Taj Pharmaceuticals Ltd.

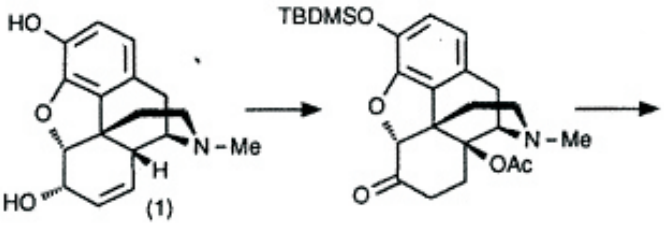
Noroxymorphone

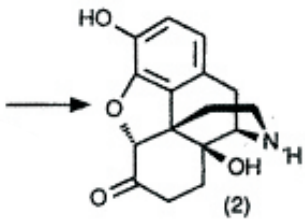
CAS No. : 33522-95-1

Synonyms

Morphinan-6-one, 4,5-epoxy-314 dihydroxy (5alpha); Noroxymorphone ARS-(FOR R&D USE ONLY); Noroxymorphone Hydrochloride ARS-(FOR R&D USE ONLY)

CAS No.: 33522-95-1
Molecular Weight: 287.30
Chemical Formula: C16H17N04





A brief synthesis of noroxymorphone (2) from morphine (1) is described. Overall yield 40-45% on 10g scale.

A brief synthesis of noroxymorphone is described which involves the oxidation of 3-O-tbutyldimethy lsilylmorphine by manganese dioxide. The initial product is the corresponding morphinone which is further oxidised to the 14-hydroxymorphinone. After hydrogenation the 7,8-dihydro-14-hydroxymorphinone is acetylated and N-demethylation of the 14-O-acetylated product is achieved using vinyl chloroformate as the reagent. The overall yield from morphine is 40–45%.

FIELD OF THE INVENTION

This invention relates to N-(2-methoxyethyl)-noroxymorphone. More particularly, this invention relates to N-(2-methoxyethyl)-noroxymorphone and pharmacologically acceptable acid addition salts thereof, the preparation thereof, and pharmaceutical compositions containing same.

DETAILED DESCRIPTION OF THE INVENTION

Applicants' invention relates to N-(2-methoxyethyl)- noroxymorphone of the formula ##STR1## and pharmacologically acceptable acid addition salts thereof with inorganic or organic acids, pharmaceutical compositions containing them, and procedures for the preparation thereof. The compound of Formula I and said acid addition salts thereof (hereinafter referred to as "the compounds of formula I") are useful as analgesics.

N-Substituted noroxymorphone compounds are known. For example, compounds of the formula ##STR2## wherein R represents (IIa) CH 3 , (IIb) CH 2 --CH□CH 2 , or (IIc) CH 2 --□are disclosed in U.S. Pat. Nos. 2,806,033, 3,254,088, and 3,332,950, respectively. These compounds are known as oxymorphone, naloxone, and naltrexone, respectively. The novel compounds of the formula ##STR3## wherein (IIIa) R 1 =H, R 2 =C 2 H 5 , and n=2; (IIIb) R 1 =CH 3 , R 2 =CH 3 , and n=2; (IIIc) R 1 =CH 3 , R 2 =C 2 H 5 , and n=2; and (IIId) R 1 =H, R 2 =CH 3 , and n=3, were prepared for comparison pruposes.

The compounds of Formula I may be prepared as follows:

Method A

Noroxymorphone of the formula ##STR4## is alkylated with 2-methoxyethyl-halide of the formula X--(CH 2) 2 --OCH 3 (V)

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wherein X represents a chlorine, bromine, or iodine atom. Either the calculated quantity or a slight excess of the alkylation agent of Formula V is used, and the work is preferably done in the presence of acid-binding substances such as triethylamine, dicyclohexylethylamine, sodium carbonate, potassium carbonate, calcium oxide, or, especially, sodium bicarbonate. It is advantageous to carry out the reaction in an inert solvent, such as, chloroform, methylene chloride, benzene, acetone, dioxane, tetrahydrofuran, or dimethylformamide. It is preferred to use mixtures of dimethylformamide and tetrahydrofuran.

The reaction temperature may vary within wide limits. The temperatures used are preferably between ambient temperature and the boiling point of the solvent used. After the reaction, the reaction products are isolated, purified, and crystallized using known methods and optionally converted into suitable acid addition compounds.

Method B

A compound of the formula ##STR5## is reacted with dilute acid to provide ketal splitting.

The noroxymorphone of Formula IV is normally obtained from thebaine in sterically uniform form. The starting compound of Formula VI required for Method B can be obtained from noroxymorphone by ketalization with glycol in the presence of acid, acylation of the ketal of Formula VII with methoxyacetic acid chloride to form the acyl derivative of Formula VIII, and subsequent reduction with lithium aluminium hydride according to the following reaction scheme: ##STR6##

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

The compounds of Formula I 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 opioid agonist-antagonist with a non-morphine-like activity profile not found in other substances. Some pharmacological data which serve to distinguish it over related substances are discussed below.

The strong analgesic property 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 closely related analgesic oxymorphone of Formula IIa (ED 50 =0.032 mg/kg s. c.).

The non-morphine-like activity profile can be recognized from the absence of typical side effects produced by opiates. In contrast to the comparison substances mentioned above, namely, morphone, 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 the compound of Formula I and the opiates, which have a high potential for misuse, can also be seen in that the substance is not capable of relieving the withdrawal symptoms occuring 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 closely 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 of morphine antagonists which trigger withdrawal symptoms, dependent upon dosage. According to the 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."

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One particular advantage of the compound of Formula I 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 upon 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 opioid kappa agonists of the benzomorphane series, to which a high therapeutic range is also ascribed (for example, 1800 for ethylketazocine), is the absence of any strong sedation. This can be recognized in the comparison substances as an inhibition of locomotion in mice in or near the therapeutic dosage range. In the compound of Formula I, however, this effect was not observed in the range tested up to very high doses of 100 mg/kg.

The independent opioid activity profile of the compound of Formula I is obtained from studies on test organs, such as the vas deferens of the mouse and the guinea pig ileum and receptor preparations.

Systematic modification of the structure of Formula I has always resulted in substances with substantially less favorable properties. The corresponding N-(2-ethoxyethyl) compound of Formula IIIa, for example, has only 1/20 of the activity of the compound of Formula I, while the N-(3-methoxypropyl) compound of Formula IIId has only 1/25. Moreover, the compound of Formula IIId is similar to morphine in its effects. Etherification of the phenolic hydroxy group to yield the structures of Formulas IIIb and IIIc reduces the activity, for example, to 1/84 in the case of the compound of Formula IIIb.

The compounds of Formula I may be administered by enteral or parenteral route. The dosage for enteral and parenteral administration is from about 0.5 to 100 mg (from about 0.0007 to 1.3 mg/kg), preferably from about 1 to 20 mg (from about 0.013 to 0.27 mg/kg). The compounds of Formula I may also be combined with other pain-relieving agents or with active substances of other kinds such as sedatives, tranquilizers, or hypnotics. Suitable galenic forms for administration include, for example, tablets, capsules, suppositories, solutions, suspensions, powders, and emulsions. These may be prepared using the galenic excipients and carriers, disintegrants, lubricants, or substances for obtaining delayed release which are conventionally used. These galenic 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 cores produced analogously to the tablets and coating them with agents conventionally used for coating tablets, such as polyvinylpyrrolidone, shellac, gum arabic, talc, titanium dioxide, or sugar.

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

Syrups of the active substances or combinations of active substances according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerine, or sugar or a flavor-improving agent, for example, a flavoring such as vanillin or orange 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.

Injection solutions are prepared in conventional manner, such as, by the addition of preservatives such as p-hydroxybenzoates or stabilizers such as complexones, and then sealed in injection vials or ampules.

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 then encapsulating them in gelatine capsules.

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 facts or polyethylene glycol or the derivatives thereof.

The following examples are intended to illustrate the invention and should not be construed as limiting it thereto.

DRUG DESCRIPTION

Noroxymorphone is one of the major metabolites of oxycodone. Although oxycodone is commonly used in the treatment of acute and chronic pain, little is known about the antinociceptive effects of noroxymorphone. We present an in vivo pharmacological characterization of noroxymorphone in rats.

METHODS: The antinociceptive properties of noroxymorphone were studied with thermal and mechanica models of nociception in rats.(diethoxycarbonyl)normorph which may be prepared by reaction of morphine with ethy chloroformate, is converted to (diethoxycarbonyl) normorphinone, a novel compound, by oxidation. The novel normorphinone derivative is converted to (diethoxycarbonyl)normorphinone enol acetate, a second novel compound, by esterification with acetic anhydride or acetyl halide.

A 14-hydroxy group is introduced into the novel dienol est by oxidation with peracid. The resultant 14-hydroxy-3,17-(diethoxycarbonyl)normorphinone, a third novel compoun catalytically hydrogenated to produce 3,17-(diethoxycarbo noroxymorphone. The latter intermediate may be converte noroxymorphone by hydrolysis.

Note /Government Notification: These chemicals are designated as those that are used in the manufacture of the controlled substances and are important to themanufacture of the substances. For any (Control Substance) products Import and Export *** subjected to your country government laws /control substance ACT.

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The Controlled Substances Act (CSA) was enacted into law by the Congress of the United States as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970.[1] The CSA is the federal U.S. drug policy under which the manufacture, importation, possession, use and distribution of certain substances is regulated. The Act also served as the national implementing legislation for the Single Convention on Narcotic Drugs

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