" B was added to 65 ml. of a dioxane solution containing 20 g. of the product. 20 ml. of a solution of 5 g. of acrylonitrile in dioxane was dropped into the mixture at 20° to 36°C and the mixture was stirred for 45 minutes at 40°C. The reaction mixture was treated as in Preparation A, and 18.6 g. of 4 - acetyl - 4 - (3 - methoxyphenyl) - 5 - phenyl - *n* - valeronitrile was obtained (M.P. 119° to 120°C). 17.5 g of the product and 13 ml. of Raney nickel were added to 90 ml. of methanol and autoclaved for one hour at 110° to 120°C. The reaction mixture was treated as described in Preparation A. 13 g. of 3 - benzyl - 3 - (3 - methoxyphenyl) - 2 - methyl - piperidine was obtained. The perchlorate in the form of colourless needles melting at 183° to 185°C was obtained after recrystallisation from acetone-ether.

Analysis: Calculated for $C_{20}H_{26}O_5NCl$
C, 60.68; H, 6.62; N, 3.54
Found: C, 61.00; H, 6.54; N, 3.50.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1.

2 g. of 3 - (3 - methoxyphenyl) - 3-methyl - piperidine was added to a solution consisting of 2.0 g. of phenacyl bromide, 1.5 g. of potassium carbonate and 30 ml. of ethanol, and the mixture was refluxed for 2 hours over a water bath. The reaction mixture was poured into water and extracted with ether. After drying, a methanol solution of hydrogen bromide was added to the ethereal extract, whereby crystals of 3 - (3 - methoxyphenyl) - 3 - methyl - 1 - phenacyl - piperidine hydrobromide were precipitated. The product was obtained as colourless needles melting at 183° to 185°C after recrystallisation from acetone-ethanol-ether. Yield: 2.5 g.

Analysis: Calculated for $C_{21}H_{26}BrNO_2$
C, 62.37; H, 6.48; N, 3.46
Found: C, 62.31; H, 6.61; N, 3.98

2.0 g. of the hydrobromide was refluxed for 30 minutes with 10 ml. of 48% hydrobromic acid. The mixture was distilled under reduced pressure to remove hydrogen bromide. The residue was dissolved in water, made alkaline with ammonia and extracted with ethyl acetate. The extract was dried and the solvent was removed by evaporation. The residue was dissolved in acetone and hydrogen chloride gas was bubbled through the solution, whereby 3 - (3 - hydroxyphenyl) - 3 - methyl-1 - phenacyl - piperidine hydrochloride was obtained in the form of colourless needles melting at 227° to 229°C after recrystallisation from acetone - ethanol - ether. Yield: 1.4 g.

Analysis: Calculated for $C_{20}H_{24}ClNO_2$
C, 69.45; H, 6.99; N, 4.04
Found: C, 69.45; H, 7.03; N, 4.08

EXAMPLE 2.

In accordance with the same procedure as described in Example 1 except that 3-(3-methoxyphenyl) - 3 - *n* - propyl - piperidine was used instead of 3 - (3 - methoxyphenyl)-3 - methyl - piperidine, 3 - (3 - methoxyphenyl) - 1 - phenacyl - 3 - *n* - propyl-piperidine hydrochloride was prepared. The hydrochloride had a M.P. of 170° to 172°C. The hydrochloride was hydrolysed as in Example 1, whereby 1 - phenacyl - 3 - *n*-

propyl - 3 - (3 - hydroxyphenyl) - piperidine hydrochloride was obtained. The hydrochloride was an amorphous powder which showed no definite melting point.

EXAMPLE 3.

2.0 g. of 2,3 - dimethyl - 3 - (3 - methoxyphenyl) - piperidine, 1.9 g. of phenacyl bromide and 2.0 g. of anhydrous potassium carbonate were dissolved in 40 ml. of ethanol and refluxed for 3 hours. After filtration, the reaction mixture was evaporated to remove ether. The residue was extracted with ether, dried with anhydrous potassium carbonate, and evaporated to remove ether. The oil remaining was converted to hydrobromide and recrystallised from ethanol, whereby colourless prisms of 2,3 - dimethyl - 3 - (3 - methoxyphenyl)-1 - phenacyl - piperidine hydrobromide were obtained. Yield: 2.0 g. M.P. 199° to 210°C.

Analysis: Calculated for $C_{22}H_{27}NO_2.HBr$
C, 63.15; H, 6.75
Found: C, 63.46; H, 6.58.

1.2 g. of the hydrobromide was treated with 48% hydrobromic acid, whereby colourless needles of 2,3 - dimethyl - 3 - (3 - hydroxyphenyl) - 1 - phenacyl - piperidine hydrobromide were obtained. Yield: 0.8 g. M.P. 219° to 221°C (recrystallised from ethanol).

Analysis: Calculated for $C_{21}H_{25}NO_2.HBr$
C, 62.37; H, 6.48
Found: C, 62.41; H, 6.21

EXAMPLE 4.

1.7 g. of 3 - (3 - methoxyphenyl) - 2-methyl - 3 - *n* - propyl - piperidine was mixed with 1.6 g. of phenacyl bromide and 1.7 g. of anhydrous potassium carbonate in 30 ml. of acetone. The mixture was refluxed for 10 minutes, filtered and evaporated to remove acetone. The residue was dissolved in ether, washed with water and shaken with 100 ml. of 5% hydrochloric acid. Ether was removed from the mixture. The residue was washed with ether, made alkaline with potassium carbonate and extracted with ether. The extract was dried, and the ether was removed by evaporation. A small amount of ether and petroleum ether were added to the residue successively, whereby crystals of 3 - (3-methoxyphenyl) - 2 - methyl - 1 - phenacyl-3 - *n* - propyl - piperidine were obtained. Yield: 1.2 g. M.P. 106° to 114°C.

By concentrating the mother liquor, 0.2 g. of the product was obtained. The hydrochloride was obtained in the form of needles melting at 183° to 185°C after recrystallisation from acetone-ethanol-ether. Yield: 1.5 g. The purified crystals had a M.P. of 188° to 190°C.

Analysis: Calculated for $C_{24}H_{32}O_2NCl \cdot 1/2H_2O$
C, 70.30; H, 8.11; N, 3.41
Found: C, 70.45; H, 8.21; N, 3.37

1 g. of the hydrochloride was refluxed for 30 minutes with 6 ml. of 47% hydrobromic acid in acetic acid. After removing the solvents, the residue was treated as described in Example 1, whereby 0.8 g. of 3 - (3-hydroxyphenyl) - 2 - methyl - 1 - phenacyl-3 - *n* - propyl - piperidine hydrochloride was obtained. M.P. 219°—221°C.

Analysis: Calculated for $C_{23}H_{30}O_2NCl$
C, 71.21; H, 7.80; N, 3.61
Found: C, 71.16; H, 7.51; N, 3.68

EXAMPLE 5.

2.2 g. of 3 - benzyl - 3 - (3 - methoxyphenyl) - 2 - methyl - piperidine was refluxed for 10 hours with 1.6 g. of phenacyl bromide and 2.0 g. of anhydrous potassium carbonate in 50 ml. of acetone. The reaction mixture was filtered and the filtrate was evaporated to remove acetone. The residue was dissolved in ether, washed with water, dried with anhydrous potassium carbonate and the ether was removed by evaporation. The remaining oil was converted to the hydrochloride and recrystallised from acetone-ether, whereby colourless needles of 3 - benzyl - 3 - (3-methoxyphenyl) - 2 - methyl - 1 - phenacyl-piperidine hydrochloride was obtained. M.P. 142° to 144°C with decomposition. Yield: 2.9 g.

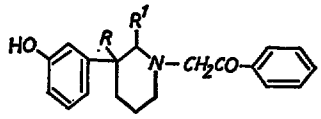
Analysis: Calculated for $C_{28}H_{32}O_2NCl.H_2O$
C, 71.85; H, 7.30; N, 2.99
Found: C, 71.66; H, 7.03; N, 3.00

1.5 g. of the hydrochloride was hydrolysed with 5 ml. of 47% hydrobromic acid by a similar procedure as described in Example 1, whereby 3 - benzyl - 3 - (3 - hydroxyphenyl) - 2 - methyl - 1 - phenacyl - piperidine was obtained. The hydrochloride was obtained as needles melting at 182° to 184°C with decomposition (recrystallised from acetone-methanol).

Analysis: Calculated for $C_{27}H_{30}O_2HBr \cdot 1/2H_2O$
C, 66.25; H, 6.38; N, 2.86
Found: C, 66.60; H, 6.14; N, 2.78.

WHAT WE CLAIM IS:—

1. A compound having the formula:



(I)

in which R is a lower alkyl group containing up to 4 carbon atoms or a benzyl group and R^1 is a hydrogen atom or a lower alkyl group containing up to 4 carbon atoms, and acid addition salts thereof.

2. 3 - (3 - Hydroxyphenyl) - 3 - methyl-1 - phenacyl - piperidine and its hydrochloride.

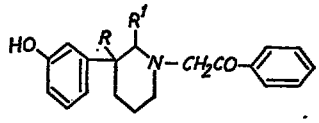
3. 3 - (3 - Hydroxyphenyl) - 3 - *n* - propyl-1 - phenacyl - piperidine hydrochloride.

4. 3 - (3 - Hydroxyphenyl) - 2,3 - dimethyl - 1 - phenacyl - piperidine and its hydrobromide.

5. 3 - (3 - Hydroxyphenyl) - 2 - methyl-3 - n - propyl - 1 - phenacyl - piperidine hydrochloride.

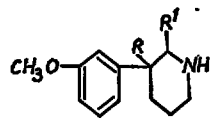
6. 3 - (3 - Hydroxyphenyl) - 2 - methyl-3 - benzyl - 1 - phenacyl - piperidine and its hydrochloride.

7. A process for the preparation of a substituted 3 - (3 - hydroxyphenyl) - 1 - phenacyl - piperidine having the formula:



(I)

in which R is a lower alkyl group containing up to 4 carbon atoms or a benzyl group and R^1 is a hydrogen atom or a lower alkyl group containing up to 4 carbon atoms, which comprises reacting a compound of the formula:



(II)

wherein R and R^1 have the same meanings as stated above with a phenacyl halide in the presence of an acid acceptor to form the corresponding N-phenacyl derivative, and hydrolysing the derivative with a hydrohalic acid.

8. A process according to claim 7 in which the acid acceptor is an alkali metal carbonate, an alkali metal bicarbonate, an alkali metal hydroxide or an organic base.

9. A process for the preparation of substituted 3 - (3 - hydroxyphenyl) - 1 - phenacyl - piperidine compounds having the formula (I) herein substantially as hereinbefore described with reference to the Examples.

10. Substituted 3 - (3 - hydroxyphenyl)-1 - phenacyl - piperidine compounds having the formula (I) herein whenever prepared by a process according to any one of claims 7 to 9.

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BK.

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