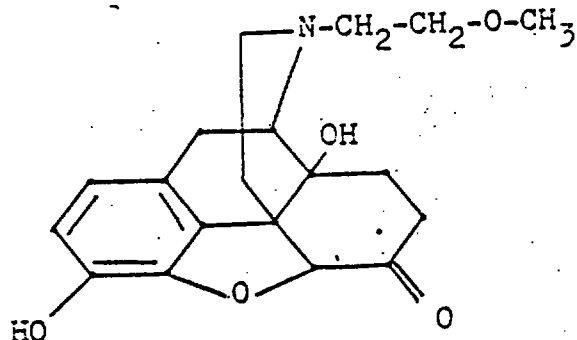


N-(2-Methoxyethyl)-noroxymorphone

The invention relates to N-(2-methoxyethyl)-noroxymorphone and its acid addition salts, to processes for its preparation, and to pharmaceutical preparations containing it. The compounds have been found to have a therapeutic effect on the central nervous system, and may be used as non-addictive analgesics.

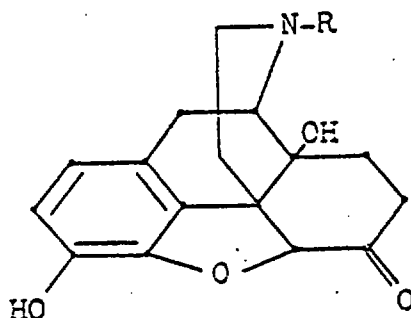
The present invention relates in one aspect to compounds of general formula (I)



I

10 and acid addition salts thereof.

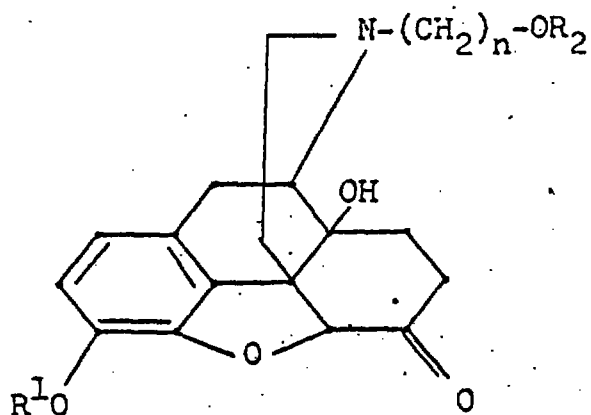
The compound of formula I has some similarities with the known compounds of formula



II

- IIa : -R = -CH₃ (oxymorphone known from US-PS 2 806 033)
 15 IIb : -R = -CH₂-CH=CH₂ (naloxone known from US-PS 3 254 088)
 IIc : -R = -CH₂- (naltrexone known from US-PS 3 332 950)

and some new compounds of formula III which we have prepared for comparison purposes:

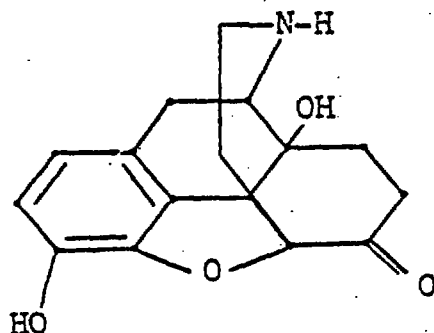


III

- IIIa : $-R^1 = -H$; $-R^2 = -C_2H_5$; $n = 2$
 5 IIIb : $-R^1 = -CH_3$; $-R^2 = -CH_3$; $n = 2$
 IIIc : $-R^1 = -CH_3$; $-R^2 = -C_2H_5$; $n = 2$
 IIId : $-R^1 = -H$; $-R^2 = CH_3$; $n = 3$

According to a further aspect of the invention we also provide a process for the preparation of a compound of formula I which comprises either

- 10 a) reacting a noroxymorphone of formula (IV)

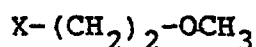


IV

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- 3 -

with a 2-methoxyethyl halide of formula (V)

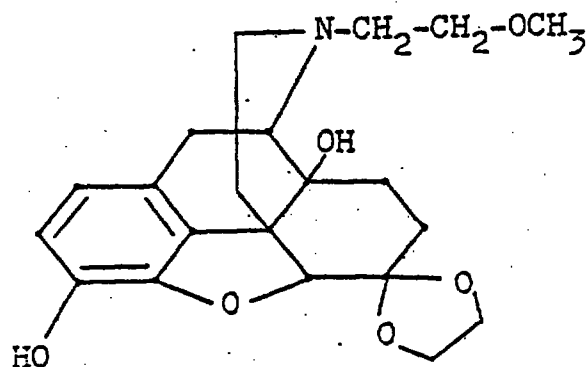


V

wherein X represents a chlorine, bromine or iodine atom,

5 or

b) Ketal splitting an N-(2-methoxyethyl)-noroxymorphone ethylene ketal of formula (VI)



VI

10 with a dilute acid, followed if desired by converting the base of formula I obtained into an acid addition salt.

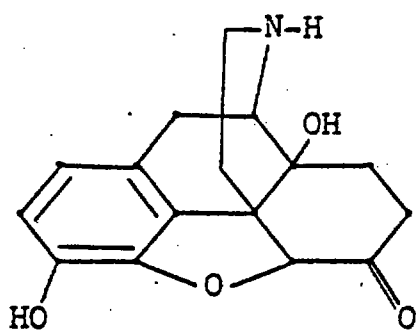
In reaction (a), the noroxymorphone of formula IV may conveniently be obtained from thebaine in sterically uniform form.

15 Either the stoichiometric amount or a slight excess of the alkylating agent of general formula V may be used in the alkylation and the reaction is conveniently effected in the presence of an acid-binding substance such as triethylamine, dicyclohexylethyl-
20 amine, sodium carbonate, potassium carbonate, calcium oxide or, preferably, sodium hydrogen carbonate. It is advantageous to carry out the reaction in an inert solvent, e.g. in chloroform, methylene chloride, benzene, acetone, dioxan, tetrahydrofuran or dimethyl-

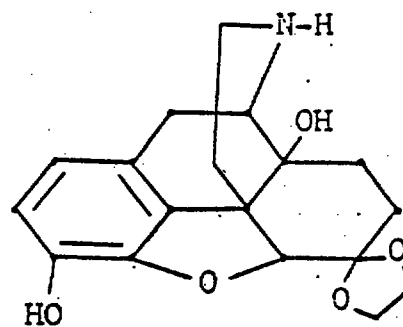
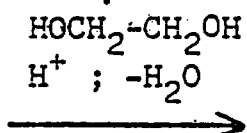
- formamide. It is also convenient to use mixtures of dimethylformamide and tetrahydrofuran. The reaction temperature may vary within wide limits. The temperatures used are preferably between ambient temperature and
- 5 the boiling point of the solvent used. After the reaction, the reaction products may be isolated, purified and crystallised using known methods and optionally converted into suitable acid addition compounds.
- 10 The starting compound of formula VI required for process (b) may be obtained from noroxymorphone by ketalising with glycol in the presence of acid, acylating the ketal of formula VII with methoxyacetic acid chloride to form the acyl derivative of formula
- 15 VIII and subsequently reducing with the acyl derivative lithium aluminium hydride according to the following reaction scheme:

15

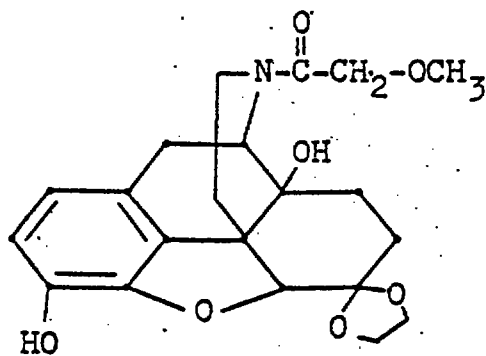
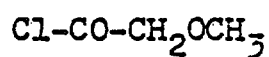
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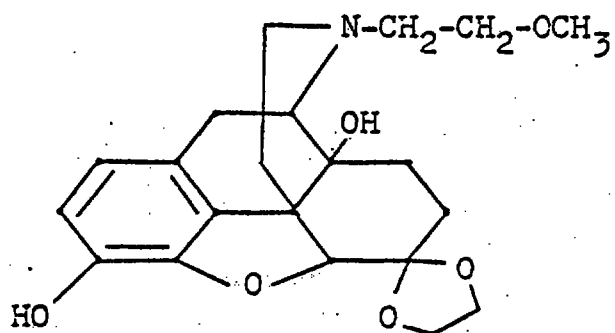
IV



VII



VIII



VI

The compound of formula I according to the invention is a base and may be converted into physiologically acceptable acid addition salts thereof in conventional manner. Acids suitable for salt formation include, for example, hydrochloric, hydrobromic, hydriodic, hydrofluoric, sulphuric, phosphoric, nitric, acetic, propionic, butyric, valeric, pivalic, caproic, oxalic, malonic, succinic, maleic, fumaric, lactic, tartaric, citric, malic, benzoic, phthalic, cinnamic, salicylic and ascorbic acid, 8-chlorotheophylline, methanesulphonic and ethanephosphonic acid.

The compound of formula I and the acid addition salts thereof have been found to have a therapeutically useful effect on the central nervous system and can be used as non-addictive analgesics, i.e. pain-relieving agents.

The compound of formula I is an opiate-like agonist-antagonist with a non-morphine-like activity profile not found in other substances. Some pharmacological data which serve to illustrate this and show why it is preferred over related substances are discussed hereinafter.

The strong analgesic component can be demonstrated in the writhing test. In this test, the compound of formula I, having an ED_{50} of 0.013 mg/kg s.c., is about 36 times stronger than morphine, which has an ED_{50} of 0.47 mg/kg s.c., or about 2.5 times stronger than the structurally related analgesic oxymorphone of formula IIa (ED_{50} = 0.032 mg/kg s.c.).

The non-morphine-like activity profile can be recognised from the absence of typical side effects produced by opiates. In contrast to the comparison substances mentioned above, namely morphine and oxymorphone and other opiates, the hydrochloride of the compound of formula I does not show, for example, either the Straub morphine tail phenomenon or so-called compulsive circular motion. The difference between the hydrochloride of compound I and the opiates, which have a high

potential for misuse, can also be seen in the fact that the substance is not capable of relieving the withdrawal symptoms occurring in morphine-dependent monkeys after the morphine has been withdrawn. In this experiment, the hydrochloride of the compound of formula I behaves rather as an antagonist, in that it aggravates the withdrawal symptoms.

The morphine-antagonistic component can be demonstrated in the Haffner test by the reversal of the analgesia produced by morphine. The compound of formula I, having an AD_{50} of 0.3 mg/kg s.c., has about 1/10 of the antagonistic activity of the structurally related comparison substance naloxone of formula IIb (AD_{50} = 0.03 mg/kg s.c.). In morphine-dependent monkeys, there is found to be increased sensitivity to morphine antagonists which trigger withdrawal symptoms, depending on dosage. In this experiment, the compound of formula I is as strong as naloxone. Unlike the compound of formula I, naloxone and the second substance naltrexone of formula IIc have no analgesic activity but are so-called "pure antagonists".

One particular advantage of the compound according to the invention over other opiate-type analgesics, agonists and agonist-antagonists is its unusually high therapeutic range, which is 103,846 with an LD_{50} of 1350 mg/kg s.c. in mice, based on the effect in the writhing test. The comparison values are 1600 for the standard analgesic morphine and 169 for the agonist-antagonist pentazocine which is used therapeutically as an analgesic.

Another advantage of the compound of formula I over newer substances, not yet used therapeutically, selected from the opiate-type kappa agonists of the benzomorphan series, to which a high therapeutic range is also ascribed (e.g. 1800 for ethylketazocine), is the absence of any strong sedative property. This can be recognised in the comparison substances as an inhibition of locomotion in mice in or near

the therapeutic dosage range. In the compound according to the invention, however, this effect was not observed in the range tested up to very high doses of 100 mg/kg.

The independent opiate-type activity profile
5 of the compound of formula I according to the invention is obtained from studies on test organs, such as the vas deferens of the mouse and the guinea pig ileum and receptor preparations.

Modification of the structure of formula I
10 has resulted in substances with less favourable properties. The corresponding N-(2-ethoxyethyl) compound of formula IIIa, for example, has only 1/20, whilst the N-(3-methoxypropyl) compound of formula IIIc has only 1/25 of the activity of the compound of formula I
15 according to the invention. Moreover, compound IIIc is similar to morphine in its effects. Etherification of the phenolic hydroxy group to yield the structures of formulae IIId and IIIf reduces the activity, e.g. to 1/84 in the case of the compound of formula IIId.

20 According to another aspect of the invention we provide a pharmaceutical composition comprising as active ingredient the compound of formula I or an acid addition salt thereof, together with a pharmaceutical carrier, diluent or excipient.

25 The compounds of the invention may be used for pain relief, and may be administered by enteral or parenteral or rectal route. The dosage for administration is suitably between 0.5 and 100 mg, of active substance preferably between 1 and 20 mg. The compound
30 of formula I and the acid addition salts thereof may also be combined with other pain-relieving agents or with active substances of other kinds such as sedatives, tranquillizers and hypnotics. Suitable forms for administration include, for example, tablets,
35 capsules, suppositories, solutions, suspensions, powders or emulsions; these may be prepared using the excipients and carriers or disintegrants or lubricants or substances for obtaining delayed release which

are conventionally used. These preparations may be made in the usual way using known methods of production.

The tablets may consist of several layers. Similarly, coated tablets may be prepared by taking
5 cores produced analogously to the tablets and coating them with agents conventionally used for coating tablets, such as polyvinylpyrrolidone or shellac, gum arabic, talc, titanium dioxide or sugar.

In order to obtain delayed release or avoid
10 incompatibilities, the core may also consist of several layers. Similarly, the tablet coating may also be made up of several layers in order to obtain delayed release, and the excipients mentioned above for the tablets may be used.

15 Syrups of the active substance or combinations of active substances according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerine or sugar and a flavour-improving agent, e.g. a flavouring such as vanillin or orange
20 extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as condensation products of fatty alcohols with ethylene oxide or preservatives such as p-hydroxybenzoates.

25 Solutions for injection may be prepared in a conventional manner e.g. by adding preservatives such as p-hydroxybenzoates or stabilisers such as complexones and then sealed in injection vials or ampoules.

30 Capsules containing the active substances or combinations of active substances may, for example, be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and encapsulating them in gelatine capsules.

35 Suitable suppositories may be prepared, for example, by mixing the active substances or combinations of active substances intended for this purpose with

conventional carriers such as neutral fats or polyethylene glycol or the derivatives thereof.

The following Examples illustrate the invention without restricting the scope of protection sought
5 therefor.

(21)

- 11 -

Example 1

N-(2-Methoxyethyl)-noroxymorphone (process a)

3.24 g (0.01 mol) of noroxymorphone hydrochloride,
2.6 g (0.03 mol) of sodium bicarbonate and 1.52 g
5 (0.011 mol) of 2-methoxyethylbromide are stirred
vigorously in 35 ml of dimethylformamide for 24 hours
at 60°C. The mixture is then concentrated by evaporation
in vacuo and the residue is shaken with 45 ml of
methylene chloride, 5 ml of isopropanol and 20 ml
10 of water. The organic phase is washed three times,
each time with 20 ml of water, then dried with sodium
sulphate and concentrated by evaporation in vacuo.
The crude product (3.3 g) is purified by chromatography
on silica gel, using methanol/chloroform/conc. ammonia
15 (90:10:0.5) as eluent. The fractions containing
the pure substance are concentrated by evaporation.
The residue (2.7 g) crystallises when treated with
20 ml of diethyl ether. The crystal suspension is
kept overnight in the refrigerator, then suction
20 filtered, washed with a little ether and dried at
70°C. 1.7 g (49.3%) of N-(methoxyethyl)-noroxymorphone
are obtained, melting point 164-168°C. After recrystal-
lisation from methanol/water (2:1) the substance
melts at 170-173°C.

25

Example 2

N-(2-Methoxyethyl)-noroxymorphone (Process b)

a) N-Methoxyacetyl-noroxymorphone-ethyleneketal

A solution of 47.8 g (0.44 mol) of methoxyacetyl-
30 chloride in 331 ml of absolute methylene chloride
is added dropwise to a vigorously stirred solution/sus-
pension of 66.2 g (0.2 mol) of noroxymorphone-ethylene
ketal in 662 ml of absolute methylene chloride and
80 ml of triethylamine, at a reaction temperature
35 of 10°C, within about 2 hours, whilst the mixture
is cooled with ice. A clear solution is obtained
which is refluxed for 1 hour. After it has cooled,

the methylene chloride solution is washed three times with water, dried with sodium sulphate and concentrated by evaporation in the rotary evaporator, finally in vacuo. The residue is taken up in 100 ml of toluene and the solution is evaporated again. The crystalline residue (91.2 g) consists of N-methoxyacetyl-noroxymorphone-ethylene ketal, which is further reacted without intermediate purification.

b) N-(2-Methoxyethyl)-noroxymorphone ethylene ketal

10 The evaporation residue described above is dissolved in 1400 ml of absolute tetrahydrofuran, with heating. After cooling to 25-30°C, the solution is added dropwise, within 4 hours, to a vigorously stirred suspension of 24.0 g (0.63 mol) of lithium
15 aluminium hydride in 600 ml of absolute tetrahydrofuran. The reaction mixture is cooled to ensure that the reaction temperature does not rise above 30 to 35°C. Then the reaction mixture is refluxed for 2 hours. It is then cooled and 300 ml of water are added dropwise,
20 at 0 to 5°C, with cooling and with vigorous stirring. After 2.6 litres of saturated diammonium tartrate solution have been added, the mixture is stirred for 2 hours. Then the (lighter) tetrahydrofuran solution is separated off and concentrated by evaporation
25 in vacuo. The aqueous solution is extracted twice, each time with 400 ml of methylene chloride. The evaporation residue of the tetrahydrofuran phase is dissolved with the methylene chloride extracts, the solution is washed twice, each time with 400 ml
30 of water, then dried with sodium sulphate and concentrated by evaporation in vacuo. The residue (69 g) consists of the ethylene ketal of N-(2-methoxyethyl)-noroxymorphone which is subjected to the following ketal splitting without purification.

22

- 13 -

c) N-(2-methoxyethyl)-noroxymorphone hydrochloride

For the ketal splitting, the above residue is refluxed for 1 hour with a mixture of 70 ml of water and 40 ml of conc. HCl. The clear brown solution is cooled and mixed with 800 ml of acetone. N-(2-methoxyethyl)-noroxymorphone hydrochloride crystallises out. After it has been left to stand overnight in the refrigerator, it is suction filtered, washed with acetone and dried at 60°C. 74.0 g (70.7%) of N-(2-methoxyethyl)-noroxymorphone hydrochloride are obtained, melting point 205°C. After recrystallisation from 167 ml of water (in which it is dissolved at boiling temperature) and 1.4 litres of acetone (added after the aqueous solution has cooled to 50°C), 62.0 g of pure substance are obtained with a melting point of 265 to 267°C. The analytically pure substance obtained by further recrystallisation from methanol melts at 269 to 270°C.

20 Examples of formulations

Example A: Tablets

Active substance according to the invention	20.0 mg
Lactose	120.0 mg
25 Corn starch	50.0 mg
Colloidal silicic acid	2.0 mg
Soluble starch	5.0 mg
Magnesium stearate	<u>3.0 mg</u>
	200.0 mg

30 The active substance is mixed with some of the excipients and granulated with a solution of the soluble starch in water. After the granulate had dried, the remaining excipients are added and the mixture is compressed to form tablets.

Example B: Coated tablets

	Active substance according to the invention	15.0 mg
	Lactose	100.0 mg
5	Corn starch	95.0 mg
	Colloidal silicic acid	2.0 mg
	Soluble starch	5.0 mg
	Magnesium stearate	<u>3.0 mg</u>
		220.0 mg

- 10 The active substance and excipients are compressed to form tablet cores as described in Example A and these cores are coated with sugar, talc and gum arabic in the usual way.

15 Example C: Suppositories

	Active substance according to the invention	10.0 mg
	Lactose	150.0 mg
	Suppository mass q.s. ad	1.7 g

- 20 The active substance and lactose are mixed together and the mixture is uniformly suspended in the molten suppository mass. The suspensions are poured into chilled moulds to form suppositories weighing 1.7 g.

25

Example D: Ampoules

	Active substance according to the invention	1.0 mg
	Sodium chloride	10.0 mg
30	Doubly distilled water q.s. ad	1.0 ml

The active substance and sodium chloride are dissolved in doubly distilled water and the solution is transferred under sterile conditions into ampoules.

Example E: Drops

Active substance according to the invention	0.70 g
methyl p-hydroxybenzoate	0.07 g
5 propyl p-hydroxybenzoate	0.03 g
Demineralised water q.s. ad	100.00 ml

The active substance and preservatives are dissolved in demineralised water and the solution is filtered and transferred into vials each containing 10 100 ml.



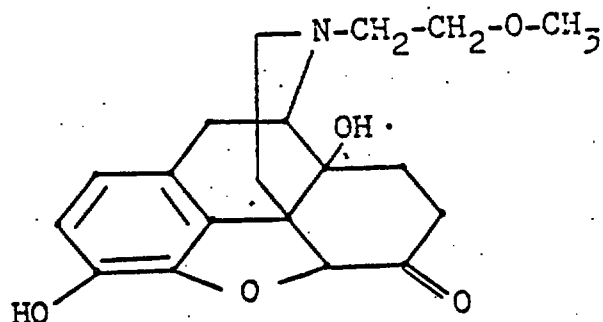
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Claims

1. N-(2-Methoxyethyl)-noroxymorphone of formula (I)

5



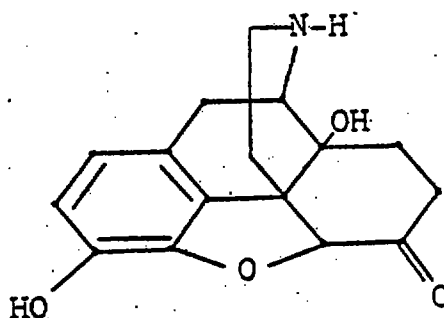
I

and the acid addition salts thereof.

2. A process for the preparation of a compound as claimed in claim 1, which comprises either

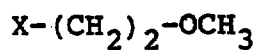
a) reacting a noroxymorphone of formula (IV)

10



IV

with a 2-methoxyethyl halide of formula (V)



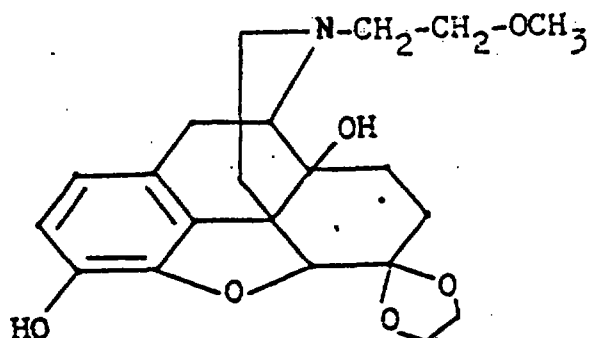
V



wherein X represents a chlorine, bromine or iodine atom,

or

- b) ketal splitting an N-(2-methoxyethyl)-noroxymorphone
5 ethylene ketal of formula (VI)



VI

with a dilute acid, followed if desired by converting the base of formula I obtained into an acid addition salt.

- 10 3. A process as claimed in claim 2 (a) wherein the reaction is carried out in the presence of an acid binding agent and in an inert solvent at a temperature between ambient temperature and the boiling point of the solvent.
- 15 4. A process for the preparation of N-(2-methoxyethyl)-noroxymorphone or an acid addition salt thereof substantially as hereinbefore described with reference to the Examples.
- 20 5. N-(2-Methoxyethyl)-noroxymorphone or an acid addition salt thereof whenever prepared by a process as claimed in any of claims 2, 3 or 4.
- 25 6. A pharmaceutical composition comprising a compound of formula I as claimed in either claim 1 or claim 5 in association with a pharmaceutical excipient, carrier or diluent.
7. A compound of formula I as defined in claim 1 or an acid addition salt thereof for use in the relief of pain.