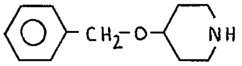
(12) UK Patent Application (19) GB (11) 2 044 260 A

(21) Application No **8005923**
(22) Date of filing **21 Feb 1980**
(30) Priority data
(31) **7906070**
(32) **9 Mar 1979**
(33) **France (FR)**
(43) Application published
15 Oct 1980
(51) **INT CL^3**
C07D 211/44
A61K 31/445
(52) Domestic classification
C2C 1532 215 220 226
22Y 250 251 25Y 29X 29Y
30Y 332 351 355 360 362
364 36Y 43X 500 50Y 621
623 624 661 665 672 675
699 778 802 80Y AA MM
WH
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicants
Metabio-Joullie, 23-25
Avenue Morane-Saulnier
92360 Meudon La Foret,
France
(72) Inventors
Christian Warolin
Roland Schneider
(74) Agents
Brookes & Martin

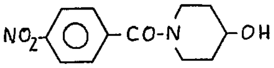
(54) New piperidine derivatives process for their preparation and their therapeutic applications

(57) 4-Benzyloxy-piperidine

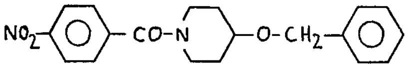


(I) is prepared by

(a) condensing 4 - hydroxy - piperidine with p-nitrobenzoyl chloride in the presence of an acid binding agent, to give a protected piperidine, having the formula:



b) benzylating the protected piperidine with benzyl chloride in the presence of a condensing agent and of an acid binding agent, to give a compound having the formula:



c) releasing the amino group of the piperidine.

The resulting base may be converted to a pharmaceutically acceptable salt, and both base and salt are therapeutically useful as antispasmodic agents.

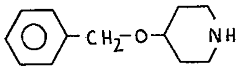
GB 2 044 260 A

SPECIFICATION

New piperidine derivatives, process for their preparation and their therapeutic applications

This invention relates to new piperidine derivatives, to a process for their preparation and to their therapeutic applications.

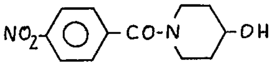
This invention relates to 4 - benzyloxy - piperidine having the formula:


(I)

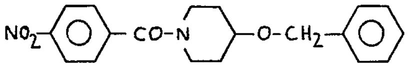
and its pharmaceutically acceptable acid addition salts.

4-Benzyloxy-piperidine and its salts may be prepared in the following manner, comprising:

a) condensing 4 - hydroxy - piperidine with p-nitrobenzoyl chloride in the presence of an acid binding agent, to give a protected piperidine, having the formula:


(II)

b) benzylating the compound of the formula (II) with benzyl chloride in the presence of a condensing agent and of an acid binding agent, to give a compound having the formula:


(III)

c) releasing the amino group of the piperidine, and

d) if desired, converting the resulting base to a salt.

The following non-limiting Example illustrates the preparation of the compound of the formula (I).

EXAMPLE

a) 1 - p - Nitrobenzoyl - 4 - hydroxy - piperidine

To an Erlenmeyer flask of 1 litre capacity, provided with a magnetic stirrer and placed in a water-bath, containing a solution of 30.34 g (0.3 mole) 4-hydroxy-piperidine and 58.04 g anhydrous potassium carbonate (0.42 mole) in 260 ml water is added 260 ml chloroform. 48.43 g (0.261 mole) p-nitrobenzyl chloride is added portion-wise to the stirred reaction medium.

The heterogeneous medium is stirred for 30 mn at room temperature, and is then diluted by addition of 260 ml ether. After stirring for a further 15 mn, the precipitate is suction filtered under slight depression, after which it is washed with 5 × 50 ml water, until there is complete absence of Cl^- ions.

The pale yellow product is dried *in vacuo* for 2-10 hours, by heating at 40-50°C, to give 52.39 g product (Yield: 80%). M.p. = 205-206°C (Kofler block).

(b) 1 - p - Nitrobenzoyl - 4 - benzyloxy - piperidine

Under a hood, to a vigorously stirred suspension of 33.21 g (0.133 mole) 1 - p - nitrobenzoyl - 4 - hydroxy - piperidine in 176 ml benzyl chloride is added a solution of 53.2 g sodium hydroxide (50wt% solution; 0.665 mole), and 2.25 g TBAS (tetrabutylammonium hydrogen sulfate) are then added thereto portionwise, in view of the exothermic character of the reaction.

The well stirred medium is heated to 50°C for 4 hours, it is then diluted with 345 ml water to dissolve the precipitated NaCl, and subsequently with 210 ml chloroform.

The medium is decanted. The aqueous phase is extracted with 100 ml $CHCl_3$ and the total organic phase is washed with 3 × 100 ml water and dried overnight over $MgSO_4$. After filtration, the chloroform is removed *in vacuo* in a rotary evaporator, and the residual solution of product in benzyl chloride is slowly poured over 1760 ml cyclohexane, under vigorous stirring.

The very pale yellow resulting precipitate is stirred for about 3 hours in the medium, after which it is filtered, washed with cyclohexane and dried *in vacuo* at 40°C, to give 39.24 g of product (Yield: 86.5%); M.p. = 119°C (Kofler block).

c) 4 - Benzyloxy - piperidine hydrobromide

To a stirred suspension of 22.12 g (0.065 mole) 1 - p - nitrobenzoyl - 4 - benzyloxy - piperidine in 390 ml 96% enthanol is added 10N aqueous potassium hydroxide (97.5 ml; 0.975 mole). The reaction medium is stirred overnight at room temperature and, the next day, at 50°C for 4 hours, under a nitrogen atmosphere.

The ethanol is removed in vacuo in a rotavapor (bath: 35-40°C). The residue is redissolved in 160 ml water, and 60 g pure NaCl are then added to salt out the product which is extracted with 160 ml ether.

The mixture of NaCl and p-nitrobenzoic acid sodium salt is filtered; the filtrate is decanted off; the ether phase is dried overnight over $MgSO_4$ after extraction of the aqueous phase with 3 × 160 ml ether.

The solvent is dried *in vacuo*, without heating: long pale yellow needles are formed from the original oil, to give 12.28 g of product (98.8%).

The base is highly hygroscopic.

This oil is dissolved in 660 ml dry de-peroxydized ether, and 55 ml of a solution (about 1.3M) of gaseous hydrobromic acid in dry de-peroxydized ether are then added thereto portionwise (a more highly concentrated solution, having a concentration of about 4M, for example, may conveniently be used), while cooling in an ice-bath.

The resulting hydrobromide precipitate is rapidly filtered, washed with ether and dried *in vacuo*, without heating. The dry salt is not hygroscopic.

This procedure gives 16.75 g of salt (95%).

The somewhat beige product is decolorized by recrystallization from about 270 ml benzene (with filtration in the hot, if required). M.p. = 1348C (Kofler block).

4 - Benzyloxy-piperidine and its pharmaceutically acceptable salts possess useful pharmacological properties. Particularly, they have an antispasmodic action on the unstriated muscles and are therapeutically useful for the treatment of arterial (arteritis, angina pectoris), digestive, visceral (hepatic and nephretic colics), vesical and uterine spasms.

Results of toxicological and pharmacological investigations which demonstrate said properties are given below.

a) *Acute toxicity*

The LD_{50} was determined in Swiss NMRI mice with

4-benzyloxy-piperidine hydrobromide:
– oral route LD_{50} 75 mg/kg
– i.v. route LD_{50} 32.5 mg/kg

b) *Antispasmodic action*

The tests are effected on the isolated duodenum of rats surviving in oxygenated Tyrode liquid at a temperature of 37°C (20 ml cell, Valette type water-bath for isolated organs).

The toxicity and movements of the isolated organ are recorded using the method according to Magnus (R.) (Arch. Ges. Physiol. 1904, *102*; 123) by means of a stress guage connected to an Electromed electronic recorder.

The antagonism exerted by the test material is investigated against the musculotropic contracturing effects of barium chloride.

Papaverine is used as reference antagonistic material.

The molar concentration of test material which decreases by a factor of 50% the effects of barium chloride is determined.

The results obtained are set forth in the following Table.

Compound	50% Inhibitory molar concentrations
4-Benzyloxy-piperidine (hydrobromide)	1.8 × 10^{-5} M
Papaverin	1.25 × 10^{-5} M

It is apparent from the results obtained that the activity of 4-benzyloxy-piperidine is substantially equal to that of papaverin.

4-Benzyloxy-piperidine, and preferably its pharmaceutically acceptable salts, are administrable to humans by the oral route (typically as capsules containing 10 mg active ingredient, 3-5 times daily) or by the perenteral route, typically by the intramuscular route (as an aqueous solution containing 5 mg active ingredient, 3-2 times daily).

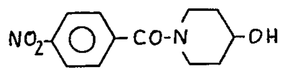
CLAIMS

1. 4-Benzyloxy-piperidine or a pharmaceutically acceptable salt thereof.

2. A pharmaceutically acceptable derivative or adduct of a compound as claimed in Claim 1.

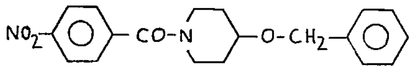
3. A process for the preparation of a compound as claimed in Claim 1, comprising:

a) condensing 4-hydroxy-piperidine with p-nitrobenzoyl chloride in the presence of an acid binding agent, to give a protected piperidine, having the formula:



(II)

b) benzylating the compound of the formula (II) with benzyl chloride in the presence of a condensing agent and of an acid binding agent, to give a compound having the formula:



c) releasing the amino group of the piperidine, and

d) optionally converting the resulting base to a salt.

4. A process as claimed in Claim 1 substantially as described in the Examples.

5. A therapeutic composition having an antispasmodic action, comprising as active ingredient, a compound as claimed in Claim 1 or 2 and a therapeutically acceptable carrier.

6. A composition as claimed in Claim 5 comprising, as active ingredient, a pharmaceutically acceptable salt of 4-benzyloxy-piperidine.

7. A composition as claimed in Claim 5 or 6 formulated for oral administration.

8. A composition as claimed in Claim 5 or 6 formulated for parenteral administration.

9. A composition as claimed in Claim 5 substantially as described herein.

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd., Berwick-upon-Tweed, 1980.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.