

AB ASTRA
Södertälje/Sweden

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**Substituted 4-phenyl-4-piperidinecarboxamides with both
local anaesthetic and analgesic effect as well as
processes for their preparation**

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Substituted 4-phenyl-4-piperidinecarboxamides with both local anaesthetic and analgesic effect as well as processes for their preparation

Field of the invention

The present invention is directed to new compounds having both local anaesthetic and analgesic effect, a process for their preparation and their use in the manufacture of pharmaceutical preparations.

Background of the invention

Pethidine is a frequently used analgesic. It has also a weak local anaesthetic effect. The anaesthetic/analgesic effect of pethidine after spinal administration is often insufficient in both respects. Instead combinations of bupivacaine and fentanyl or morfin are being used. The opiate analgesics have several severe draw-backs, as e.g. development of tolerance, addiction, risk for respiratory depression. There is, thus, a need for agents giving a local anaesthesia with a remaining analgesic effect. Such agents should be used after spinal or epidural injections as local anaesthetics intraoperatively. Thereafter the compounds would give good post-operative pain relief.

Prior art

Hardy D.G. et al describe in J. Med. Chem. 8, pp. 847-851 (1965) the structure-activity relationship of some analogues of pethidine, which have an analgesic activity. The Swedish patent 96980 describes 1-methyl-1-phenyl-piperidin-4-carboxylic acid and two amides thereof. No specific pharmaceutical effect is given in the document, only that the compounds can be used in the manufacture of new drugs. From FR 2156470 derivatives of 1-(3,3-diphenyl-propyl)-piperidine are known, which due to their high lipid solubility only can be active as analgetics not as local anaesthetics. In Acta Pol Pharm 1979,36(4), p. 439-4, (Chemical Abstracts 93(1980) 7970v) some amides of 1-butyl-4-phenyl-4-piperidinecarboxylic acid are described.

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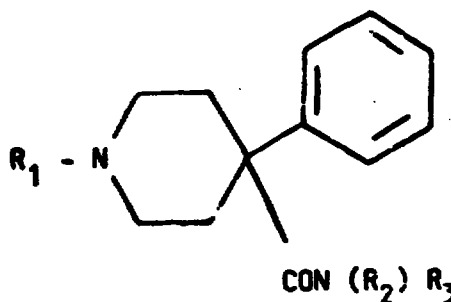


These amides seem to have analgesic, but not local anaesthetic effect.

Outline of the invention

5 It has been found that compounds of the following formula IV or pharmaceutically acceptable salts thereof not only give an unexpectedly good effect as spinal and epidural anaesthetics but also have an additional analgesic effect that lasts for a long time after the anaesthetic effect
10 has declined. Thus no combination of active compounds need to be given, thus avoiding the risks connected with these mentioned above. The compounds according to the invention are defined by the following formula IV

15



20

IV

wherein

R_1 is an alkyl group with 2-6 carbon atoms or an alkoxyalkyl group $R_4O-(CH_2)_m-$, wherein R_4 is an alkyl
25 group with 1-4 carbon atoms and m is 2-4, R_2 and R_3 are the same or different and each an alkyl group with up to 6 carbon atoms or R_2 and R_3 form together a chain $(CH_2)_n$ wherein n is 4-6 or one of R_2 and R_3 is hydrogen and a
30 straight or branched alkyl group with 1-6 carbon atoms as well as pharmaceutically acceptable salts thereof.

Preferred compounds according to the invention are those, wherein R_1 , R_2 and R_3 are alkyl groups.

35 Especially preferred is the compound wherein the group R_1 is hexyl, R_2 is methyl or ethyl and R_3 is ethyl.



Preferred salts according to the invention are pharmaceutically acceptable salts. The hydrochloride is especially preferred.

5 Preparation

Compounds of the formula IV above were prepared according to the following:

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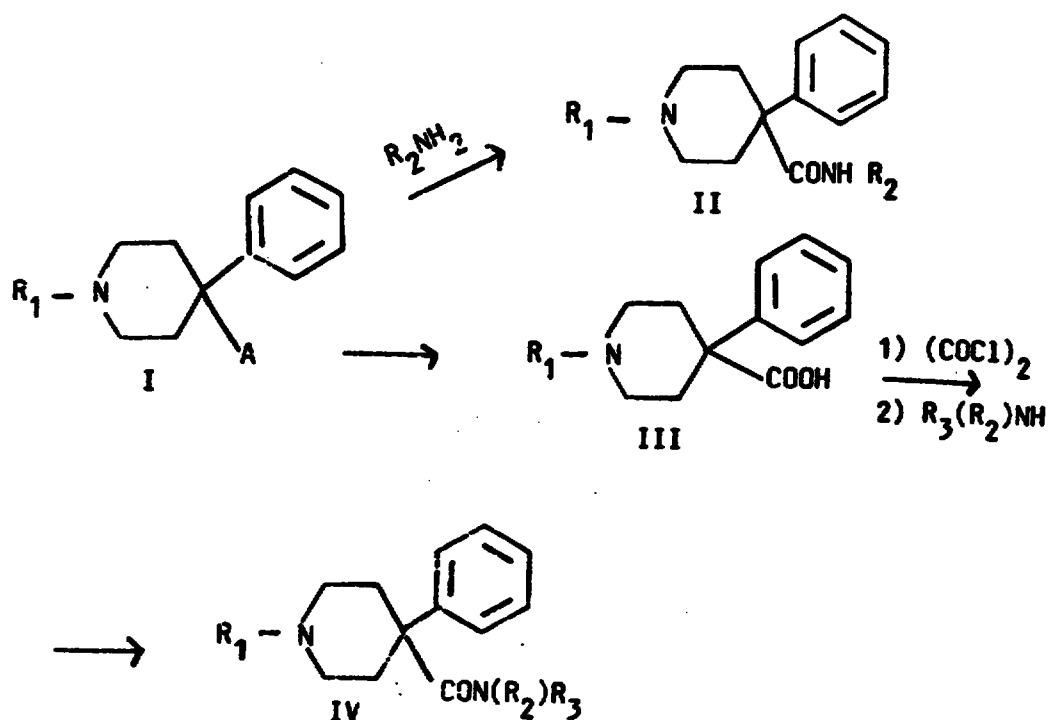
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wherein A, R_1 , R_2 , and R_3 are as defined above.



The compounds of the formula I wherein A is CN or $-\text{CO}_2\text{C}_2\text{H}_5$ and R_1 is as defined above were prepared from the corresponding secondary amine ($\text{R}_1=\text{H}$) with the exception of the compound wherein R_1 is CH_3 and A is $\text{CO}_2\text{C}_2\text{H}_5$, which is the commercially available compound pethidine. The compounds of the formula II are prepared directly from I wherein A is $-\text{CO}_2\text{C}_2\text{H}_5$ (c.f. Example 1) by reaction with an alkylamine or are prepared in the same way as the compounds of the formula IV. These are obtained by first hydrolyzing the compounds of the formula I to the carboxylic acids of the formula III, which then are reacted with oxalyl chloride and the appropriate amine to yield a compound of the formula IV.

Detailed description of the preparation

The examples denoted I1 - I6 describe intermediates in the preparation of the compounds of the formula IV.

COMPOUNDS I

Example I 1

Ethyl 1-hexyl-4-phenyl-4-piperidine carboxylate hydrochloride

Norpethidine (23.5 g, 0.10 mol), hexyliodide (23.5 g, 0.11 mol), anhydrous Na_2CO_3 (11.7 g, 0.11 mol) and acetonitrile (250 ml) were heated under reflux and stirring for 1,5 h. The mixture was filtered and the solvent removed. The residue was dissolved in CH_2Cl_2 , the solution washed with 100 ml of 1 N NaOH and then with water and finally dried (K_2CO_3). To the solution HCl (g) in diethyl ether was then added, whereupon the solvents were removed and the residue recrystallized from ethyl acetate. Yield 22.5 g of hydrochloride with m.p. 156-158°C.

M.p. acc. to J. Med.Chem. 8 p. 847-851 (1965), 158°C.

Example I 2Ethyl 1-[4-ethoxybutyl]-4-phenyl-4-piperidinecarboxylate hydrochloride

5 Norpethidine (15.63 g, 67 mmol), 4-ethoxybutylchloride (10.67 g, 70 mmol), Na_2CO_3 (7.77 g, 73 mmol), KI (0.6 g) and acetonitrile (150 ml) were heated under reflux and stirring for 72 h. The mixture was filtered and the solvent removed. The residue was dissolved in diethyl
10 ether, and the solution washed with water and dried (MgSO_4). Distillation yielded 17.9 g of base boiling at 160-163°C/0.05 mm Hg. B.p. acc. to J. Chem. Soc. 3062 (1958) 180°C/1 mm Hg. Hydrochloride m.p. 143-145°C.

15 Example I 31-(2-Ethoxyethyl)-4-cyano-4-phenyl-piperidine.

The title compound was prepared as described in Example I 2 from 4-cyano-4-phenylpiperidine and 2-bromoethyl ethyl ether excluding KI: Reaction time under reflux 6 hours.

20 The compound boiled at 130-135°/0.005 mm Hg.

COMPOUNDS III

25

Example I 41-Hexyl-4-phenyl-4-piperidinecarboxylic acid hydrochloride

A mixture of the ethyl ester (22.5 g, 64 mmol) 20% hydrochloric acid (225 ml) and acetic acid (70 ml) was
30 heated under reflux for 30 h. After cooling the mixture was poured into 200 ml of ice water, the acid was filtered and air dried. Yield 12.9 g. The filtrate was evaporated and the residue treated with acetonitrile yielding another 4 g of acid. Recrystallization from acetonitril yielded
35 16.9 g with m.p. 193-195°C. The acid contains solvent of crystallization.

**Example I 5****1-[4-Ethoxybutyl]-4-phenyl-4-piperidinecarboxylic acid hydrochloride**

A mixture of the ethyl ester (17.9 g, 53.7 mmol), 2N NaOH (55 ml) and ethanol (6 ml) was heated under reflux with stirring for 24 h. The solution was extracted with diethyl ether and then acidified with dilute hydrochloric acid. The solvent was evaporated and the residue extracted with acetone. The acetone solution was filtered and the solvent evaporated. The crystalline residue was dried over CaCl_2 in a vacuum desiccator and the recrystallized from THF-ethyl acetate. Yield 11.7 g with m.p. 131-133°C.

Example I 6**1-(2-Ethoxyethyl)-4-phenyl-4-piperidine-carboxylic acid hydrochloride.**

A mixture of the cyanide according to example I 3 (5.6g), KOH(5.6g), ethanol (39 ml) and water (17 ml) was heated in an autoclave at 140° C for 6 hours. The reaction mixture was acidified with concentrated hydrochloric acid, the precipitated salt was filtered and the filtrate evaporated. The residue was leached with hot acetone. From the acetone extracts 4.2 g of the title compound was obtained. n.p. 150-155° C.

COMPOUNDS II**Example 1****N-Butyl-1-methyl-4-phenyl-4-piperidinecarboxamide**

Pethidine hydrochloride (2.56 g, 9 mmol) and butylamine (5 ml) were heated in an autoclave at 180°C for 3 days. The reaction mixture was shaken between 10 ml of 1N NaOH and diethyl ether and the ether extracts dried (MgSO_4). The solvent was evaporated and the residue chromatographed on aluminium oxide with ethyl acetate as eluent. The crystalline product (1.0 g) was recrystallized from n-hexane yielding 0.59 g with m.p. 73-76.5°C.

**Example 3****N-Ethyl-1-hexyl-4-phenyl-4-piperidinecarboxamide**

This compound was prepared as above from ethyl 1-hexyl-4-phenyl-4-piperidinecarboxylate hydrochloride (3.54 g, 10 mmol) and ethylamine (2.25 g, 50 mmol). Reaction time 2 days. The crude product (1.0 g) was recrystallized from disopropyl ether, yielding 0.81 g with m.p. 92-94°C. Hydrochloride m.p. 221-223°C (from 2% aqueous acetone).

10

COMPOUNDS IV

General method of preparation. Oxalyl chloride (4 ml) was added dropwise with stirring to a solution of a piperidinecarboxylic acid (compounds III) (5-6 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred at 50°C for 2 h. The solvent was evaporated, a few ml of toluene were added and the solvent was evaporated again. The residue was dissolved in CH_2Cl_2 (10 ml) and the solution was added dropwise with stirring to a solution of the appropriate amine (35-42 mmole) in CH_2Cl_2 (20 ml), cooled in ice-water. The reaction mixture was then stirred at room temperature for a few hours. It was then shaken with 1N NaOH (20 ml), once with water, dried (K_2CO_3) and the solvent evaporated.

25

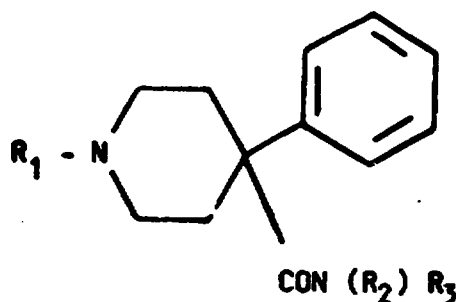
Before conversion to hydrochloride the crude base in several cases was further purified e.g. by chromatography.

30

In the following Table 1 some compounds according to the invention are given.



TABLE 1



hydrochloride					
Comp	R ₁	R ₂	R ₃	m.p °C	
15	1)	CH ₃	H	C ₄ H ₉	73-76.5
	2)	C ₆ H ₁₃	H	CH ₃	252-254
	3)	C ₆ H ₁₃	H	C ₂ H ₅	221-223
	4)	C ₆ H ₁₃	H	CH(CH ₃) ₂	145-148
20	5)	C ₆ H ₁₃	CH ₃	CH ₃	155.5-158.5
	6)	C ₆ H ₁₃	CH ₃	C ₂ H ₅	137-141
	7)	C ₆ H ₁₃	C ₂ H ₅	C ₂ H ₅	151-154
	8)	C ₆ H ₁₃	(CH ₂) ₅		217-219
	9)	C ₂ H ₅ O(CH ₂) ₄	CH ₃	CH ₃	125-128
	10)	C ₂ H ₅ O(CH ₂) ₄	CH ₃	C ₂ H ₅	115-117
25	11)	C ₂ H ₅ O(CH ₂) ₄	(CH ₂) ₅		130-132
	12)	C ₂ H ₅ OCH ₂ -CH ₂	C ₂ H ₅	C ₂ H ₅	142-144
	13)	C ₃ H ₇ O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	
	14)	C ₄ H ₉ O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	



Pharmaceutical preparations

For the preparation of pharmaceutical preparations the new compound is dissolved in a liquid diluent which is
5 suitable for injection. The preparations used are aqueous solutions which contain between 2.5 and 40.0 mg/ml of the active compound calculated as the hydrochloride salt.

Biological studies

10

Spinal anaesthesia

The compounds according to the invention were tested for spinal anaesthesia in the mouse. There were six animals in each group. As reference compound pethidine, the starting
15 materials for compounds 2) - 8), namely ethyl 1-hexyl-4-phenyl-4-piperidinecarboxylate hydrochloride (Example I 1) and 9) and 10), namely ethyl 1-[4-ethoxybutyl]-4-phenyl-4-piperidinecarboxylate hydrochloride, (Example I 2) known from the above cited J. Med. Chem. were tested. The
20 results are presented in the following Table 2.

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**TABLE 2**

Mean duration (min) of motor block and full analgesia (tail-flick) in mice after subarachnoid injection of 5 μ l of the test solution. The durations are calculated from 5 the time of injection.

	Compound	Conc. %	Motor bl Duration	Tail-flick min
10	3	1	10	15
	4		14	35
	5		14	20
	6		20	40
	7		27	50
15	8		19	40
	9		3	10
	10		6	10
	11		6	10
	12		3	10
20	I 1		15	40
	I 2		5	25
25	3	2	22	30
	4		24	30
	5		21	25
	6		36	55
	7		48	85
	8 ¹		49	>120
	9		6	10
	10		7	10
30	11		12	35
	12		6	10
	I 2		10	15
	Pethidine		4	15
35	1	4	17	20
	Pethidine		10	25

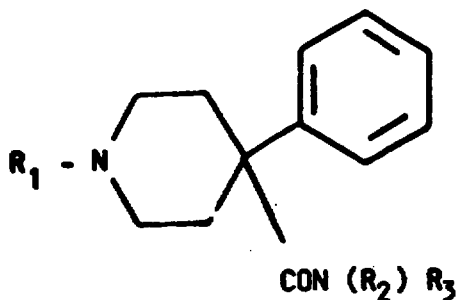
¹ The animals were irritated, squeaky

**Discussion**

- As can be seen from Table 2 the compounds according to the invention give a better local anaesthetic effect than the known analgesic pethidine. As the local anaesthetic effect
- 5 is combined with a good analgesic effect, the compounds according to the invention are more useful than pethidine. They can also replace the combinations of one analgesic and one anaesthetic agent with good result.
- 10 The best mode of carrying out the invention known at present is to use the compounds 6 or 7.

**CLAIMS**

1. Compounds of the formula IV



wherein R_1 is an alkyl group with 2-6 carbon atoms or an alkoxyalkyl group $R_4\text{O}(\text{CH}_2)_m-$, wherein R_4 is an alkyl group with 1-4 carbon atoms and m is 2-4, R_2 and R_3 are the same or different and each an alkyl group with up to 6 carbon atoms or R_2 and R_3 form together a chain $(\text{CH}_2)_n$ wherein n is 4-6 or one of R_2 and R_3 is hydrogen and the other is a straight or branched alkyl group with 1-6 carbon atoms as well as pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R_1 , R_2 and R_3 are alkyl groups.

3. A compound according to claim 2, wherein R_1 is hexyl, R_2 is methyl and R_3 is ethyl.

4. A compound according to claim 2, wherein R_1 is hexyl and R_2 and R_3 are both ethyl.

5. A pharmaceutical preparation for control blockade by epidural or intrathecal route containing a compound according to claim 1.

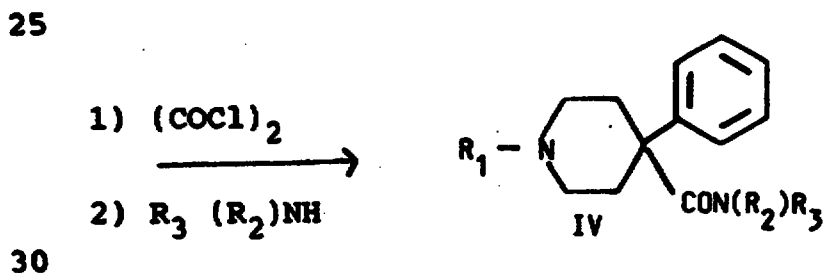
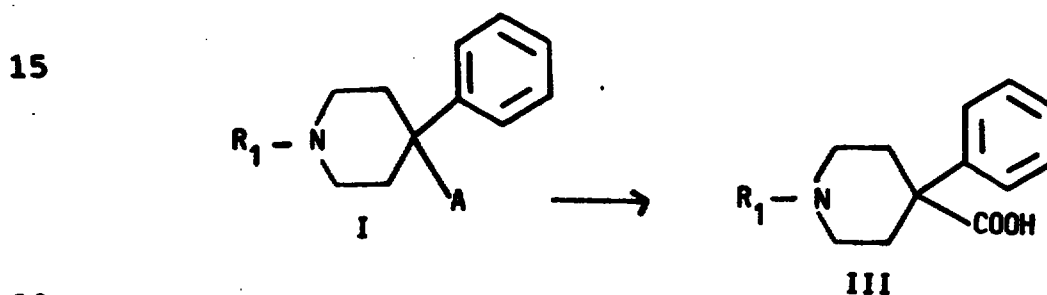
6. A pharmaceutical preparation for anaesthesia and analgesia containing a compound according to claim 1.



7. Use of a compound according to claim 1 for the manufacture of a pharmaceutical preparation with anaesthetic and analgetic effect.

5 8. A process for the preparation of a compound of Formula IV according to claim 1 wherein

a) an ester or nitrile of the formula I is hydrolyzed to the corresponding acid of the formula III, which then is reacted
10 with 1) oxalyl chloride and 2) the appropriate amine to yield the end product of the formula IV



wherein R_1 , R_2 and R_3 are as defined above in claim 1 and A is $-\text{CN}$ or $-\text{CO}_2\text{C}_2\text{H}_5$; or

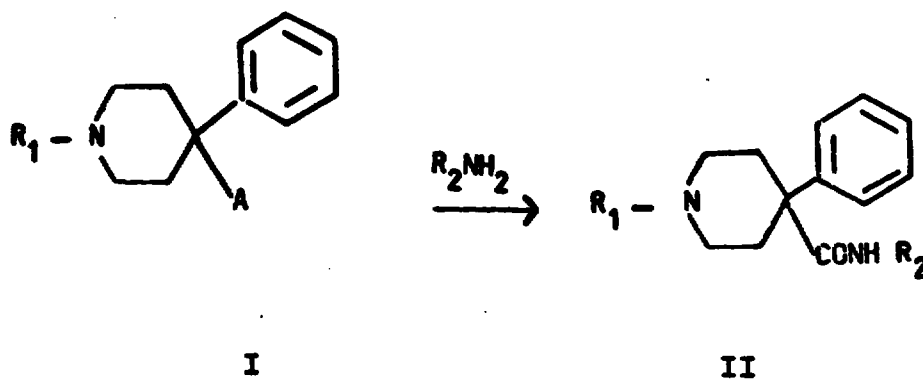
35 b) a compound of the formula I, wherein A is $-\text{CO}_2\text{C}_2\text{H}_5$ is



reacted with an amine R_2NH_2 to yield a compound of the formula II, wherein R_1 and R_2 are as defined above, that is a compound of formula IV, wherein R_2 or R_3 is hydrogen.

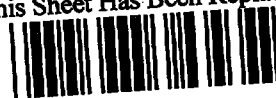
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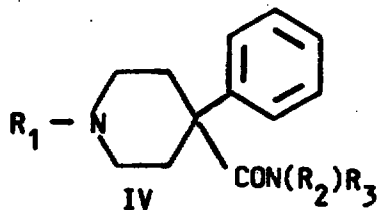


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9. A method for inducing anaesthesia and analgesia comprising administration to mammals including man needing local anaesthesia and analgesia an effective amount of a
20 compound according to claim 1.

**ABSTRACT**

Compounds of the formula IV for use as local anaesthetics and analgetics, as well as a method for their preparation,
5 their pharmaceutical preparations and their use.



16 OCT 1996

AB ASTRA

Södertälje/Sweden

REPLACED SHEETS SG

- ☒ Description : paged 1 to paged 11
☒ Claim(s) : paged 12 to paged 14
☐ Drawing(s) : paged 1 to paged 1
☒ Abstract : paged 15 to paged 15

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DATE OF RECEIPT 16/10/96

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2-103400



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Background of the invention

Pethidine is a frequently used analgesic. It has also a weak local anaesthetic effect. The anaesthetic/analgesic effect of pethidine after spinal administration is often insufficient in both respects. Instead combinations of bupivacaine and fentanyl or morfin are being used. The opiate analgesics have several severe draw-backs, as e.g. development of tolerance, addiction, risk for respiratory depression. There is, thus, a need for agents giving a local anaesthesia with a remaining analgesic effect. Such agents should be used after spinal or epidural injections as local anaesthetics intraoperatively. Thereafter the compounds would give good post-operative pain relief.

Prior art

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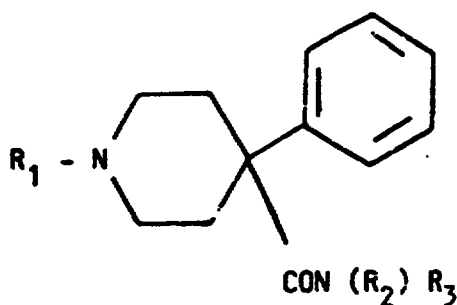


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These amides seem to have analgesic, but not local anaesthetic effect.

Outline of the invention

It has been found that compounds of the following formula IV or pharmaceutically acceptable salts thereof not only give an unexpectedly good effect as spinal and epidural anaesthetics but also have an additional analgesic effect that lasts for a long time after the anaesthetic effect has declined. Thus no combination of active compounds need to be given, thus avoiding the risks connected with these mentioned above. The compounds according to the invention are defined by the following formula IV



wherein

R_1 is an alkyl group with 2-6 carbon atoms or an alkoxyalkyl group $R_4O-(CH_2)_m-$, wherein R_4 is an alkyl group with 1-4 carbon atoms and m is 2-4, R_2 and R_3 are the same or different and each an alkyl group with up to 6 carbon atoms or R_2 and R_3 form together a chain $(CH_2)_n$ wherein n is 4-6 or one of R_2 and R_3 is hydrogen and a straight or branched alkyl group with 1-6 carbon atoms as well as pharmaceutically acceptable salts thereof.

Preferred compounds according to the invention are those, wherein R_1 , R_2 and R_3 are alkyl groups.

Especially preferred is the compound wherein the group R_1 is hexyl, R_2 is methyl or ethyl and R_3 is ethyl.

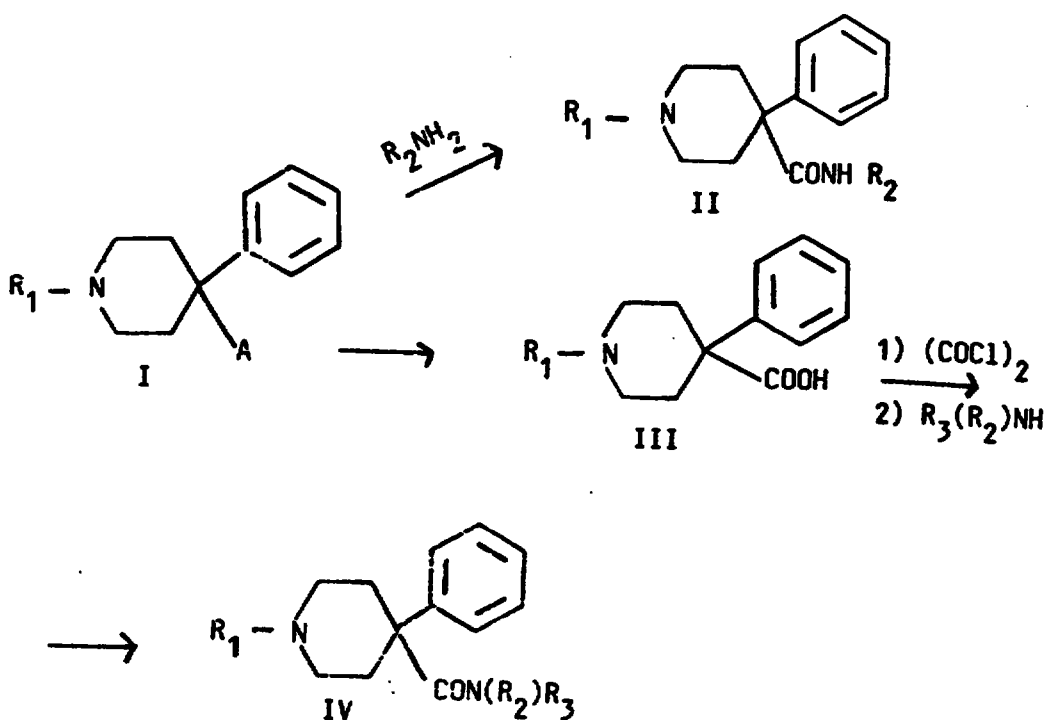


16 OCT 1996

Preferred salts according to the invention are pharmaceutically acceptable salts. The hydrochloride is especially preferred.

Preparation

Compounds of the formula IV above were prepared according to the following:



wherein A, R₁, R₂, and R₃ are as defined above.



16 OCT 1996

The compounds of the formula I wherein A is CN or $-\text{CO}_2\text{C}_2\text{H}_5$ and R_1 is as defined above were prepared from the corresponding secondary amine ($\text{R}_1=\text{H}$) with the exception of the compound wherein R_1 is CH_3 and A is $\text{CO}_2\text{C}_2\text{H}_5$, which is the commercially available compound pethidine. The compounds of the formula II are prepared directly from I wherein A is $-\text{CO}_2\text{C}_2\text{H}_5$ (c.f. Example 1) by reaction with an alkylamine or are prepared in the same way as the compounds of the formula IV. These are obtained by first hydrolyzing the compounds of the formula I to the carboxylic acids of the formula III, which then are reacted with oxalyl chloride and the appropriate amine to yield a compound of the formula IV.

Detailed description of the preparation

The examples denoted I1 - I6 describe intermediates in the preparation of the compounds of the formula IV.

COMPOUNDS I

Example I 1

Ethyl 1-hexyl-4-phenyl-4-piperidine carboxylate hydrochloride

Norpethidine (23.5 g, 0.10 mol), hexyliodide (23.5 g, 0.11 mol), anhydrous Na_2CO_3 (11.7 g, 0.11 mol) and acetonitrile (250 ml) were heated under reflux and stirring for 1,5 h. The mixture was filtered and the solvent removed. The residue was dissolved in CH_2Cl_2 , the solution washed with 100 ml of 1 N NaOH and then with water and finally dried (K_2CO_3). To the solution HCl (g) in diethyl ether was then added, whereupon the solvents were removed and the residue recrystallized from ethyl acetate. Yield 22.5 g of hydrochloride with m.p. 156-158°C.

M.p. acc. to J. Med.Chem. 8 p. 847-851 (1965), 158°C.



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Example I 2Ethyl 1-[4-ethoxybutyl]-4-phenyl-4-piperidinecarboxylate hydrochloride

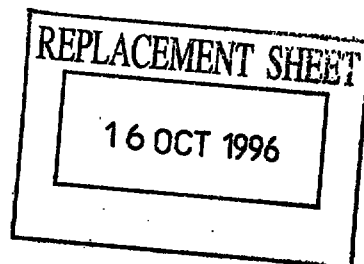
Norpethidine (15.63 g, 67 mmol), 4-ethoxybutylchloride (10.67 g, 70 mmol), Na_2CO_3 (7.77 g, 73 mmol), KI (0.6 g) and acetonitrile (150 ml) were heated under reflux and stirring for 72 h. The mixture was filtered and the solvent removed. The residue was dissolved in diethyl ether, and the solution washed with water and dried (MgSO_4). Distillation yielded 17.9 g of base boiling at 160-163°C/0.05 mm Hg. B.p. acc. to J. Chem. Soc. 3062 (1958) 180°C/1 mm Hg. Hydrochloride m.p. 143-145°C.

Example I 31-(2-Ethoxyethyl)-4-cyano-4-phenyl-piperidine.

The title compound was prepared as described in Example I 2 from 4-cyano-4-phenylpiperidine and 2-bromoethyl ethyl ether excluding KI: Reaction time under reflux 6 hours. The compound boiled at 130-135°/0.005 mm Hg.

COMPOUNDS IIIExample I 41-Hexyl-4-phenyl-4-piperidinecarboxylic acid hydrochloride

A mixture of the ethyl ester (22.5 g, 64 mmol) 20% hydrochloric acid (225 ml) and acetic acid (70 ml) was heated under reflux for 30 h. After cooling the mixture was poured into 200 ml of ice water, the acid was filtered and air dried. Yield 12.9 g. The filtrate was evaporated and the residue treated with acetonitrile yielding another 4 g of acid. Recrystallization from acetonitril yielded 16.9 g with m.p. 193-195°C. The acid contains solvent of crystallization.

Example I 51-[4-Ethoxybutyl]-4-phenyl-4-piperidinecarboxylic acid hydrochloride

A mixture of the ethyl ester (17.9 g, 53.7 mmol), 2N NaOH (55 ml) and ethanol (6 ml) was heated under reflux with stirring for 24 h. The solution was extracted with diethyl ether and then acidified with dilute hydrochloric acid. The solvent was evaporated and the residue extracted with acetone. The acetone solution was filtered and the solvent evaporated. The crystalline residue was dried over CaCl_2 in a vacuum desiccator and the recrystallized from THF-ethyl acetate. Yield 11.7 g with m.p. 131-133°C.

Example I 61-(2-Ethoxyethyl)-4-phenyl-4-piperidine-carboxylic acid hydrochloride.

A mixture of the cyanide according to example I 3 (5.6g), KOH(5.6g), ethanol (39 ml) and water (17 ml) was heated in an autoclave at 140° C for 6 hours. The reaction mixture was acidified with concentrated hydrochloric acid, the precipitated salt was filtered and the filtrate evaporated. The residue was leached with hot acetone. From the acetone extracts 4.2 g of the title compound was obtained. n.p. 150-155° C.

COMPOUNDS IIExample 1N-Butyl-1-methyl-4-phenyl-4-piperidinecarboxamide

Pethidine hydrochloride (2.56 g, 9 mmol) and butylamine (5 ml) were heated in an autoclave at 180°C for 3 days. The reaction mixture was shaken between 10 ml of 1N NaOH and diethyl ether and the ether extracts dried (MgSO_4). The solvent was evaporated and the residue chromatographed on aluminium oxide with ethyl acetate as eluent. The crystalline product (1.0 g) was recrystallized from n-hexane yielding 0.59 g with m.p. 73-76.5°C.

This Sheet Has Been Replaced



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REPLACEMENT SHEET

16 OCT 1996

Example 3

N-Ethyl-1-hexyl-4-phenyl-4-piperidinecarboxamide

This compound was prepared as above from ethyl 1-hexyl-4-phenyl-4-piperidinecarboxylate hydrochloride (3.54 g, 10 mmol) and ethylamine (2.25 g, 50 mmol). Reaction time 2 days. The crude product (1.0 g) was recrystallized from diisopropyl ether, yielding 0.81 g with m.p. 92-94°C. Hydrochloride m.p. 221-223°C (from 2% aqueous acetone).

COMPOUNDS IV

General method of preparation. Oxalyl chloride (4 ml) was added dropwise with stirring to a solution of a piperidinecarboxylic acid (compounds III) (5-6 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred at 50°C for 2 h. The solvent was evaporated, a few ml of toluene were added and the solvent was evaporated again. The residue was dissolved in CH_2Cl_2 (10 ml) and the solution was added dropwise with stirring to a solution of the appropriate amine (35-42 mmole) in CH_2Cl_2 (20 ml), cooled in ice-water. The reaction mixture was then stirred at room temperature for a few hours. It was then shaken with 1N NaOH (20 ml), once with water, dried (K_2CO_3) and the solvent evaporated.

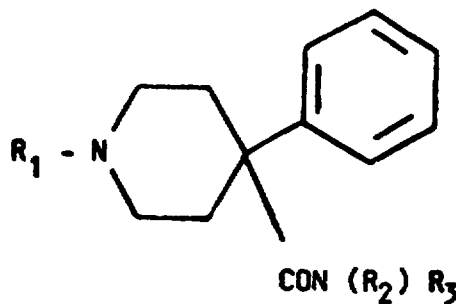
Before conversion to hydrochloride the crude base in several cases was further purified e.g. by chromatography.

In the following Table 1 some compounds according to the invention are given.



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TABLE 1



Comp	R ₁	R ₂	hydrochloride	
			R ₃	m.p °C
1)	CH ₃	H	C ₄ H ₉	73-76.5
2)	C ₆ H ₁₃	H	CH ₃	252-254
3)	C ₆ H ₁₃	H	C ₂ H ₅	221-223
4)	C ₆ H ₁₃	H	CH(CH ₃) ₂	145-148
5)	C ₆ H ₁₃	CH ₃	CH ₃	155.5-158.5
6)	C ₆ H ₁₃	CH ₃	C ₂ H ₅	137-141
7)	C ₆ H ₁₃	C ₂ H ₅	C ₂ H ₅	151-154
8)	C ₆ H ₁₃	(CH ₂) ₅	(CH ₂) ₅	217-219
9)	C ₂ H ₅ O(CH ₂) ₄	CH ₃	CH ₃	125-128
10)	C ₂ H ₅ O(CH ₂) ₄	CH ₃	C ₂ H ₅	115-117
11)	C ₂ H ₅ O(CH ₂) ₄	(CH ₂) ₅	(CH ₂) ₅	130-132
12)	C ₂ H ₅ OCH ₂ -CH ₂	C ₂ H ₅	C ₂ H ₅	142-144
13)	C ₃ H ₇ O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	
14)	C ₄ H ₉ O(CH ₂) ₂	C ₂ H ₅	C ₂ H ₅	



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Pharmaceutical preparations

For the preparation of pharmaceutical preparations the new compound is dissolved in a liquid diluent which is suitable for injection. The preparations used are aqueous solutions which contain between 2.5 and 40.0 mg/ml of the active compound calculated as the hydrochloride salt.

Biological studies

Spinal anaesthesia

The compounds according to the invention were tested for spinal anaesthesia in the mouse. There were six animals in each group. As reference compound pethidine, the starting materials for compounds 2) - 8), namely ethyl 1-hexyl-4-phenyl-4-piperidinecarboxylate hydrochloride (Example I 1) and 9) and 10), namely ethyl 1-[4-ethoxybutyl]-4-phenyl-4-piperidinecarboxylate hydrochloride, (Example I 2) known from the above cited J. Med. Chem. were tested. The results are presented in the following Table 2.

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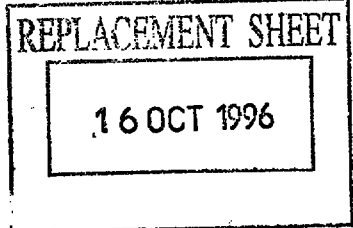
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TABLE 2

Mean duration (min) of motor block and full analgesia (tail-flick) in mice after subarachnoid injection of 5 μ l of the test solution. The durations are calculated from the time of injection.

Compound	Conc. %	Motor bl Duration	Tail-flick min
3	1	10	15
4		14	35
5		14	20
6		20	40
7		27	50
8		19	40
9		3	10
10		6	10
11		6	10
12		3	10
I 1		15	40
I 2		5	25
3	2	22	30
4		24	30
5		21	25
6		36	55
7		48	85
8 ¹		49	>120
9		6	10
10		7	10
11		12	35
12		6	10
I 2		10	15
Pethidine		4	15
1	4	17	20
Pethidine		10	25

¹ The animals were irritated, squeaky



Discussion

As can be seen from Table 2 the compounds according to the invention give a better local anaesthetic effect than the known analgesic pethidine. As the local anaesthetic effect is combined with a good analgesic effect, the compounds according to the invention are more useful than pethidine. They can also replace the combinations of one analgesic and one anaesthetic agent with good result.

The best mode of carrying out the invention known at present is to use the compounds 6 or 7.

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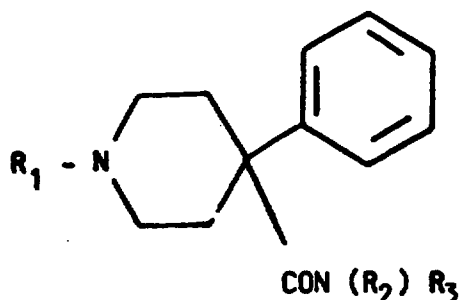


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CLAIMS

1. Compounds of the formula IV

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wherein R₁ is an alkyl group with 2-6 carbon atoms or an alkoxyalkyl group R₄O(CH₂)_m-, wherein R₄ is an alkyl group with 1-4 carbon atoms and m is 2-4, R₂ and R₃ are the same or different and each an alkyl group with up to 6 carbon atoms or R₂ and R₃ form together a chain (CH₂)_n wherein n is 4-6 or one of R₂ and R₃ is hydrogen and the other is a straight or branched alkyl group with 1-6 carbon atoms as well as pharmaceutically acceptable salts thereof.

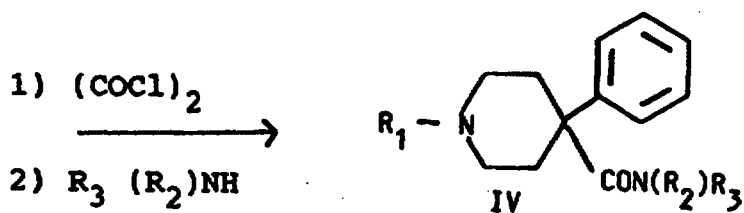
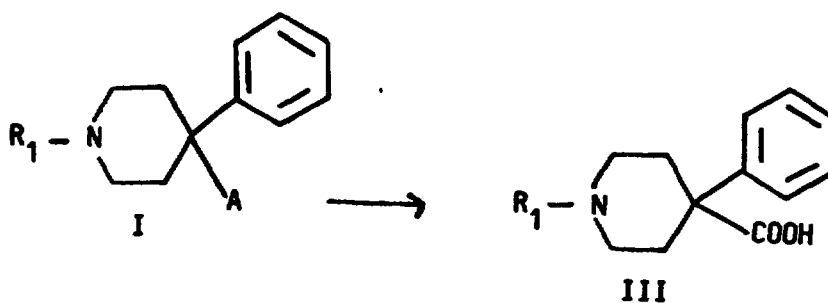
2. A compound according to claim 1, wherein R₁, R₂ and R₃ are alkyl groups.
3. A compound according to claim 2, wherein R₁ is hexyl, R₂ is methyl and R₃ is ethyl.
4. A compound according to claim 2, wherein R₁ is hexyl and R₂ and R₃ are both ethyl.
5. A pharmaceutical preparation for control blockade by epidural or intrathecal route containing a compound according to claim 1.
6. A pharmaceutical preparation for anaesthesia and analgesia containing a compound according to claim 1.



7. Use of a compound according to claim 1 for the manufacture of a pharmaceutical preparation with anaesthetic and analgetic effect.

8. A process for the preparation of a compound of Formula IV according to claim 1 wherein

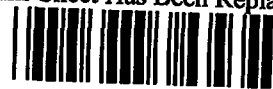
a) an ester or nitrile of the formula I is hydrolyzed to the corresponding acid of the formula III, which then is reacted with 1) oxalyl chloride and 2) the appropriate amine to yield the end product of the formula IV



wherein R_1 , R_2 and R_3 are as defined above in claim 1 and A is $-\text{CN}$ or $-\text{CO}_2\text{C}_2\text{H}_5$; or

b) a compound of the formula I, wherein A is $-\text{CO}_2\text{C}_2\text{H}_5$ is

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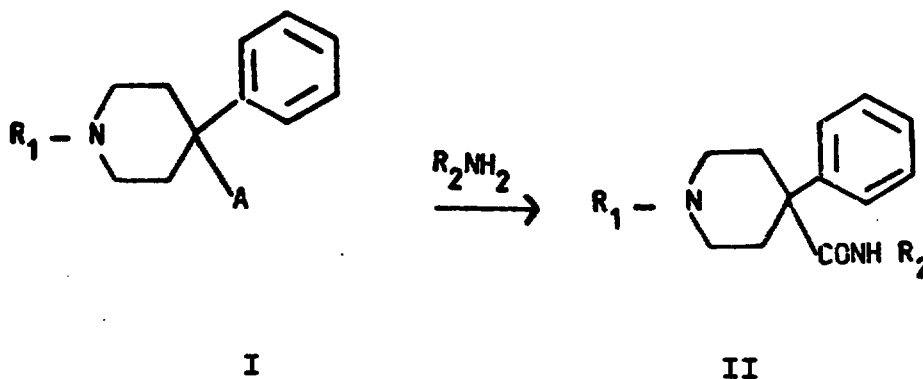


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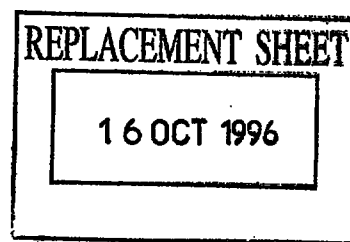


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reacted with an amine R_2NH_2 to yield a compound of the formula II, wherein R_1 and R_2 are as defined above, that is a compound of formula IV, wherein R_2 or R_3 is hydrogen.



9. A method for inducing anaesthesia and analgesia comprising administration to mammals including man needing local anaesthesia and analgesia an effective amount of a compound according to claim 1.

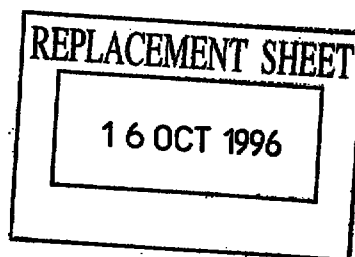
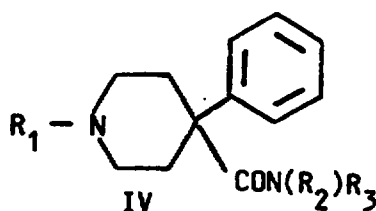




**SUBSTITUTED 4-PHENYL-4-PIPERIDINECARBOXAMIDES WITH BOTH LOCAL
ANAESTHETIC & ANALGESIC EFFECT AS WELL AS PROCESSES
FOR THEIR PREPARATION**

ABSTRACT

Compounds of the formula IV for use as local anaesthetica and analgetica, as well as a method for their preparation, their pharmaceutical preparations and their use.



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☒ Description : paged ...1. to paged ...5.
☒ Claim(s) : paged ...6. to paged ...7.
☐ Drawing(s) : paged ... to paged ...
☒ Abstract : paged ...8. to paged ...8.

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SUBSTITUTED 4-PHENYL-4PIPERIDINECARBOXAMIDES WITH BOTH LOCAL ANAESTHETIC AND ANALGESIC EFFECT AS WELL AS PROCESSES FOR THEIR PREPARATION

Description

Field of the invention

The present invention is directed to new compounds having both local anaesthetic and analgesic effect, a process for their preparation and their use in the manufacture of pharmaceutical preparations.

Background of the invention

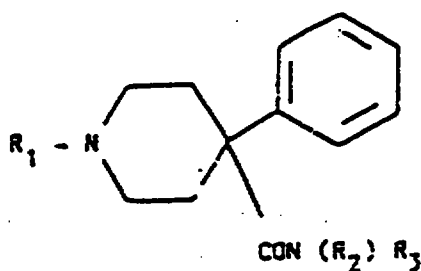
Pethidine is a frequently used analgesic. It has also a weak local anaesthetic effect. The anaesthetic/analgesic effect of pethidine after spinal administration is often insufficient in both respects. Instead combinations of bupivacaine and fentanyl or morphin are being used. The opiate analgesics have several severe draw-backs, as e.g. development of tolerance, addiction, risk for respiratory depression. There is, thus, a need for agents giving a local anaesthesia with a remaining analgesic effect. Such agents should be used after spinal or epidural injections as local anaesthetics intracoperatively. Thereafter the compounds would give good post-operative pain relief.

Prior art

Hardy O.G. et al describe in J. Med. Chem. 8, pp. 847-851 (1965) the structure-activity relationship of some analogues of pethidine, which have an analgesic activity. The Swedish patent 96980 describes 1-methyl-1-phenyl-piperidin-4-carboxylic acid and two amides thereof. No specific pharmaceutical effect is given in the document, only that the compounds can be used in the manufacture of new drugs. From FR 2156470 derivatives of 1-(3,3-diphenyl-propyl)-piperidine are known, which due to their high lipid solubility only can be active as analgetics not as local anaesthetics. In Acta Pol Pharm 1979,36(4), p. 439-4, (Chemical Abstracts 93(1980) 7970v) some amides of 1-butyl-4-phenyl-4-piperidinecarboxylic acid are described.

These amides seem to have analgesic, but not local anaesthetic effect.

Outline of the invention It has been found that compounds of the following formula IV or pharmaceutically acceptable salts thereof not only give an unexpectedly good effect as spinal and epidural anaesthetics but also have an additional analgesic effect that lasts for a long time after the anaesthetic effect has declined. Thus no combination of active compounds need to be given, thus avoiding the risks connected with these mentioned above. The compounds according to the invention are defined by the following formula IV



wherein R_1 is an alkyl group with 2-6 carbon atoms or an alkoxyalkyl group $R_4O-(CH_2)_m-$, wherein R_4 is an alkyl group with 1-4 carbon atoms and m is 2-4, R_2 and R_3 are the same or different and each an alkyl group with up to 6 carbon atoms or R_2 and R_3 form together a chain $(CH_2)_n$ wherein n is 4-6 or one of R_2 and R_3 is hydrogen and a straight or branched alkyl group with 1-6 carbon atoms as well as pharmaceutically acceptable salts thereof.

Preferred compounds according to the invention are those, wherein R_1 , R_2 and R_3 are alkyl groups.

Especially preferred is the compound wherein the group R_1 is hexyl, R_2 is methyl or ethyl and R_3 is ethyl.

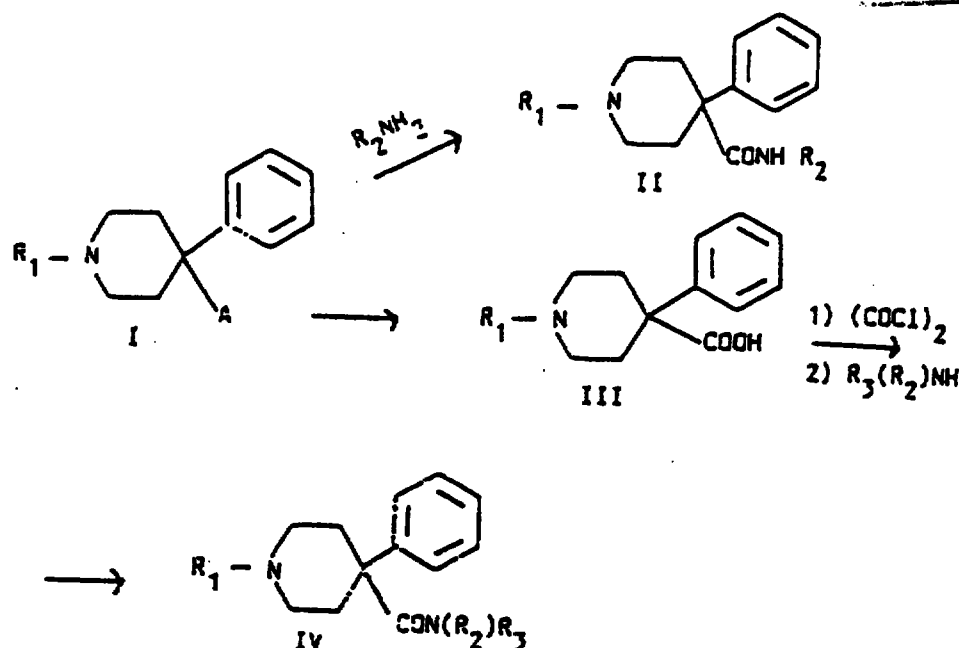
Preferred salts according to the invention are pharmaceutically acceptable salts. The hydrochloride is especially preferred.

Preparation

Compounds of the formula IV above were prepared according to the following:

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wherein A, R_1 , R_2 , and R_3 are as defined above.

The compounds of the formula I wherein A is CN or $-CO_2C_2H_5$ and R_1 is as defined above were prepared from the corresponding secondary amine ($R_1=H$) with the exception of the compound wherein R_1 is CH_3 and A is $CO_2C_2H_5$, which is the commercially available compound pethidine. The compounds of the formula II are prepared directly from I wherein A is $-CO_2C_2H_5$ (c.f. Example 1) by reaction with an alkylamine or are prepared in the same way as the compounds of the formula IV. These are obtained by first hydrolyzing the compounds of the formula I to the carboxylic acids of the formula III, which then are reacted with oxalyl chloride and the appropriate amine to yield a compound of the formula IV.

Detailed description of the preparation

The examples denoted I 1 - I 6 describe intermediates in the preparation of the compounds of the formula IV.

COMPOUNDS I

Example I 1 Ethyl 1-hexyl-4-phenyl-4-piperidine carboxylate hydrochloride

Norpethidine (23.5 g, 0.10 mol), hexyl iodide (23.5 g, 0.11 mol), anhydrous Na_2CO_3 (11.7 g, 0.11 mol) and acetonitrile (250 ml) were heated under reflux and stirring for 1.5 h. The mixture was filtered and the solvent removed. The residue was dissolved in CH_2Cl_2 , the solution washed with 100 ml of 1 N NaOH and then with water and finally dried (K_2CO_3). To the solution HCl (g) in diethyl ether was then added, whereupon the solvents were removed and the residue recrystallized from ethyl acetate. Yield 22.5 g of hydrochloride with m.p. 156-158°C.

M.p. acc. to J. Med. Chem. 8 p. 847-851 (1965), 158°C.

Example I 2

Ethyl 1-[4-ethoxybutyl]-4-phenyl-4-piperidinecarboxylate hydrochloride

Norpethidine (15.63 g, 67 mmol), 4-ethoxybutyl chloride (10.67 g, 70 mmol), Na_2CO_3 (7.77 g, 73 mmol), KI (0.6 g) and acetonitrile (150 ml) were heated under reflux and stirring for 72 h. The mixture was filtered and the solvent removed. The residue was dissolved in diethyl ether, and the solution washed with water and dried ($MgSO_4$). Distillation yielded 17.9 g of base boiling at 180-183°C/0.05 mm Hg. B.p. acc. to J. Chem. Soc. 3062 (1958) 180°C/1 mm Hg.

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Hydrochloride m.p. 143-145°C.

Example 1 3

1-(2-Ethoxyethyl)-4-cyano-4-phenyl-piperidine.

The title compound was prepared as described in Example 1 2 from 4-cyano-4-phenylpiperidine and 2-bromoethyl ethyl ether excluding KI: Reaction time under reflux 6 hours. The compound boiled at 130-135°/0.005 mm Hg.

COMPOUNDS III

Example 1 4

1-Hexyl-4-phenyl-4-piperidinecarboxylic acid hydrochloride

A mixture of the ethyl ester (22.5 g, 64 mmol) 20% hydrochloric acid (225 ml) and acetic acid (70 ml) was heated under reflux for 30 h. After cooling the mixture was poured into 200 ml of ice water, the acid was filtered and air dried. Yield 12.9 g. The filtrate was evaporated and the residue treated with acetonitrile yielding another 4 g of acid. Recrystallization from acetonitrile yielded 16.9 g with m.p. 193-195°C. The acid contains solvent of crystallization.

Example 1 5

1-(4-Ethoxybutyl)-4-phenyl-4-piperidinecarboxylic acid hydrochloride

A mixture of the ethyl ester (17.9 g, 53.7 mmol), 2N NaOH (55 ml) and ethanol (6 ml) was heated under reflux with stirring for 24 h. The solution was extracted with diethyl ether and then acidified with dilute hydrochloric acid. The solvent was evaporated and the residue extracted with acetone. The acetone solution was filtered and the solvent evaporated. The crystalline residue was dried over CaCl_2 in a vacuum desiccator and the recrystallized from THF-ethyl acetate. Yield 11.7 g with m.p. 131-133°C.

Example 1 6

1-(2-Ethoxyethyl)-4-phenyl-4-piperidine-carboxylic acid hydrochloride.

A mixture of the cyanide according to example 1 3 (5.6g), KOH(5.6g), ethanol (39 ml) and water (17 ml) was heated in an autoclave at 140° C for 6 hours. The reaction mixture was acidified with concentrated hydrochloric acid, the precipitated salt was filtered and the filtrate evaporated. The residue was leached with hot acetone. From the acetone extracts 4.2 g of the title compound was obtained, n.p. 150-155° C.

COMPOUNDS II

Example 1

N-Butyl-1-methyl-4-phenyl-4-piperidinecarboxamide

Pethidine hydrochloride (2.56 g, 9 mmol) and butylamine (5 ml) were heated in an autoclave at 180°C for 3 days. The reaction mixture was shaken between 10 ml of 1N NaOH and diethyl ether and the ether extracts dried (MgSO_4). The solvent was evaporated and the residue chromatographed on aluminium oxide with ethyl acetate as eluent. The crystalline product (1.0 g) was recrystallized from n-hexane yielding 0.59 g with m.p. 73-76.5°C.

Example 3

N-Ethyl-1-hexyl-4-phenyl-4-piperidinecarboxamide

This compound was prepared as above from ethyl 1-hexyl-4-phenyl-4-piperidinecarboxylate hydrochloride (3.54 g, 10 mmol) and ethylamine (2.25 g, 50 mmol). Reaction time 2 days. The crude product (1.0 g) was recrystallized from diisopropyl ether, yielding 0.81 g with m.p. 92-94°C. Hydrochloride m.p. 221-223°C (from 2% aqueous acetone).

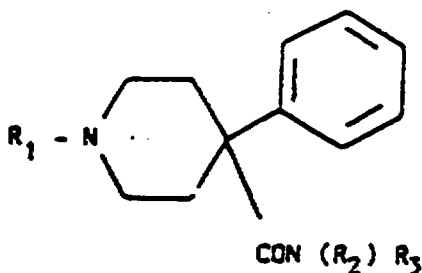
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COMPOUNDS IV

General method of preparation. Oxalyl chloride (4 ml) was added dropwise with stirring to a solution of a piperid inecarboxylic acid (compounds III) (5-6 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred at 50°C for 2 h. The solvent was evaporated, a few ml of toluene were added and the solvent was evaporated again. The residue was dissolved in CH_2Cl_2 (10 ml) and the solution was added dropwise with stirring to a solution of the appropriate amine (35-42 mmole) in CH_2Cl_2 (20 ml), cooled in ice-water. The reaction mixture was then stirred at room temperature for a few hours. It was then shaken with 1N NaOH (20 ml), once with water, dried (K_2CO_3) and the solvent evaporated.

Before conversion to hydrochloride the crude base in several cases was further purified e.g. by chromatography. In the following Table 1 some compounds according to the invention are given.

TABLE 1

Comp	R_1	R_2	hydrochloride	
			R_3	m.p. $^\circ\text{C}$
1)	CH_3	H	C_4H_9	73-76.5
2)	C_6H_{13}	H	CH_3	252-254
3)	C_6H_{13}	H	C_2H_5	221-223
4)	C_6H_{13}	H	$\text{CH}(\text{CH}_3)_2$	145-148
5)	C_6H_{13}	CH_3	CH_3	155.5-158.5
6)	C_6H_{13}	CH_3	C_2H_5	137-141
7)	C_6H_{13}	C_2H_5	C_2H_5	151-154
8)	C_6H_{13}	$(\text{CH}_2)_5$	$(\text{CH}_2)_5$	217-219
9)	$\text{C}_2\text{H}_5\text{O}(\text{CH}_2)_4$	CH_3	CH_3	125-128
10)	$\text{C}_2\text{H}_5\text{O}(\text{CH}_2)_4$	CH_3	C_2H_5	115-117
11)	$\text{C}_2\text{H}_5\text{O}(\text{CH}_2)_4$	$(\text{CH}_2)_5$	$(\text{CH}_2)_5$	130-132
12)	$\text{C}_2\text{H}_5\text{OCH}_2\text{-CH}_2$	C_2H_5	C_2H_5	142-144
13)	$\text{C}_3\text{H}_7\text{O}(\text{CH}_2)_2$	C_2H_5	C_2H_5	
14)	$\text{C}_4\text{H}_9\text{O}(\text{CH}_2)_2$	C_2H_5	C_2H_5	

Pharmaceutical preparations

For the preparation of pharmaceutical preparations the new compound is dissolved in a liquid diluent which is

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suitable for injection. The preparations used are aqueous solutions which contain between 2.5 and 40.0 mg/ml of the active compound calculated as the hydrochloride salt.

Biological studies

Spinal anaesthesia

The compounds according to the invention were tested for spinal anaesthesia in the mouse. There were six animals in each group. As reference compound pethidine, the starting materials for compounds 2) - 8), namely ethyl 1-hexyl-4-phenyl-4-piperidinecarboxylate hydrochloride (Example 1) and 9) and 10), namely ethyl 1-(4-ethoxybutyl)-4-phenyl-4-piperidinecarboxylate hydrochloride, (Example 1 2) known from the above cited J. Med. Chem. were tested. The results are presented in the following Table 2.

TABLE 2

Mean duration (min) of motor block and full analgesia (tail-flick) in mice after subarachnoid injection of 5 µl of the test solution. The durations are calculated from the time of injection.			
Compound	Conc. %	Motor bl Duration	Tail-flick min
3	1	10	15
4		14	35
5		14	20
6		20	40
7		27	50
8		19	40
9		3	10
10		6	10
11		6	10
12		3	10
11		15	40
12		5	25
3	2	22	30
4		24	30
5		21	25
6		36	55
7		48	85
8 ¹		49	>120
9		6	10
10		7	10
11		12	35
12		6	10
12		10	15
Pethidine		4	15
1 ¹	4	17	20
Pethidine		10	25

¹ The animals were intubated, apnoeic

Discussion

As can be seen from Table 2 the compounds according to the invention give a better local anaesthetic effect than the known analgesic pethidine. As the local anaesthetic effect is combined with a good analgesic effect, the compounds according to the invention are more useful than pethidine. They can also replace the combinations of one analgesic and one anaesthetic agent with good result.

The best mode of carrying out the invention known at present is to use the compounds 6 or 7.



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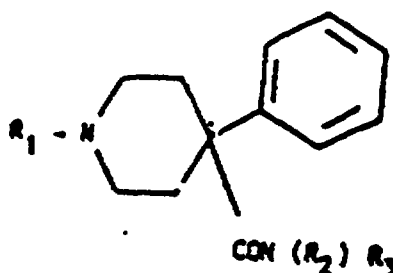
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Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. A compound of the formula IV



wherein

R_1 is an alkyl group with 2-6 carbon atoms or an alkoxyalkyl group $R_4O(CH_2)_m$, wherein R_4 is an alkyl group with 1-4 carbon atoms and m is 2-4;

R_2 and R_3 are the same or different and each an alkyl group with up to 6 carbon atoms, or R_2 and R_3 form together a chain $(CH_2)_n$, wherein n is 4-6 or one of R_2 and R_3 is hydrogen and the other is a straight or branched alkyl group with 1-6 carbon atoms;

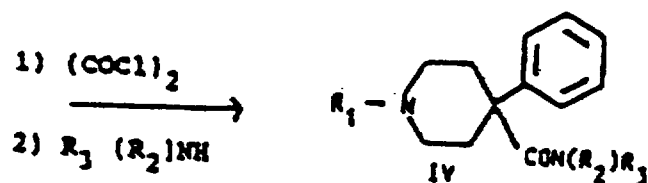
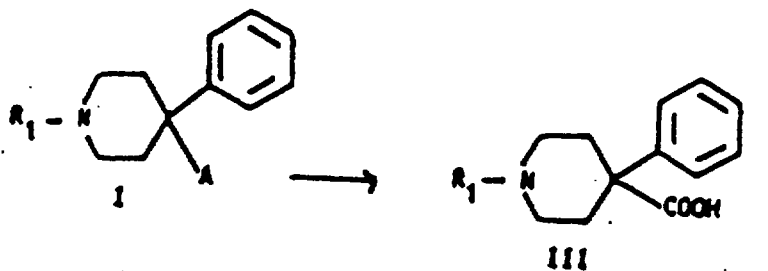
as well as pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R_1 , R_2 and R_3 are alkyl groups.
3. A compound according to claim 2, wherein R_1 is hexyl, R_2 is methyl and R_3 is ethyl.
4. A compound according to claim 2, wherein R_1 is hexyl and R_2 and R_3 are both ethyl.
5. A compound according to claim 1 for use in therapy.
6. Use of a compound according to claim 1 for the manufacture of a pharmaceutical preparation with anaesthetic and analgetic effect.
7. A pharmaceutical preparation comprising a compound according to claim 1 as active ingredient, together with a liquid diluent suitable for injection.
8. A pharmaceutical preparation according to claim 7, for use in inducing anaesthesia and analgesia.
9. A pharmaceutical preparation according to claim 7, in form for administration epidurally or intrathecally.
10. A process for the preparation of a compound of formula IV according to claim 1 wherein
 - a) an ester or nitrile of the formula I is hydrolyzed to the corresponding acid of the formula III, which then is reacted with 1) oxalyl chloride and 2) the appropriate amine to yield the end product of the formula IV

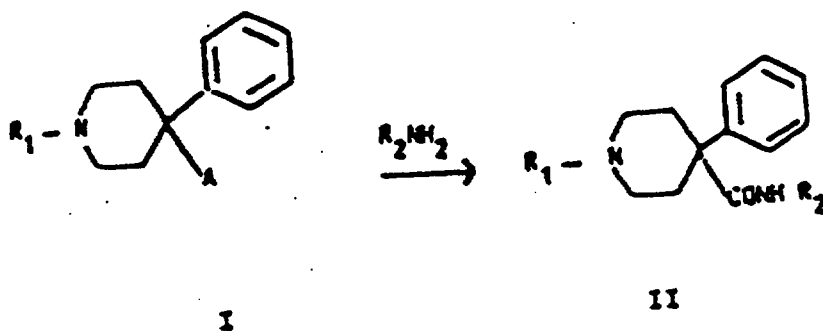
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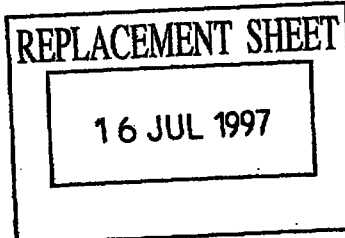


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wherein R_1 , R_2 and R_3 are as defined above in claim 1 and A is $-CN$ or $-CO_2C_2H_5$; or
b) a compound of the formula I, wherein A is $-CO_2C_2H_5$ is reacted with an amine R_2NH_2 to yield a compound of the formula II, wherein R_1 and R_2 are as defined above, that is a compound of the formula IV, wherein R_2 or R_3 is hydrogen.





SUBSTITUTED 4-PHENYL-4-PIPERIDINECARBOXAMIDES WITH BOTH LOCAL
ANAESTHETIC & ANALGESIC EFFECT AS WELL AS PROCESSES
FOR THEIR PREPARATION

ABSTRACT

Compounds of the formula IV for use as local anaesthetica and analgetica, as well as a method for their preparation, their pharmaceutical preparations and their use.

