AU9525817

(12) PATENT ABRIDGMENT (11) Document No. AU-B-25817/95
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 690996

(54) Title
NEW ANTAGONIST COMPOUNDS

International Patent Classification(s)
(51)[6] **C07D 489/09** **C07D 491/18** **A61K 031/485**

(21) Application No. : **25817/95** (22) Application Date : **09.05.95**

(87) PCT Publication Number : **WO95/31463**

(30) Priority Data

(31) Number	(32) Date	(33) Country
9401728	**18.05.94**	**SE SWEDEN**

(43) Publication Date : **05.12.95**

(44) Publication Date of Accepted Application : **07.05.98**

(71) Applicant(s)
ASTRA AKTIEBOLAG

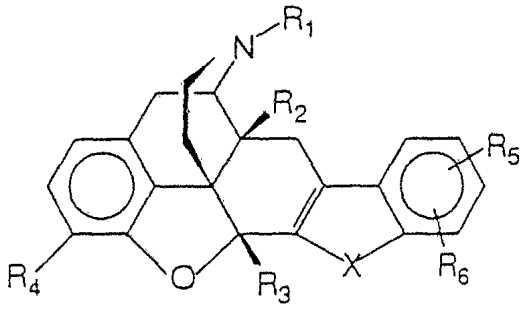
(72) Inventor(s)
HELMUT SCHMIDHAMMER

(74) Attorney or Agent
E F WELLINGTON & CO , 312 St Kilda Road, MELBOURNE VIC 3004

(56) Prior Art Documents
US 5225417

(57) Claim

1. A compound according to the formula (I)



(I)

wherein

R_1 represents C_1-C_{10} alkenyl; C_4-C_{10} cycloalkylalkyl wherein the cycloalkyl is C_3-C_6 cycloalkyl and the alkyl is C_1-C_4 alkyl; C_4-C_{10} cycloalkenylalkyl wherein the cycloalkenyl is C_3-C_6 cycloalkenyl and the alkyl is C_1-C_4 alkyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_8-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_2-C_6 alkenyl;

.../2

R_2 represents hydrogen, hydroxy, C_1-C_6 alkoxy; C_1-C_6 alkenyloxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_7 C_{16} arylalkenyloxy wherein the aryl is C_6-C_{10} aryl and the alkenyloxy is C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy; C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy;

R_3 represents hydrogen, C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; hydroxy(C_1-C_6)alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2H; CO_2(C_1-C_6 alkyl);

R_4 is hydrogen, hydroxy; C_1-C_6 alkoxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy; C_2-C_{10} alkyloxyalkoxy wherein alkyloxy is C_1-C_4 alkyloxy and alkoxy is C_1-C_6 alkoxy;

R_5 and R_6 each independently represent hydrogen; OH; C_1-C_6 alkoxy; C_1-C_6 alkyl; hydroxyalkyl wherein the alkyl is C_1-C_6 alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO_2H; CO_2(C_1-C_6 alkyl); $CONH_2$; CONH(C_1-C_6 alkyl); CON(C_1-C_6 alkyl)$_2$; amino; C_1-C_6 monoalkyl amino; C_1-C_6 dialkyl amino; C_5-C_6 cycloalkyl-amino; SH; SO_3H; SO_3(C_1-C_6 alkyl); SO_2(C_1-C_6 alkyl); SO_2NH_2; SO_2NH(C_1-C_6alkyl); SO_2NH (C_7-C_{20} arylalkyl); SO(C_1-C_6 alkyl); or R_5 and R_6 together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano,

.../3

thiocyanato; C_1-C_6 alkyl; trifluoromethyl; C_1-C_6 alkoxy, CO_2H, $CO(C_1$-C_6 alkyl), amino, C_1-C_6 monoalkylamino, C_1-C_6 dialkylamino, SH; SO_3H;SO_3 (C_1-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), $SO(C_1$-C_6 alkyl), and

X represents oxygen; sulfur; CH = CH or NR_9 wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl;
and wherein

aryl is unsubstituted or mono- or di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CO_2H, CO_2 (C_1-C_3)alkyl, $CONH_2$, $CONH(C_1$-C_3 alkyl), $CON(C_1$-C_3 alkyl), $CO(C_1$-C_3 alkyl), amino, (C_1-C_3 monoalkyl)amino, (C_1-C_3 dialkyl)amino, C_5-C_6 cyhloalkylamino (C_1-C_3 alkanoyl)amino, SH, SO_3H, SO_3 (C_1-C_3 alkyl), SO_2 (C_1-C_3 alkyl), $SO(C_1$-C_3 alkyl), C_1-C_3 alkylthio or C_1-C_3 alkanoylthio; and

with the following provisos:

(i) when R_2 is hydroxy, R_3 may only be hydrogen when R_4 is hydrogen, OCH_2OCH_3, $OCH_2OC_2H_5$ or $OC(Ph)_3$; or

(ii) R_3 may only be hydrogen when R_4 is C_2-C_{10} alkyloxyalkoxy, and/or when R_2 is C_7-C_{16} arylalkenyloxy or C_1-C_6 alkenyloxy;

as well as pharmacologically acceptable salts thereof.

17. A method for the treatment of a subject requiring suppression of rejection of transplants after organ transplantations, wherein an effective amount of a compound

or a pharmacologically acceptable salt according to any one of claims 1 to 7 and 9, or a pharmaceutical composition according to claim 14, is administered to a subject requiring suppression of rejection of transplants after organ transplantations.

OPI DATE 05/12/95 APPLN. ID 25817/95
AOJP DATE 18/01/96 PCT NUMBER PCT/SE95/00503

AU9525817

INT.

(51) International Patent Classification 6 :
C07D 489/09, 491/18, A61K 31/485

A1

(11) International Publication Number: WO 95/31463

(43) International Publication Date: 23 November 1995 (23.11.95)

(21) International Application Number: PCT/SE95/00503

(22) International Filing Date: 9 May 1995 (09.05.95)

(30) Priority Data:
9401728-2 18 May 1994 (18.05.94) SE

(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SCHMIDHAMMER, Helmut [AT/AT]; Unterbergerstrasse 18, A-6020 Innsbruck (AT).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

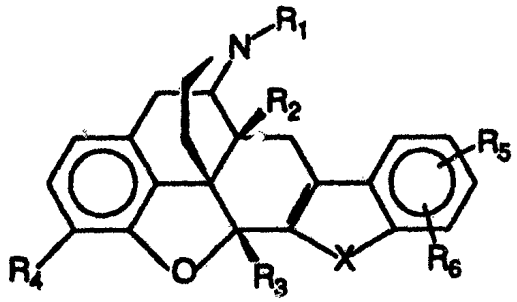
Published
With international search report.

690996

(54) Title: NEW ANTAGONIST COMPOUNDS

(57) Abstract

New morphinane derivatives of formula (I), their pharmaceutically acceptable salts, a process for their preparation and their use in the manufacture of pharmaceutical preparations.



(I)

NEW ANTAGONIST COMPOUNDS

Field of the invention

The present invention is related to novel δ opioid receptor antagonists as well as to their pharmaceutically acceptable salts, a process for their preparation and their use in the manufacture of pharmaceutical preparations.

Background of the invention

Opiod antagonists have been indispensable as tools in opioid research. For example, the chief criterion for the classification of an agonist effect as being opioid receptor mediated is the ability of known opioid antagonists naloxone or naltrexone to reversibly antagonize this effect in a competitive fashion. The usefulness of naloxone and naltrexone for this purpose stems from the fact that they are universal opioid antagonists; that is, they are capable of antagonizing the agonist effects mediated by multiple opioid receptor types.

Since it is now firmly established that there are a minimum of three opioid receptor types (μ, κ and δ), it has become increasingly evident that selective opioid antagonists are valuable pharmacological tools for identifying receptor types involved in the interaction with opioid agonists. One of the major advantages of selective opioid antagonists over selective agonists is their utility in probing the interaction of endogenous opioid peptides and new opioid agonists with opioid receptor types. Moreover, since it is sometimes not easy to distinguish among μ, κ and δ opioid receptor mediated agonist effects if the pharmacological endpoints are identical (e.g. antinociception or inhibition of a smooth muscle preparation by agonists), selective antagonists clearly have wider utility as tools than selective agonists.

The general utility of selective antagonists as pharmacological tools depends upon the correlation of in vitro and in vivo acitivity. This can be accomplished more easily with non-peptide ligands because they generally can penetrate the blood-brain barrier and therefore can be administered peripherally in vivo. Also, they are less subject to metabolism than are peptides.

In addition to their uses as pharmacological tools, selective, non-peptide opioid antagonists have been described as having potential clinical applications in the treatment of a variety of disorders where endogenous opioids play a modulatory role. These include for instance disorders of food intake, shock, constipation, mental disorders, CNS injury, alcoholism, and immune function (immune stimulation or suppression) (P.S. Portoghese et al., J. Med. Chem., Vol 34: 1757-1762, 1991).

Non-peptide, competitive, δ-selective opioid antagonists have been found recently. The prototypes are: cyprodime for μ (H. Schmidhammer et al., J. Med. Chem., Vol. 32:418-421, 1989; H. Schmidhammer et al., J. Med. Chem., Vol. 33: 1200-1206, 1990), norbinaltorphimine for κ (P. S. Portoghese et al., J. Med. Chem., Vol. 30:238-239, 1987), and naltrindole for δ opioid receptors (P.S. Portoghese et al., J. Med. Chem., Vol. 31:281-282, 1988).

These compounds (cyprodime, norbinaltorphinine and naltrindole) are being used as pharmacological tools. They have been tritium labelled and can be used as receptor selective ligands in opioid receptor binding studies to sort out the affinities of new ligands to different receptors and to determine whether a compound is selective to a special receptor.

An object of the present invention was to find new, highly selective δ opioid receptor antagonists with high potency. Another object was to find highly selective δ opioid receptor antagonists with high immunosuppressive potency. The high selectivity for δ opioid receptors would repress adverse side effects

caused by the interaction with other receptors. Still another object was to find compounds which have a brain-cell protecting effect. The problem with the δ opiod receptor antagonists known from the prior art is that they are not highly selective.

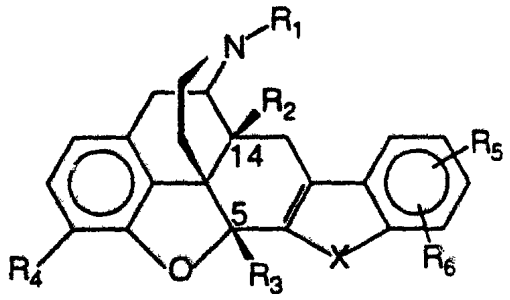
Prior art

Certain opioid agonists represented by morphine, which act on μ receptors, are known to exhibit immunosuppressive effects. The agonist enkephalin, which acts on δ opioid receptors, exhibit immunostimulating effects (Plotnikoff, Enkephalins and Endorphins, Stress and Immune System, Plenum Press, 1986). Although a number of reports have been issued concerning the immunosuppressive effects of agonists of μ receptors, it is difficult to develop an immunosuppressive agent by employing an agonist of μ receptors, since such agonists show critical side effects such as addiction, respiratory depression, constipation etc.

Recently it has been reported that δ-selective opioid antagonists have immunosuppressive effects. See EP 456 833, EP 485 636 and EP 614 898.

Outline of the invention

The present invention provides novel compounds of the formula (I)



(I)

wherein

R_1 represents C_1-C_{10} alkenyl; C_4-C_{10} cycloalkylalkyl wherein the cycloalkyl is C_3-C_6 cycloalkyl and the alkyl is C_1-C_4 alkyl; C_4-C_{10} cycloalkenylalkyl wherein the cycloalkenyl is C_3-C_6 cycloalkenyl and the alkyl is C_1-C_4 alkyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_8-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_2-C_6 alkenyl;

R_2 represents hydrogen, hydroxy, C_1-C_6 alkoxy; C_1-C_6 alkenyloxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_7-C_{16} arylalkenyloxy wherein the aryl is C_6-C_{10} aryl and the alkenyloxy is C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy; C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy;

R_3 represents hydrogen, C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; hydroxy(C_1-C_6)alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2H; CO_2(C_1-C_6 alkyl);

R_4 is hydrogen, hydroxy; C_1-C_6 alkoxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy; C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy; C_2-C_{10} alkyloxyalkoxy wherein alkyloxy is C_1-C_4 alkyloxy and alkoxy is C_1-C_6 alkoxy;

AUSTRALIAN PATENT OFFICE

R_5 and R_6 each independently represent hydrogen; OH; C_1-C_6 alkoxy; C_1-C_6 alkyl; hydroxyalkyl wherein the alkyl is C_1-C_6 alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO_2H; $CO_2(C_1$-C_6 alkyl); $CONH_2$; $CONH(C_1$-C_6 alkyl); $CON(C_1$-C_6 alkyl)$_2$; amino; C_1-C_6 monoalkyl amino; C_1-C_6 dialkyl amino, C_5-C_6 cycloalkylamino; SH; SO_3H; $SO_3(C_1$-C_6 alkyl); $SO_2(C_1$-C_6 alkyl); SO_2NH_2; $SO_2NH(C_1$-C_6 alkyl); SO_2NH (C_7-C_{16} arylalkyl); $SO(C_1$-C_6 alkyl); or R_5 and R_6 together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C_1-C_6 alkyl; trifluoromethyl; C_1-C_6 alkoxy, CO_2H, $CO(C_1$-C_6 alkyl), amino, C_1-C_6 monoalkylamino, C_1-C_6 dialkylamino, SH; SO_3H; $SO_3(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), $SO(C_1$-C_6 alkyl), and

X represents oxygen; sulfur; CH=CH or NR_9 wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl,

and wherein

aryl is unsubstituted or mono-, di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CO_2H, CO_2 (C_1-C_3)alkyl, $CONH_2$, $CONH(C_1$-C_3 alkyl), $CON(C_1$-C_3 alkyl)$_2$, $CO(C_1$-C_3 alkyl), amino, (C_1-C_3 monoalkyl)amino, (C_1-C_3 dialkyl)amino, C_5-C_6 cycloalkylamino, (C_1-C_3 alkanoyl)amino, SH, SO_3H, SO_3 (C_1-C_3 alkyl), SO_2 (C_1-C_3 alkyl), $SO(C_1$-C_3 alkyl), C_1-C_3 alkylthio or C_1-C_3 alkanoylthio; and

AUSTRALIAN PATENT OFFICE

with the following provisos:

(i) when R_2 is hydroxy, R_3 may only be hydrogen when R_4 is hydrogen, OCH_2OCH_3, $OCH_2OC_2H_5$ or $OC(Ph)_3$; or

(ii) R_3 may only be hydrogen when R_4 is C_2-C_{10} alkyloxyalkoxy, and/or when R_2 is C_7-C_{15} arylalkenyloxy or C_1-C_5 alkenyloxy;

as well as pharmacologically acceptable salts thereof.

In a preferred embodiment:

R_1 is selected from allyl, cinnamyl, cyclopropylmethyl or cyclobutylmethyl;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy, benzyloxy substituted in the aromatic ring with F, Cl, NO_2, CN, CF_3, CH_3 or OCH_3; allyloxy, cinnamyloxy or 3-phenylpropyloxy;

R_3 is selected from hydrogen, methyl, ethyl, benzyl or allyl;

R_4 is selected from hydroxy, methoxy, methoxymethoxy or acetyloxy;

R_5 and R_6 are each and independently selected from hydrogen, nitro, cyano, chloro, fluoro, bromo, trifluoromethyl; CO_2H; CO_2CH_3, $CONH_2$; $CONHCH_3$, CH_3, SH; SO_2NH_2; $N(CH_3)_2$, SO_2CH_3; and

X is selected from O, NH, NCH_3, N-benzyl, N-allyl.

In an especially preferred embodiment R_1 is allyl or cyclopropylmethyl;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy substituted in the aromatic ring with chlorine;

R_3 is selected from hydrogen or CH_3;

R_4 is hydroxy

AUSTRALIAN PATENT OFFICE

R_5 and R_6 are each independently selected from hydrogen, CO_2H, $CONH_2$, SO_2NH_2 or SO_2CH_3; and

X is selected from O or NH.

The best mode known at present is to use the compounds of Examples 1, 6, 8, 18, 24, 41 and 42.

The novel compounds according to the invention are useful as immunsuppressive agents and/or as analgesics, and also after CNS-injuries by exerting a brain-cell protecting effect.

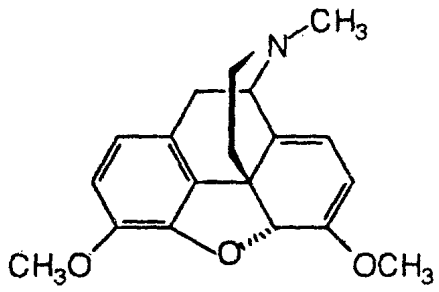
Earlier studies (cf. page 3) accomplished with δ-selective opioid antagonists have shown that this class of compounds exhibits immunosuppressive effects. Thus, the compounds of formula (I) of the present invention may be used for suppressing the rejection of transplants after organ transplantations and may be used in the treatment of rheumatic diseases, e.g. rheumatoid arthritis and/or as analgesics.

Pharmaceutically and pharmacologically acceptable salts of the compounds of formula I are also comprised in the invention. Suitable salts are inorganic salts such as HCl salt, HBr salt, sulfuric acid salt, phosphoric acid salt. Organic acid salts such as methanesulfonic acid salt, salicylic acid salt, fumaric acid salt, maleic acid salt, succinic acid salt, aspartic acid salt, citric acid salt, oxalic acid salt, orotic acid salt, although the salts are not restricted thereto, can also be used according to the invention.

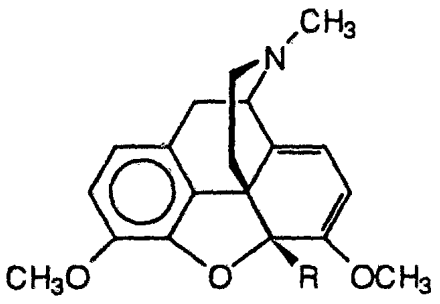
Preparation

The compounds represented by formula (I) may be obtained by the following methods:

Thebaine of the formula



is being treated with dialkylsulfates, fluorosulfonic acid alkyl esters, alkylsulfonic acid alkyl esters, arylsulfonic acid alkylesters, alkyl halides, aralkyl halides, alkylsulfonic acid aralkyl esters, arylsulfonic acid aralkyl, arylalkenyl halides, chloroformates, in solvents such as tetrahydrofurane or diethyl ether using a strong base such as n-butyl lithium, lithium diethyl amide or lithium diisopropyl amide at low temperatures (-20 to -80 °C) (s. Boden et al., J.org.Chem.,Vol.47: 1347-1349, 1982; Schmidhammer et al., Helv.Chim.Acta, Vol.71:642-647, 1988), giving compounds of the formula II

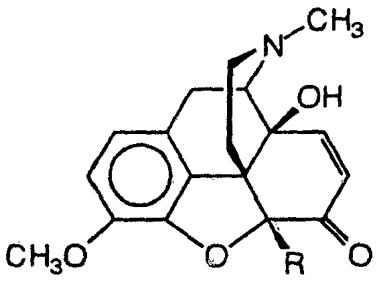


(II)

wherein

R is C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} aralkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the

alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2 (C_1-C_6 alkyl); The substituted thebaine derivatives (formula (II)) or thebaine are converted into the corresponding 14-hydroxycodeinones according to formula III

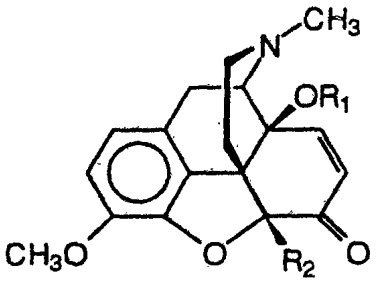


(III)

wherein

R is as defined above or being hydrogen,

by reaction with performic acid (s. Schmidhammer et al., Helv.Chim.Acta, Vol. 71:1801-1804, 1988) or m-chloroperbenzoic acid at a temperature between 0 and 60 °C. The preferred procedure is the reaction with performic acid at 0-10 °C (H. Schmidhammer et al., Helv.Chim.Acta, Vol. 71:1801-1804, 1988). These 14-hydroxycodeinones being treated with dialkyl sulfates, alkyl halides, alkenyl halides, aralkyl halides, arylalkenyl halides, chloroformates, in solvents such as N,N-dimethyl formamide or tetrahydrofurane using a strong base such as sodium hydride, potassium hydride or sodium amide giving compounds of formula (IV),



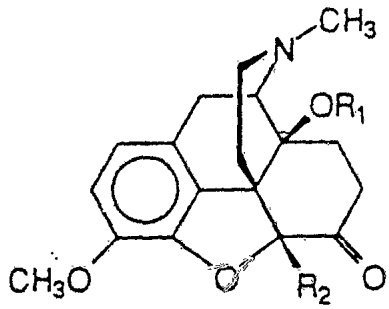
(IV)

wherein

R_1 is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl, C_1-C_6 alkanoyl, C_7-C_{20} arylalkanoyl wherein the aryl is C_6-C_{14} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{20} arylalkenoyl wherein the aryl is C_6-C_{14} aryl and the alkyl is C_1-C_6 alkenoyl;

R_2 is C_1-C_6 alkyl; C_1-C_6 alkenyl C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; $CO_2(C_1$-C_6 alkyl);

which in turn are reduced by catalytic hydrogenation using a catlayst such as palladium on charcoal and solvents such as methanol, ethanol or glacial acetic acid to give compounds of formula (V)



(V)

wherein

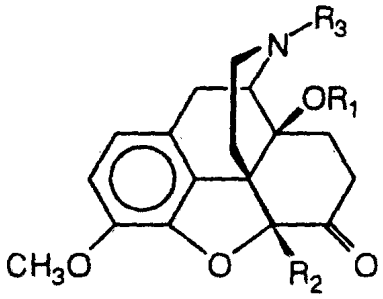
R_1 is C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl; and

R_2 is hydrogen; C_1-C_6 alkyl, C_1-C_6 alkenyl C_7-C_{16} arylalkyl wherein the aryl C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl

AUSTRALIAN PATENT OFFICE

and alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

Thereafter N-demethylation can be carried out using chloroformates or cyanogen bromide to give intermediates of formula (VI)



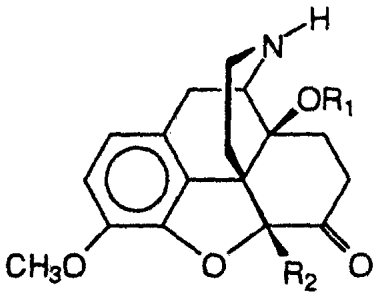
(VI)

wherein

R_1 and R_2 are as defined above in formula (IV); and

R_3 is $CO_2CHClCH_3$, $CO_2CH{=}CH_2$, $CO_2CH_2CCl_3$, $CO_2CH_2CH_3$, CO_2Ph, CN or the like.

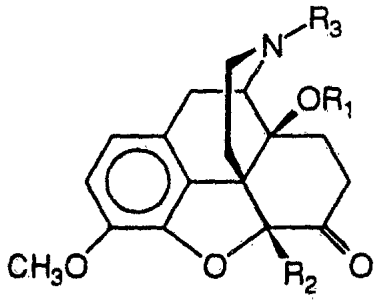
The intermediate carbamates of formula (VI) can be cleaved by refluxing in alcohols (in the case of 1-chloroethyl carbamates), by addition of hydrogen halides or halogen and subsequent refluxing in alcohols (in the case of vinyl carbamates), or by reductive cleavage using zinc in glacial acetic acid or methanol (in the case of 2,2,2-trichloroethyl carbamates). Other carbonates may be cleaved using aqueous acid, alkali or hydrazine. The intermediate cyanamides of formula (VI) can be cleaved by acid hydrolysis. Alkylation of the corresponding N-nor derivatives of formula (VII)



(VII)

wherein

R_1 and R_2 are as defined above in formula (V), can be accomplished with alkenyl halides, cycloalkylalkyl halides, cycloalkenylalkyl halides, aralkyl halides, arylalkenyl halides, in solvents such as dichloromethane, chloroform, or N,N-dimethyl formamide in the presence of a base such as sodium hydrogen carbonate or potassium carbonate to yield derivatives of formula (VIII)



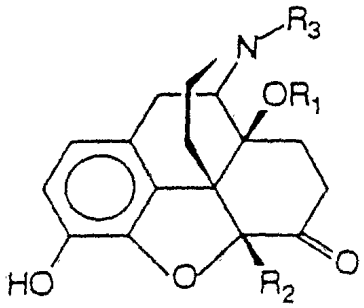
(VIII)

wherein

R_1 and R_2 are as defined above in formula (V); and

R_3 represents C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_4-C_{10} cycloalkylalkyl wherein the cycloalkyl is C_3-C_6 cycloalkyl and the alkyl is C_1-C_4 alkyl; C_4-C_{10} cycloalkylalkenyl wherein the cycloalkenyl is C_3-C_6 cycloalkenyl and the alkyl is C_1-C_4 alkyl;

Ether cleavage can be carried out using boron tribromide (in a solvent such as dichloromethane or chloroform at about 0 °C), 48 % hydrobromic acid (reflux), or other well known reagents for ether cleavage. The resulting phenols of formula (IX)

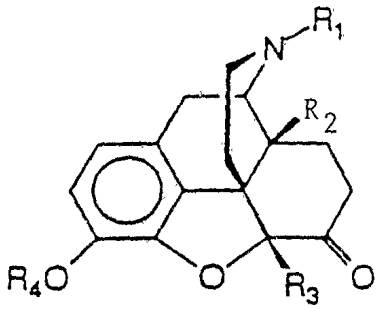


(IX)

wherein

R_1, R_2 and R_3 are as defined above,

are being alkylated using alkyl halides, alkyl sulfates, sulfonic acid esters, aralkyl halides, arylalkenyl halides or acylated using carbonic acid chlorides, or carbonic acid esters to yield compounds of formula (X)



(X)

wherein

R_1, R_2 and R_3 are as defined above; and

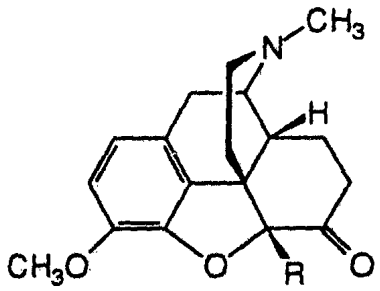
R_4 is hydrogen, C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl, C_2-C_{10} alkyloxyalkyl wherein alkyloxy is C_1-C_4 alkyloxy and alkyl is C_1-C_6 alkyl,

AUSTRALIAN PATENT OFFICE

Compounds of the formula (I) wherein R_2 is hydroxy may be obtained from compounds of formula (III) wherein R is defined as above. These compounds may be reduced by catalytic hydrogenation using a catalyst such as palladium on charcoal and solvents such as methanol, ethanol, or glacial acetic acid to give compounds of the formula (V) wherein R_1 is hydrogen and R_2 is defined for R in formula (II).

The following reaction sequence and procedures leading to compounds of formulas (VI), (VII), (VIII), (IX) and (X) wherein the substituent in position 14 is hydroxy and the other substitutents are defined as above, is analogous to the reaction sequence and procedures described above. Further conversion to compounds of the formula (I) wherein R_2 is hydroxy is described below.

Compounds of the formula (I) wherein R_2 is hydrogen may be obtained from compounds of the formula (II) wherein R is as defined above or hydrogen. Catalytic hydrogenation followed by acid hydrolysis (s. Boden et al., J. Org. Chem. Vol. 47:1347-1349, 1982) may provide compounds of formula (XI)



(XI)

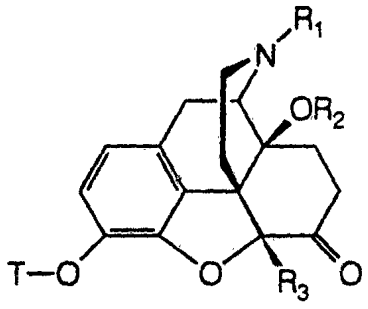
(XIa): R=H (dihydrocodeinone)

wherein R is as defined above in formula (II) or hydrogen.

Compounds of the formula (XI) and (XIa) (Mannich and Löwenheim, Arch.Pharm.Vol. 258:295, 1920) can be converted into compounds of formulas (V), (VI), (VII), (VIII), (IX), and (X) wherein the substituent in position 14 is hydrogen

and R_2 and R_3 are as defined above, similarly as outlined above. Further conversion into compounds of the formula (I) wherein R_2 is hydrogen is described below.

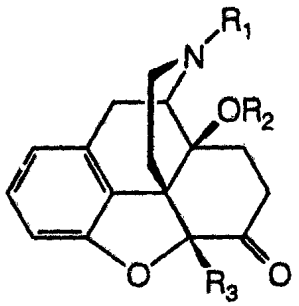
Compounds of the formula (I) wherein R_4 is hydrogen may be prepared from compounds of the formula (IX) by alkylation with 5-chloro-1-phenyl-^{1}H-tetrazole to give the corresponding phenyltetrazolyl ethers of the formula XII)



(XII)

wherein R_1, R_2 and R_3 are as defined above and R_1 also can be CH_3, and T is phenyltetrazolyl.

Catalytic hydrogenation may afford (H. Schmidhammer et al., J. Med. Chem. Vol. 27:1575-1579, 1984) compounds of the formula (XIII)

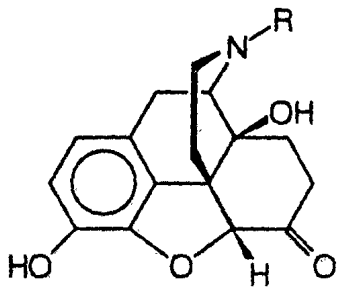


(XIII)

wherein R_1, R_2 and R_3 are as defined above and R_1 also can be CH_3;

In the case R_1 is CH_3, the N-methyl group has to be removed and the nitrogen alkylated as described above.

Alternatively, compounds of formula (I) wherein R_1 represents allyl or cyclopropylmethyl and R_3 represents H can be obtained by a shorter route starting either from naloxone (XIVa) or naltrexone (XIVa).

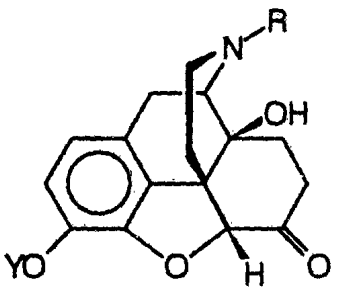


(XIV)

(XIVa): Naloxone - R is allyl

(XIVb): Naltrexone - R is cyclopropylmethyl.

The 3-hydroxy group of compounds of formula (XIV) is being protected by alkylation with benzyl bromide, methoxymethyl bromide, ethoxymethyl bromide or trityl chloride (triphenylmethyl chloride) in a solvent such as N,N-dimethyl formamide or dichloromethane in the presence of a base to yield compounds of formula (XV)

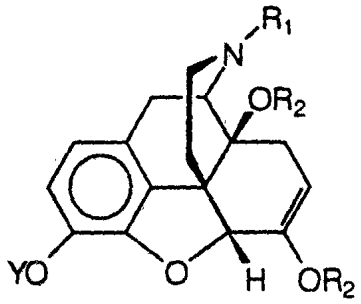


(XV)

wherein

R is allyl or cyclopropylmethyl and Y = CH_2Ph, CH_2OCH_3, $CH_2OC_2H_5$ or $C(Ph)_3$.

These compounds are alkylated, alkenylated, cycloalkylalkylated, arylalkylated or arylalkenylated with dialkyl sulfates, alkyl halides, alkenyl halides, arylalkyl halides or arylalkenyl halides in solvents such as N,N-dimethyl formamide or tetrahydrofurane using a strong base such as sodium hydride, potassium hydride or sodium amide. The resulting 6-0,14-0-dialkylated compounds of formula (XVI)



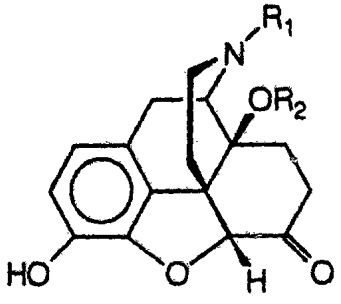
(XVI)

wherein

R_1 is allyl or cyclopropylmethyl; and

R_2 is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkoxy, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and alkenyl is C_1-C_6 alkenyl; and Y as defined above;

can be hydrolized with diluted acids like hydrochloric acid or sulfuric acid to afford compounds or formula (XVII)



(XVII)

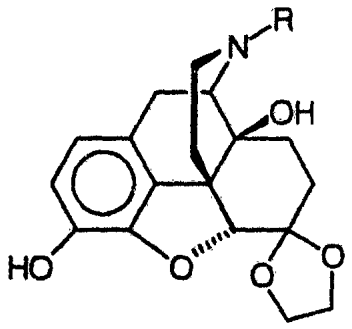
wherein

R_1 is allyl or cyclopropylmehtyl; and

R_2 is as defined above (formula XVI).

In the case R_2 is alkenyl or arylalkenyl the double bond may be reduced by catalytic hydrogenation to afford the corresponding saturated derivatives. Further conversion into compounds of formula (I) is described below.

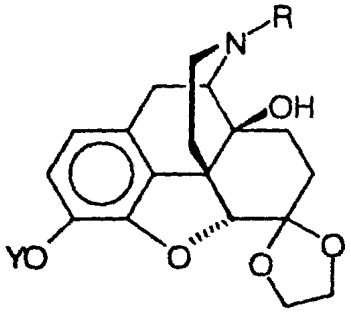
Alternatively, compounds of formula (I) wherein R_1 represents allyl or cyclopropylmethyl and R_3 represents H can be prepared also via the following route: The carbonyl group in position 6 of naloxone (XVa) and naltrexone (XVb), respectively, is being protected by reaction with ethylene glycol in the presence of an acid (e.g. methanesulfonic acid) at temperatures between 20 and 200 °C to give ketals of formula (XVIII)



(XVIII)

wherein R is allyl or cyclopropylmethyl.

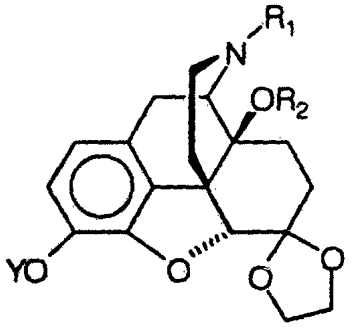
The 3-hydroxy group of these ketals is being protected by alkylation with benzyl bromide, methoxymethyl bromide, ethoxymethyl bromide or trityl chloride in a solvent such as N,N-dimethyl formamide or dichloromethane in the presence of a base to yield compounds of formula (XIX)



(XIX)

wherein R is allyl or cyclopropylmethyl and Y is as defined above.

These compounds are alkylated, alkenylated, arylalkylated or arylalkenylated with dialkyl suflates, alkyl halides, alkenyl halides, arylalkyl halides or arylalkenyl halides in solvents such as N,N-dimethyl formamide or tetrahydrofurane using a strong base such as sodium hydride, potassium hydride or sodium amide. The resulting compounds of formula (XX)



(XX)

wherein R_1 is allyl or cyclopropylmethyl, R_2 is as defined above (formula (XVI)) and Y is as defined above

can be hydrolized in diluted acids like hydrochloride acid or sulfuric acid (a typical mixture for hydrolysis is: concentrated HCl: MeOH: H_2O 3/6/1 v/v/v) to afford compounds of formula (XVII). Compounds of formula (I) wherein R_1

represents allyl or cyclopropyl-ethyl, R_3 represents H, and X represents NH or O can be prepared from compounds of formula (XVII) as described below.

Compounds of the formula (I) wherein R_3 is as defined above and X represents NH are obtained by reaction of compounds of formula (VIII), (X) or (XIII) with phenylhydrazine or substituted phenylhydrazine in solvents such as methanol, ethanol or glacial acetic acid in the presence of methanesulfonic acid, HCl or HBr. Phenylhydrazine substituted at the aromatic ring with hydroxy, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, nitro, cyano, thiocyanato, trifluoromethyl, CO_2H, CO_2 (C_1-C_6) alkyl, $CONH_2$, CONH (C_1-C_6 alkyl), CON (C_1-C_6 alkyl)$_2$, SO_2NH_2, SO_2 (C_1-C_6) alkyl or the like may be employed. The reaction may be carried out at a temperature between 20 and 160 °C, preferably between 20 and 80 °C.

Compounds of formula (I) wherein R_3 is as defined above and X represents O are obtained by reaction of compounds of formula (VIII), (IX), (X) or (XIII) with O-phenylhydroxyl amine or substituted (at the aromatic ring) O-phenylhydroxyl-amine in solvents such as methanol ethanol, or glacial acetic acid in the presence of methanesulfonic acid, HCl or HBr. O-phenylhydroxylamine substituted at the aromatic ring with hydroxy, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, nitro, cyano, thiocyanato, trifluoromethyl, CO_2H, CO_2 (C_1-C_6) alkyl, $CONH_2$, CONH (C_1-C_6 alkyl), CON (C_1-C_6 alkyl)$_2$, SO_2NH_2, SO_2 (C_1-C_6) alkyl or the like may be employed.

The invention will now be described in more detail by the following examples which are not to be construed as limiting the invention.

Examples

Example 1

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride (compound 1).

A mixture of 14-O-ethyl-5-methylnaltrexone (H. Schmidhammer et al, Helv. Chim. Acta, Vol. 76: 476-480, 1993) (580 mg, 1.51 mmol), phenylhydrazine hydrochloride (394 mg, 2.72 mmol), and 7 ml of glacial acetic acid was refluxed for 23 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x30 ml). The combined organic layers were washed with H_2O (3x80 ml), dried over Na_2SO_4 and evaporated. The remaining residue (615 mg brownish foam) was dissolved in little MeOH and Et_2O/HCl was added. Thus, 550 mg (95%) of the compound 1 were isolated. For analysis a small amount was recrystallized from MeOH. m.p. > 260°C (dec.) IR (KBr): 3200 (˙NH, NH, OH)cm^{-1}. CI-MS:m/z 457 ($M^{\cdot}$ +1). ^{1}H-NMR ((d_6)DMSO): δ 11.34, 9.21. and 8.55 (3 s, ˙NH, NH, OH), 7.32 (m, 2 arom. H), 7.08 (t, J = 8.1 Hz, 1 arom. H), 6.94 (t, J = 8.1 Hz, 1 arom. H), 6.62 (d, J = 8.1 Hz, 1 arom. H); 6.55 (d. J = 8.1 Hz, 1 arom. H), 1.86 (s, CH_3-C(5)), 1.01 (t, J = 6.8 Hz, 3H, CH_3CH_2O). Analysis calculated for $C_{29}H_{32}N_2O_3$.HCl.H_2O (511.06): C 68.16, H 6.90, N 5.48, Cl 6.94; found: C 67.87, H 6.88, N 5.30, Cl 7.28.

Example 2

Synthesis of 17-Allyl-6,7-dihydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride (compound 2).

A mixture of 14-O-ethyl-5-methylnaloxone (H. Schmidhammer et al., Helv. Chim. Acta Vol. 76:476-480, 1993) (1.2g, 2.66 mmol), phenylhydrazine hydrochloride (577 mg, 3.99 mmol), and 15 ml of glacial acetic acid was refluxed for 24 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x80 ml), 1x30 ml). The combined organic layers were washed with H_2O (3x80 ml, 1x30 ml), dried over Na_2SO_4 and evaporated. The residue (1.3 g yellow-brown foam) was purified with column chromatography (alumina basic grade IV, elution with CH_2Cl_2). The corresponding fractions were combined and evaporated to give a colorless oil which was converted into the hydrochloride salt in the usual way and crystallized from MeOH/diethyl ether to yield 200 mg (17%) of the title compound 2. M.p. 168-170°C. IR (KBr):3200('NH,OH)cm^{-1}. CI-MS: M/z 443 (M'+1). ^{1}H-NMR (CD_3OD): δ 7.39 (dd, J=7.8, 7.8 HZ, 2 arom. H), 7.14 (t, J=7.8 hz, 1 arom.H), 7.01 (t=7.8 HZ, 1 arom. H), 6.67 (s,2 arom. H), 6.02 (m, 1 olef. H), 5.72 (m, 2 olef. H), 1.99 (s, CH_3-C(5)), 1.09 (t, J=6.8 Hz, CH_3). Analysis calculated for $C_{28}H_{30}N_2O_3$. HCl. 1.5 H_2O (506.05): C 66.46, H 6.77 N 5.54, Cl 7.01; found: C 66.55, 6.68, N 5.39, Cl 6.98.

Eaxmple 3

Synthesis of 6,7-Dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-17-(2-phenyl)ethyl-6,7-2',3'-indolomorphinan hydrochloride (compound 5).

A mixture of 4,5α-epoxy-14-ethoxy-3-methoxy-5-methylmorphinan-6-one hydrochloride (H. Schmidhammer et al., Helv. Chim. Acta Vol. 76, 476-480,1993) (3.0 g, 7.88 mmol), potassium carbonate (3.9 g, 28.2 mmol), 2-phenylethyl bromide (1.41 ml, 10.4 mmol), and of 20 ml anhydrous N,N-dimethyl formamide was stirred at 80°C (bath temperature) for 2h. After cooling and addition of 130 ml of H_2O, the mixture was extracted with diethyl ether (3x60 ml). The combined organic layers were washed with H_2O (3x70 ml), dried over Na_2SO_4 and evaporated. The residue (3.6 yellow oil) was crystallized from MeOH to afford 2.1 g (70%) of 4,5α-epoxy-14-ethoxy-3-methoxy-5-methyl-17-(2-phenyl)ethylmorphinan-6-one (compound 3). M.p. 86-89°C. IR (KBr): 1725 (CO) cm^{-1}. CI-MS: m/z 448 (M^++1). ^{1}H-NMR ($CDCl_3$): δ 7.21 (m, 5 arom. H), 6.64 (d,J=8.2 Hz, 1 arom. H, 6.54 (d, J=8.2 Hz, 1 arom. H.), 3.85 (s, OCH_3), 1.60 (s, CH_3-C(5)), 1.12 (t, J=6.8 Hz, CH_3). Analysis calculated for $C_{28}H_{33}NO_4$ (447.55): C 75.14, H 7.43, N 3.13; found: C 75.04, H 7.69, N 3.26.

A solution of the compound 3 (1.5 g, 3.35 mmol) in 5 ml of 48% HBr was refluxed for 30 min and then evaporated. The residue was dissolved in MeOH and again evaporated (this procedure was repeated twice) to give a grey crystalline residue (1.7 g) which was treated with hot MeOH to yield 950 mg (63%) of the compound 4. M.p.>270°C. IR (KBr): 1720 (CO) cm^{-1}. CI-MS: m/z 434 (M^++1). ^{1}H-NMR (DMSO-d_6): δ 9.38 and 8.48 (2 s, NH, OH), 7.33 (m, 3 arom. H), 6.68 (d, J=8.2 Hz, 1 arom. H), 6.64 (d, J=8.2 Hz, 1 arom. H), 1.51 (s, CH_3-C(5)), 1.34 (t, J=6.8 Hz, CH_3).

Analysis calculated for $C_{27}H_{31}NO_4$. HBr (514.45):C 63.04, H 6.27, N 2.72, Br 15.53; found: C 63.15, H 6.48, N 2.61, Br 15.37.

A mixture of the compound 4 (700 mg, 1.61 mmol), phenylhydrazine hydrochloride (513 mg), 3.54 mmol), and 15 ml of glacial acetic acid was refluxed for 6 h. The reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x80 ml, 1x30 ml). The combined organic layers were washed with H_2O (3x80 ml), dried over Na_2SO_4 and evaporated. The residue (600 mg slightly brown foam) was converted into the hydrochloride salt in the usual way and crystallized from MeOH/diethyl ether to yield 360 mg (51%) of the title compound 5 as slightly pink crystals. M.p.>225°C. IR (KBr):3400 and 3200 (NH, NH,OH). CI-MS:m/z 507 (M^++1). ^{1}H-NMR (DMSO-d_6):δ 11.34, 9.19 and 8.97 (NH, NH, OH), 7.34 (m, 7 arom. H), 7.08 (t, J=7.9 Hz, 1 arom.), 6.94 (t, J=7,9 Hz, 1 arom. H), 6.62 (d, J=8.4 Hz, 1 arom. H), 6.57 (d, J=8.4 Hz, 1 arom. H), 1.87 (s, CH3-C(5)),0.96 (t, J=6.9 Hz, CH_3). Analysis calculated for $C_{33}H_{34}N_2O_3$. HCl.2 H_2O (579.14): C 68.44, H 6.79, N 4.84, Cl 6.12; found: C 68.81, H 6.55, N 4.72, Cl 6.40.

Example 4

Synthesis of 17-Allyl-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride (compound 6).

A mixture of 14-O-methyl-5-methylnaloxone (H. Schmidhammer et al., Helv. Chim. Acta Vol. 77:1585-1589, 1994) (1.0 g, 2.8 mmol), phenylhydrazine hydrochloride (728 mg, 5.04 mmol), and 15 ml of glacial acetic acid was refluxed for 24 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x80 ml, 1x30 ml). The combined organic layers were washed with H_2O (3x80 ml), dried over Na_2SO_4 and

evaporated. The residue (1.1 g brownish foam) was converted in the usual way into the hydrochloride salt and crystallized from acetone to yield 190 mg (19%) of the title compound 6 as slightly brown crystals. M.p. >280°C. IR (KBr): 3200 (˙NH, NH,OH), ^{1}H-NMR: δ 7.32 (dd, J=7.9, 7.9 Hz, 2 arom. H), 7.06 (t, J=7.9 Hz, 1 arom. H), 6.93 (t, =7.9 Hz, 1 arom. H), 6,63 (d, J=8.2 Hz, 1 arom. H), 6.55 (d, J=8.2 Hz, 1 arom. H), 6.02 (m, 1olef.H), 5.63 (m, 1 olef. H), 3.15 (s, OCH_3), 2.07 (s, CH_3-C(5)).

Analysis calculated for $C_{27}H_{28}N_2O_3$. HCl. 1.7 H_2O. 0.9 MeOH (524.44): C64.41, H 7.09, N 5.22; found: C 64.44, H 6.87, N 4.94.

Example 5

Synthesis of 6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-17-(2-phenyl)ethyl-6,7-2',3'-indolomorphinan Hydrochloride (compound 9).

A mixture of 4,5α-epoxy-3,14-dimethoxy-5-methylmorphinan-6-one hydrochloride (H. Schmidhammer et al., Helv. Chim. Acta Vol. 77:1585-1589, 1994) (2.24 g, 6.12 mmol), potassium carbonate (3.0 g, 21.9 mmol), 2-phenylethyl bromide (1.05 ml, 7.74 mmol), and 15 ml of anhydrous N,N-dimethyl formamide was stirred at 80°C (bath temperature) for 2 h. After cooling and addition of 110 ml of H_2O, the mixture was extracted with diethyl ether (3x60 ml). The combined organic layers were washed with H_2O (3x70 ml), dried over Na_2SO_4 and evaporated. The residue (2.9 yellow oil) was converted into the hydrobromide salt in the usual way and crystallized from MeOH to give 1.4 g (63%) of 4,5α-epoxy-3,14-dimethoxy-5-methyl-17-(2-phenyl)ethylmorphinan-6-one hydrobromide (compound 7) as colorless crystals. A small portion of this material was recrystallized from MeOH for analyses. M.p. 94-96°C. IR (KBr): 3400 (˙NH), 1720 (CO) cm^{-1}. CI-MS: m/z 434 (M˙+1). ^{1}H-NMR (DMSO-d_6) δ 10.15 (s, ˙NH), 7.30 (m, 5 arom. H), 6.74 (d, J=8.2 Hz, 1 arom. H), 6.68 (d, J=8.2 Hz, 1 arom.), 3.87 (s,

OCH_3-C(3)), 3.58 (s, OCH_3-C(14)), 1.60 (s, CH_3-C(5)). Analysis calculated for $C_{27}H_{31}NO_4$. HBr (514.44): C 63.04, H 6.27, N 2.72; found: C 63.18, H 6.60, N 2.39.

A solution of the compound 7 (1.4 g, 3.32 mmol) in 5 ml of 48% HBr was refluxed for 30 min and then evaporated. The residue was dissolved in MeOH and again evaporated (this operation was repeated once) to afford a brownish crystalline residue (1.8 g) which was treated with hot MeOH to yield 590 mg (42%) of the compound 8.HBr. A small portion was recrystallized for analyses. M.p.>316°C. IR (KBr):3400 (˙NH, OH), 1722 (CO)cm^{-1}. CI-MS: m/z 420 ($M^{\cdot}$+1). ^{1}H-NMR (DMSO-d_6) δ 8.95 and 8.45 (2s, ˙NH,OH), 6.90 (m, 5 arom. H), 6.23 (dd, J=8.2, 8.2 Hz, 2 arom. H), 2.97 s, OCH3), 1.08 (s, CH_3-C(5)). Analysis calculated for $C_{26}H_{29}NO_4$. HBr. 0.2 MeoH (506.85): C 62.09, H 6.13, N 2.76, Br 16.77; found: C 61.79, H 6.18, N 2.63, Br 16.12.

A mixture of the compound 8. HBr (468 mg, 0.93 mmol), phenylhyrazine hydrochloride (343 mg, 2.36 mmol), and 15 ml of glacial acetic was refluxed for 7 h. After cooling, the reaction mixture was poured on ice, alkalized with con. NH_4OH and extracted with CH_2Cl_2 (3x70 ml, 1x30 ml). The combined organic layers were washed with H_2O (3x80 ml), dried over Na_2SO_4 and evaporated. The residue (410 mg slightly brown foam) was converted into the hydrochloride salt in the usual way and crystallized from MeOH/diethyl ether to give 390 mg (83%) of the title compound 9 as slightly pink crystals. An analytic sample was obtained by recrystallization of a small portion of this material from MeOH/diethyl ether. M.p. 257-260°C (dec.). IR (KBr): 3460 (˙NH, NH, OH) cm^{-1}. CI-MS: m/z 493 ($M^{\cdot}$+1). ^{1}H-NMR (DMSO-d_6) δ 11.30, 9.20 and 9.05 (3 S, ˙NH, NH, OH), 7.25 (m, 7 arom. H), 7.10 (t, J=8.2 Hz, 1 arom. H), 6.96 (t, J=8.2 Hz, 1 arom. H), 6.59 (dd, J= 8.2, 8.2 Hz, 2 arom. H), 3.32 (s, OCH_3), 1.87 (s, CH_3-C(5)). Analysis calculated for

$C_{32}H_{32}N_2O_3$. HCl. 3.7 MeOH (647.63): C 66.21, H 7.44, N 4.33; found: C 66.04, H 7.13, N 4.60.

Example 6

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'indolomorphinan Hydrochloride (compound 10).

A mixture of 14-O-methyl-5-methylnaltrexone (H.Schmidhammer et al., Helv. Chim. Acta Vol. 77: 1585-1589, 1994) (620 mg, 1.68 mmol), phenylhydrazine hydrochloride (365 mg, 2.52 mmol), and 7 ml of glacial acetic acid was refluxed for 17.5 h. After cooling, the reaction mixture was poured on ice, alkalized with NH_4OH and extracted with CH_2Cl_2 (3x70 ml, 1x20 ml). The combined organic layers were washed with H_2O (3x80 ml), dried over Na_2SO_4 and evaporated. The residue (1.11 g brown foam) was purified by column chromatography (silica gel 230-400 mesh, mobile phase CH_2Cl_2/MeOH 90:9). The corresponding fractions were combined and evaporated to afford a slightly yellow foam which was dissolved in MeOH and treated with ethereal HCl to yield 520 mg (65%) of the compound 10 as colorless crystals. For analyses a small sample was recrystallized from MeOH. M.p. >250°C (dec.). IR (KBr):3515 and 3220 (NH, NH, OH)cm^{-1}. CI-MS: m/z 443 (M^++1). ^{1}H-NMR (DMSO-d_6): δ 11.30, 9.12, 8.93 (3 s, NH, NH, OH), 7.34 (m, 2 arom. H), 7.09 (t, J=8.3 Hz, 1 arom. H), 6.95 (t, J=8.3 HZ, 1 arom. H), 6.63 (d, J=8.1 Hz, 1 arom. H), 6.56 (d, J=8.1 Hz, 1 arom. H), 3.24 (s, OCH_3), 1.87 (s, CH_3-C(5)). Analysis calculated for $C_{28}H_{30}N_2O_3$. HCl. 0.7 H_2O (491.67):C 68.41, H 6.64, N 5.70, Cl 7.21; found: C 68.52, H 6.86, N 5.65, Cl 7.48.

Example 7

Synthesis of 17-Allyl-6,7-dehydro-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2',3'-indolomorphinan. CH_3SO_3H (compound 15).

A mixture of 7,8-dihydro-5-methyl-14-n-propyloxycodeinone described in our copending application with priority from May 18, 1994) (9; 2.67 g, 7.19 mmol), $KHCO_3$ (3.6 g, 35.93 mmol), 1-chloroethyl chloroformate (4.73 ml, 43.12 mmol), and 35 ml of 1,2-dichloroethane was stirred under reflux for 3.5 h. After cooling, the inorganic material was filtered off and the filtrate evaporated. The residue (4.67 g of a yellowish oil of 17-(1-chloroethoxy)- carbonyl-4,5α-epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one (compound 11); pure by TLC) was not further purified and characterized. A solution of the compound 11 in MeOH was refluxed for 1 h and then evaporated. The residue (3.54 g slightly brown foam) was crystallized from 2.5 ml MeOH/2 ml diethyl ether to give 1.68 g (66%) of 4,5α-epoxy-3-methoxy-5-methyl-14-n-propyloxy-morphinan-6-one hydrochloride (compound 12). M.p. 186-188°C. IR (KBr): 3425 ($^+NH_2$), 1725 (CO)cm^{-1}. EI-MS: m/z 357 (M^+). ^{1}H-NMR (DMSO-d_6): σ 10.11 and 8.15 (2 broad s, $^+NH_2$), 6.83 (d, J=8.2 Hz, 1 arom. H), 6.74 (d, J=8.2 Hz, 1 arom. H), 3.78 (s, CH_3O), 1.48 (s, CH_3-C(5)), 0.95 (t, J=7.4 Hz, CH_3). Analysis calculated for $C_{21}H_{27}NO_4$. HCl. 0.6 MeOH (413.14): C 62.80, H 7.42, N 3.39, Cl 8.58; found: C 62.66, H 7.34, N 3.40, Cl 8.98. A mixture of the compound 12 (1.45 g, 3.68 mmol), allyl bromide (0.36 ml, 4.06 mmol), potassium carbonate (2.9 g, 20.8 mmol), and 10 ml of anhydrous N,N-dimethyl formamide was stirred at 80°C (bath temperature) for 1.5 h. The inorganic solid was filtered off and the filtrate evaporated to give 1.7 g of a yellowish oily residue. This residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The residue (1.375 g of a slightly yellow oil) was crystallized from

ethanol to yield 1.28 g (88%) of 17-allyl-4,5α-epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one (compound 13) as slightly yellow crystals. M.p. 122-124°C. IR(KBr): 1720 (CO)cm^{-1}. EI-MS: m/z 397 (M^+). ^{1}H-NMR ($CDCl_3$): δ 6.63 (d, J=8.3 Hz, 1 arom. H), 6.55 (d, J=8.3 Hz, 1 arom. H), 5.79 (m, 1 olef. H), 5.13 (m, 2 olef. H), 3.84 (s, OCH3), 1.60 (s, CH_3-C(5)), 1.00 (t, J=7.4 Hz, CH3). Analysis calculated for $C_{24}H_{31}NO_4$ (397.51): C 72.52, H 7.86, N 3.52; found: C 72.14, H 7.76, N 3.44. A 1 M solution of boron tribromide in CH_2Cl_2 (10.8 ml) was added to an ice-cooled solution of the compound 13 (577 mg, 1.45 mmol) in 75 ml of CH_2Cl_2 at once. After stirring at 0-5°C for 2 h, a mixture of 20 g ice and 4 ml of conc. NH_4OH was added. The resulting mixture was stirred at room temperature for 30 min and the extracted with CH_2Cl_2 (3x50 ml). The combined organic layers were washed with brine (70 ml), dried over Na_2SO_4 and evaporated. The residue (600 mg brownish foam) was converted into the hydrobromide salt in the usual way and crystallized from MeOH to afford 314 mg (47%) of 17-allyl-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxymorphinan-6-one hydrobromide (compound 14). M.p. 244-247°C (dec.). IR (KBr): 3441 and 3332 (NH, OH), 6.68 (d, J=8.2 Hz, 1 arom. H), 6.62 (d, J=8.2 Hz, 1 arom. H), 5.92 (m, 1 olef. H), 5.67 (m,2 olef. H), 1.49 (s, CH_3-C(5)), 0.96 (t, J=7.2 Hz, CH_3).

A mixture of the compound 14 (300 mg, 0.65 mmol), phenylhydrazine hydrochloride (187 mg, 1.29 mmol), and 30 ml of glacial acetic acid was refluxed for 7.5 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x60 ml). The combined organic layers were washed with H_2O (3x80 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated. The residue (325 mg brownish foam) was converted into the methane sulfonate in the usual way and recrystallized from MeOH/diethyl ether to yield

264 mg (74%) of the title compound 15. Recrystallization of a small portion of this material from ethanol afforded an analytical sample. M.p. >256°C. FAB-MS: m/z 457 (M^++1), ^{1}H-NMR (DMSO-d_6): δ 11.29, 9.17 and 8.45 (3 s, $^+$NH, NH, OH), 7.32 (d, J=8.2 Hz, 2 arom. H), 7.10 (t, J=8.2 Hz, 1 arom. H), 6.94 (t, J=8.2 Hz, 1 arom. H), 6.59 (s, 2 arom. H), 5.90 (m, 1 olef. H), 5.68 (m, 2 olef. H), 1.88 (s, CH_3-C(5)), 0,55 (t, J=7.3 Hz, CH_3). Analysis calculated for $C_{29}H_{32}N_2O_3H$. 0.5 H_2O (561.70): C 64.15, H 66.4, N 4.99, S 5.72; found: C 64.08, H 6.87, N 5.09, S 5.87.

Example 8

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2,3'-indolomorphinan. CH_3SO_3H (compound 18).

A mixture of 4,5α-epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one hydrochloride (compound 12 of Example 7) (1.46 g, 3.71 mmol), potassium carbonate (2.24 g, 16.24 mmol), cyclopropylmethyl chloride (0.43 ml, 4.44 mmol), and 15 ml of anhydrous N,N-dimethyl formamide was stirred at 85°C (bath temperature) for 36 h. The inorganic solid was filtered off and the filtrate evaporated. A solution of the residue in 30 ml of CH_2Cl_2 was washed with H_2O (3x30 ml), dried over Na_2SO_4 and evaporated. The residue (1,69 g orange-yellow oil) was dissolved in diethyl ether and treated with ethereal HCl to give 920 mg (55%) of 17-(cyclopropylmethyl)-4,5α-epoxy-3-methoxy-5-methyl-14-n-propyloxymorphinan-6-one hydrochloride (compound 16) as colorless powder. M.p. 156-158°C. IR (KBr): 3400 ($^+$NH), 1723 (CO) cm^{-1}. CI-MS: m/z 412 (M^++1). ^{1}H-NMR (DMSO-d_6): δ 8.57 (s, $^+$NH), 6,85 (d, J=8.2 Hz, 1 arom. H), 6.75 (d, J=8.2 Hz, 1 arom. H), 3.79 (s, OCH_3), 1.51 (s, CH_3-C(5)), 0.97 (t, J=7.4 Hz, CH_3). Analysis

calculated for $C_{25}H_{33}NO_4$. HCl. 0.6 H_2O (458.81): C 65.45, H 7.73, N 3.05, Cl 7.73; found: C 65.45, H 7.85, N 3.08, Cl 7.84.

A 1 M solution of boron tribromide in CH_2Cl_2 (7.3 ml) was added at once to an ice-cooled solution of the compound 16 (480 mg, 0.97 mmol) in 50 ml of CH_2Cl_2. After 50 min stirring at 0-5°C, a mixture of 13 g ice and 3 ml conc. NH_4OH was added. The resulting mixture was stirred at room temperature for 30 min and the extracted with CH_2Cl_2 (3x30 ml). The combined organic layers were washed with brine (45 ml), dried over Na_2SO_4 and evaporated. The residue (204 mg slightly brown foam) was treated with 0.5 ml hot MeOH to afford 302 mg (55%) of 17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxymorphinan-6-one (compound 17). M.p. 184-186°C. IR (KBr): 3390 (OH), 1720 (CO)cm^{-1}. CI-MS: m/z 397 (M^++1). ^{1}H-NMR ($CDCl_3$): δ10.24 (broad s, OH), 6.73 (d, J=8.2 Hz, 1 arom. H), 6.65 (d, J=8.2 Hz, 1 arom. H)1.62 (s, CH_3-C(5)), 1.00 (t,J=7.3 Hz, CH3). Analysis calculated for $C_{24}H_{31}NO_4$. 0.6 MeOH (416.74): C 70.90, H 8.08, N 3.36; found: C 70.76, H 7.73, N 3.52.

A mixture of compound 17 (230 mg, 0.58 mmol), phenylhydrazine hydrochloride (142 mg, 0.98 mmol), and 23 ml of glacial acetic acid was refluxed for 3.5 h. After cooling, the reaction mixture was poured on ice, alkalized with con. NH_4OH and extracted with CH_2Cl_2 (3x40 ml). The combined organic layers were washed with H_2O 2x50 ml) and brine (50 ml), dried and evaporated. The residue (262 mg yellow-brown foam) was converted in the usual way into the methane sulfonate and crystallized from MeOH/diethyl ether to yield 204 mg (62%) of the compound 18. M.p. 295-298 (dec.) FAB-MS: m/z 471 (M^++1). ^{1}H-NMR (DMSO-d_6) δ 11.27, 9.12 and 8.46 (3s, $^+$NH, NH, OH), 7.14 (m, 4 arom. H), 6.59 (s, 2 arom. H),

1.90 (s, CH3-C(5)), 0.67 (t, J=7.3 Hz, CH_3) Analysis calculated for $C_{30}H_{34}N_2O_3 \cdot CH_3SO_3H \cdot 1.5\ H_2O$ (584.74): C 62.71, H 6.96, N 4.72, S 5.40; found: C 62.67, H 6.96, N 4.79, S 5.40.

Examples 9-24, and 28-30 illustrate further compounds, which can be prepared according to one of the methods described above.

Example 9

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-3-(methoxymethoxy)-6,7-2',3'-benzo[b]furanomorphinan (compound 19).

M.p.129-130°C. 1H-NMR ($CDCl_3$): δ 7.45 (d, J = 8.3 Hz, 1 arom. H), 7,37 (d, J = 8.3 Hz, 1 arom. H), 7.25 (m, 1 arom. H), 7.16 (m, 1 arom.), 6.86 (d, J = 8.3 Hz, 1 arom. H), 6.60 (d, J = 8.3 Hz, 1 arom. H), 5.63 (s, H-C(5)), 5.17 and 5.06 (2 d, J = 6.6, 6.6 Hz, OCH_2O), 3.42 (s, CH_3O).

Example 10

17-Cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-14-hydroxy-3-(methoxymethoxy)-6,7-2',3'-(N-methoxymethylindolo)morphinan (compound 20).

^{1}H NMR ($CDCl_3$): δ 7.44 (m, 2 arom. H), 7.20 (m, 1 arom. H), 7.07 (m, 1 arom. H), 6.82 (d,J = 8 Hz, 1 arom. H), 6.58 (J = 8 Hz), 5.81 (s, H-C(5)), 5.79 and 5.50 (2 d, J = 10.8, 10.8 Hz, NCH_2O), 5.12 and 5.50 (2 d, J = 6.4, 6.4 Hz, OCH_2O), 3,41 and 3.33 (2 s, 2 CH_3O).

Example 11

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzyloxy)-4,5α-epoxy-14-3-(methoxymethoxy)-6,7-2',3'-benzo[b]furanomorphinan (compound 21).

M.p. 180-182 °C. 1H NMR ($CDCl_3$): δ 7.41 (d, J = 8.3 Hz, 1 arom. H), 7.33 (d, J = 8.3 Hz, 1 arom. H), 7.23 (m, 1 arom. H) 7.14 (m, 2 arom. H), 7.03 and 7.01 (2 d, J = 7.3, 7.3 Hz), 6.84 (d, J, 8.3 Hz, 1 arom. H) 6.59 (d, J = 8.3 Hz, 1 arom. H), 5.56 (s, H-C(5)), 5.32 and 4.68 (2 d, J = 8.7, 8.7 Hz, OCH_2Ar), 5.16 and 5.05 (2 d, J = 6.6, 6.6 Hz, OCH_2O), 3.41 (s, CH_3O).

Example 12

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzyloxy)-4,5α-epoxy-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan (compound 22).

M.p. 193-195 °C (dec). 1H NMR ($CDCl_3$): δ 7.42 (d, J = 8.3 Hz, 1 arom. H), 7.33 (d, J = 8 Hz, 1 arom. H), 7.24 (m, 1 arom. H) 7.14 (m, 2 arom. H), 7.03 and 7.01 (2 d, J = 7.3 Hz, 1 arom. H), 6.64 (d, J, 8.1 Hz, 1 arom. H) 6.56 (d, J = 8.1 Hz, 1 arom. H), 5.58 (s, H-C(5)), 5.32 and 4.68 (2 d, J = 8.6 Hz, OCH_2 Ar).

Example 13

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-14-(3'-nitrobenzyloxy)-6,7-2',3'-benzo[b]furanomorphinan (compound 23).

^{1}H NMR ($CDCl_3$): δ 8.25 (s, 1 arom. H), 7.28 (m, 4 arom. H), 7.15 (m, 1 arom. H) 6.87 (d, J = 8.3 Hz, 1 arom. H), 6.62 (d, J = 8.3 Hz, 1 arom. H), 5.66 (s, H-C(5)), 5.17

and 5.07 (2 d, J =6.6 Hz, OCH_2O) 4.92 and 4.44 (2 d, J = 11.5 Hz, OCH_2Ar), 3.42 (s, CH_3O).

Example 14

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(3'-nitrobenzyloxy)-6,7-2',3'-benzo[b]furanomorphinan hydrochloride (compound 24).

M.p. > 230 °C (dec). 1H NMR (DMCO-d6): δ 9.40 (s, OH), 9.15 (broad s, ^+NH), 7.84 (s, 1 arom. H) 7.60 (d, J = 8.8 Hz, 1 arom. H), 7.53 (d, J = 7.6 Hz, 1 arom. H), 7.45 (d, J = 8 Hz, 1 arom. H) 7.23 (d, J = 7.6 Hz, 1 arom. H), 7.19 (d, J = 7.6 Hz, 1 arom. H), 6.98 (m, 1 arom. H) 6.88 (d, J = 7.6 Hz, 1 arom. H) 6.69 (d, J =8.3 Hz, 1 arom. H), 6.66 (d, J = 8.3 Hz, 1 arom. H), 6.03 (s, H-C(5)), 4.98 and 4.87 (2 d, J = 14, 14 Hz, OCH_2Ph).

Example 15

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-14-(2-naphtylmethoxy)-6,7-2'-3'-benzo[b]furanmorphinan (compound 25).

M.p. 198-201 °C. 1H NMR ($CDCl_3$): δ 7.72-7.08 (m, 11 arom. H), 6.86 (d, J = 8.3 Hz, 1 arom. H), 6.62 (d, J = 8.3 Hz, 1 arom. H), 5.68 (s, H-C(5)), 5.17 and 5.07 (2 d, J = 6.6, 6.6 Hz, OCH_2O), 5.01 and 4.57 (2 d, J = 11.2, 11.2 Hz, OCH_2Ar), 3,42 (s, CH_3O).

Example 16

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(2'-naphtylmethoxy)-6,7-2',3'-benzo[b]furanomorphinan hydrochloride (compound 26).

M.p. > 215 °C. 1H NMR (DMSO-d6): δ 9.42 (s, OH), 9.00 (broad s, $^{+}$NH), 7.68-6.85 (m, 11 arom. H), 6.71 (d, J = 8 Hz, 1 arom. H), 6.67 (d, J = 8 Hz, 1 arom. H), 6.04 (s, H-C(5)), 4.92 (s, OCH_2Ar).

Example 17

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-(2'-fluorobenzyloxy)-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanmorphinan (compound 27).

^{1}H NMR (DMSO-d6): δ 7.56 (d, J = 8 Hz, 1 arom. H), 7.49 (d, J = 8 Hz, 1 arom. H), 7.31 (m, 1 arom. H), 7.21 (m, 1 arom . H), 6.81 (d, J = 8.4 Hz, 1 arom. H), 6.67 (d, J = 8.4 Hz), 5.72 (s, H-C(5)), 5.06 and 5.01 (2 d, J = 6.4, 6.4 Hz, OCH_2O), 4.89 and 4.57 (2 d, J = 11.6, 11.6 Hz, OCH_2 Ar), 3,33 (s, CH_3O).

Example 18

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-(2'-fluoro-benzyloxy)-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan Hydrochloride (compound 28).

M.p. > 215 °C. 1H NMR ($CDCl_3$): δ 9.45 (s, OH), 9.04 (broad s, $^{+}$NH), 7.54 (d, J = 8.4 Hz, 1 arom. H) 7.31-6.73 (m, 7 arom. H), 6.71 (d, J = 8.2 Hz, 1 arom. H), 6.66 (d, J = 8.2 Hz, 1 arom. H), 5.98 (s, H-C(5)), 4.81 and 4.84 (2 d, J = 12 Hz, OCH_2 Ar).

Example 19

14-Cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanomorphinan (compound 29).

M.p. 156-159 °C. 1H NMR ($CDCl_3$): δ 7.47 (d, J = 8 Hz, 1 arom. H), 7.33 (d, J = 8 Hz, 1 arom. H), 7.28-7.07 (m, 7 arom. H), 6.84 (d, J = 8.4 Hz, 1 arom. H), 6.59 (d, J = 8.4 Hz, 1 arom . H), 6.38 (d, J = 16 Hz, 1 olef. H), 6.13 (m, 1 olef. H), 5.68 (s, H-C(5)), 5.16 and 5.06 (2 d, J = 6.4, 6.4 Hz, OCH_2O), 4.46 and 4.11 (2 m,OCH_2Ar), 3,42 (s, CH_3O).

Example 20

14-Cinnamyloxy-17-cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7-2'-3'-benzo[b]furanomorphinan Salicylate (compound 30).

^1H NMR ($CDCl_3$): δ 7.94 (d, J = 8 Hz, 1 arom. H), 7.35 (d, J = 8 Hz, 1 arom. H), 7.30-6.73 (m, 12 arom. H), 6.56 (d, J = 8 Hz, 1 arom. H), 5.96 (s, 2 olef. H), 5.55 (s, H-C(5)), 4.33-4.02 (m, OCH_2Ar).

Example 21

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-methoxy-3-(methoxymethoxy)-6,7-2'-3'-benzo[b]furanomorphinan (compound 31).

^1H NMR (DMSO-d6): δ 7.7.56 (d, J = 8 Hz, 1 arom. H), 7.52 (d, J = 8 Hz, 1 arom. H), 7.32 (dd, J = 8, 8 Hz, 1 arom. H), 5.64 (s, H-C(5)), 5.05 and 5.00 (2 d, J = 6.4, 6.4 Hz, OCH_2O), 3.32 (CH_3O).

Example 22

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-6,7-2′-3′-benzo[b]furanomorphinan hydrochloride (compound 32).

M.p. > 240 °C. ^{1}H NMR (DMSO-d6): δ 9.47 (s, OH), 9.17 (broad s, $^+$NH), 7.61 (d, J = 8 Hz, 1 arom. H), 7.53 (d, J = 8 Hz, 1 arom. H), 7.36 (dd, J = 8, 8 Hz, 1 arom. H), 7.27 (dd, J = 8, 8 Hz, 1 arom. H), 6.72 (d, J = 8.4 Hz, 1 arom. H), 6.65 (d, J = 8.4 Hz, 1 arom. H), 5.90 (s, H-C(5)), 3.35 (s, CH_3O).

Example 23

17-(Cyclopropylmethyl)-14-(2′-chlorobenzyloxy)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-6,7-2′-3′-(N-methoxymethylindolo)morphinan (compound 33).

^{1}H NMR ($CDCl_3$): δ 7.56 (m, 1 arom. H), 7.44 (m, 1 arom. H), 7.37-7.17 (m, 3 arom . H), 7.01 (m, 1 arom. H), 6.91 (m, 1 arom. H), 6.83 (d, J = 8.2 Hz, 1 arom. H), 6.59 (dd, J = 8.2, 8.2 Hz, 1 arom. H), 5.90 (s, H-C(5)), 5.82 and 5.55 (2 d, J = 11.2, 11.2 Hz, NCH_2O), 5.13 and 5.03 (2 d, J = 6.4, 6.4 Hz, OCH_2O), 4.98 and 4.56 (2 d, J = 13, 13 Hz, OCH_2Ar), 3.40 and 3.26 (2 s, 2 CH_3O).

Example 24

17-(Cyclopropylmethyl)-14-(2'-chlorobenzyloxy)-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7-2'-3'-indolomorphinan hydrochloride (compound 34).

M.p. > 250 °C (dec). 1H NMR (DMSO-d6): δ 11.38 (s, NH), 9.38 (s, OH), 8.76 (broad s, $^{+}$NH), 7.34-6.85 (m, 8 arom. H), 6.72 (d, J = 8 Hz, 1 arom. H), 6.64 (d, J = 8 Hz, 1 arom. H), 5.93 (s, H-C(5)), 4.80 and 4.67 (2 d, J = 13, 13 Hz, OCH_2Ar).

Example 25

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-3,14-dimethoxy-4,5α-epoxy-6,7-2'-3'-benzo[b]furanomorphinan (compound 35).

Sodium hydride (144 mg, 6 mmol; obtained from 240 mg of 60% sodium hydride dispersion in oil by washings with n-hexane) was added to a solution of naltriben methanesulfonate (P.S. Portoguese et al., J. Med. Chem., Vol. 34: 1715-1720, 1991) 500 mg, 0.97 mmol) in 10 ml of anhydrous N,N-dimethyl-formamide at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and then at room temperature for another 30 min. After cooling to 0 °C, dimethyl sulfate (380 µl, 4 mmol) was added and stirring was continued at first at 0 °C for 30 min and then at room temperature for 3 h. Excess sodium hydride was destroyed by addition of MeOH and H_2O. The resulting mixture was extracted with ethyl acetate (3 x 40 ml), the combined organic layers were washed with H_2O (2 x 30 ml) and brine (2 x 30 ml), dried over Na_2SO_4 and evaporated to give a crystalline residue which was recrystallized from MeOH to afford 320 mg (74 %) of compound 35. M.p. 221-224 °C (dec.). 1H NMR ($CDCl_3$): δ 7.47-7.14 (m, 4 arom. H), 6.64 (d, J =8.4 Hz, 1 arom.

H), 6.59 (d, J = 8.4 Hz, 1 arom . H), 5.62 (s, H-C(5)), 3.78 (s, CH_3O-C(3)), 3.31 (s, CH_3O-C(14)).

Example 26

Synthesis of 17-Cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-14-hydroxy-6,7-2',3'-benzo[b]furanomorphinan (compound 36).

A mixture of 3-deoxyonaltrexone (R. Krassnig and H. Schmidhammer, Heterocycles, Vol. 38: 877-881, 1994) (1,3 g, 3.99 mmol), O-phenylhydroxylamine hydrochloride (750 mg, 5.15 mmol), methanesulfonic acid (0.75 ml, 11.55 mmol), and ethanol (30 ml) was refluxed for 20 h. After cooling, the mixture was diluted with H_2O, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (4 x 40 ml). The combined organic layers were washed with H_2O (2 x 30 ml) and brine (30 ml), dried over Na_2SO_4 and evaporated to give a brownish oil which was crystallized form MeOH to yield 1.1 mg (69 %) of compound 36. M.p. > 260 °C. ^{1}H NMR ($CDCl_3$): δ 7.45 (d, J = 8 Hz, 1 arom. H), 7.37 (d, J = 8 Hz, 1 arom. H), 7.26-7.13 (m, 2 arom. H), 7.01 (dd, J = 7.8, 7.8 Hz, 1 arom. H), 6.67 (d, J = 7.8 Hz, 1 arom. H), 6.59 (d, J = 7.8 Hz, 1 arom. H), 5.59 (s, H-C(5)), 5.00 (broad s, OH).

Example 27

Synthesis of 17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-6,7-2'-3'-indolomorphinan hydrochloride (compound 37).

A mixture of 3-deoxyonaltrexone (R. Krassnig and H. Schmidhammer, Heterocycles, Vol. 38: 877-881, 1994) (1,5 g, 4.6 mmol), phenylhydrazine hydrochloride (1.0 mg, 6.9 mmol), 1M HCl in ether (5 ml), and methanol (20 ml)

was stirred at room temperature for 3 days. After concentration to ca. half of the original volume in vacuo, the solution was refrigerated overnight. The colorless crystals formed were collcted to yield 1.54 g (77 %) of compound 37. M.p. > 240 °C (dec.). 1H NMR (DMSO-d6): δ 11.37 (s, NH), 9.01 (broad s, $^{+}$NH), 7.36-6.94 (m, 5 arom. H), 6.78 (d, J = 7.8 Hz, 1 arom. H), 6.59 (d, J = 7.8 Hz, 1 arom. H), 6.55 (s, OH).

Example 28

17(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(3'-chlorobenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan, hydrochloride (compound 39).

^{1}H NMR (DMSO-d6): δ 9.40 (s, OH), 8.59 (broad s, +NH), 7.53-6.90 (m, 8 arom. H), 6.65 (s, 2 arom. H), 6.03 (s, H-C(5)), 4.74 and 4.62 (2 d, J=13.6, 13.6 Hz, OCH_2(3'-ClPh)). Analysis calculated for $C_{33}H_{30}ClNO_4$. HCl. 1.5 H_2O: C 65.67, H 5.68, N 2.32; found: C 65.31, H 5.37, N 2.33.

Example 29

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(2'-chlorobenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan Hydrochloride (compound 41).

M.p. > 220°C. ^{1}H NMR (DMSO-d6): δ 9.40 (s, OH), 8.59 (broad s, +NH), 7.56-6.90 (m, 8 arom. H), 6.66 (m, 2 arom. H), 6.03 (s, H-C(5)), 4.74 (s, OCH_2(2-ClPh)). Analysis calculated for $C_{33}H_{30}ClNO_4$. Hcl. 1.5 H_2O: C 65.67, H 5.68, N, 2.32. Found: C 65.72, H 5.48, N 2.25.

Example 30

14-Allyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-1'-allyl-6,7-2',3'-indolomorphinan hydrochloride (compound 42).

NMR of the free base (colorless oil)

^{1}H NMR ($CDCl_3$): δ 7.40 (d, J = 8.4 Hz, 1 arom. H), 7.24 (m, 1 arom. H), 7.15 (m, 1 arom. H), 7.03 (m, 1 arom. H), 6.57 (d, J = 8.4 Hz, 1 arom. H), 6.50 (d, J = 8.4 Hz, 1 arom. H), 6.08 (m, 1 olef. H), 5.76 (m, 1 olef. H), 5.72 (s, H-C(5)), 5.15-4.75 (m, 6 H, CH_2N,2 CH_2 = C), 4.24 and 3.92 (2 dd, J = 12.4, 4.8 Hz, CH_2O).

This free base was dissolved in ethyl ether and treated with HCl/ether solution HCl at 0°C. Isolation of the precipitate provided the title compound 42 as a solid.

Pharmaceutical preparations

For the preparation of a pharmaceutical formulation, the active ingredient may be formulated to an injection, capsule, tablet, suppository, solution or the like. Oral formulation and injection are preferably employed. The pharmaceutical formulation may comprise the δ-selective antagonist alone or may also comprise expedients such as stabilizers, buffering agents, diluents, isotonic agents, antiseptics and the like. The pharmaceutical formulation may contain the above described active ingredient in the amount of 1-95 % by weight, preferably 10-60 % by weight. The dose of the active ingredient may be appropriately selected depending on the objects of administration, administration route and conditions of the patients. The active ingredient may be administered in doses between 1 mg and 1 g per day in case of administration by injection and in doses between 10 mg and 5 g per day in case of oral administration. The preferred dose for injection is 20-500 mg per day.

Biological studies

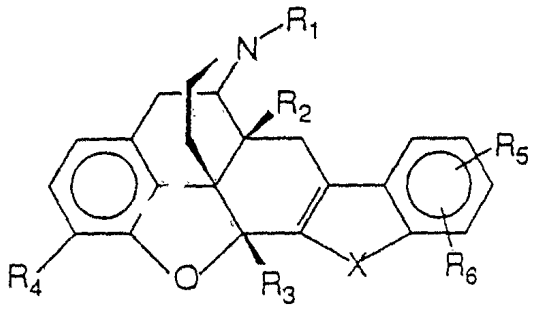
δ-Antagonism was assessed using the electrical stimulated guinea-pig ileum longitudinal muscle preparation (GPI; containing μ and κ opioid receptors) and mouse vas deferens preparation (MVD; containing μ, κ and δ opioid receptors) (H. Schmidhammer et al., J. Med. Chem., Vol. 32: 418-421, 1989; H Schmidhammer et al., J. Med. Chem., Vol. 33: 1200-1206, 1990). The activity of the compound 1 of the Examples for inhibiting the suppression of contraction of the organs by three receptor selective agonists (DAMGO, μ; Cl 977, κ; DPDPE, δ) was measured. The compound exhibited δ-selective opioid antagonism with very good μ/δ and κ/δ selectivity ratios.

Conclusion

The pharmacological studies of the novel morphinan derivatives of formula (I) of the present invention have shown that these compounds have selectivity for δ opioid receptors and are effective as opioid antagonists.

The claims defining the invention are as follows:

1. A compound according to the formula (I)



(I)

wherein

R_1 represents C_1-C_{10} alkenyl; C_4-C_{10} cycloalkylalkyl wherein the cycloalkyl is C_3-C_6 cycloalkyl and the alkyl is C_1-C_4 alkyl; C_4-C_{10} cycloalkenylalkyl wherein the cycloalkenyl is C_3-C_6 cycloalkenyl and the alkyl is C_1-C_4 alkyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_8-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_2-C_6 alkenyl;

R_2 represents hydrogen, hydroxy, C_1-C_6 alkoxy; C_1-C_6 alkenyloxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_7-C_{16} arylalkenyloxy wherein the aryl is C_6-C_{10} aryl and the alkenyloxy is C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy; C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy;

R_3 represents hydrogen, C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; hydroxy(C_1-C_6)alkyl; alkoxyalkyl

AUSTRALIAN PATENT OFFICE

wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2H; CO_2(C_1-C_6 alkyl);

R_4 is hydrogen, hydroxy; C_1-C_6 alkoxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy; C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy; C_2-C_{10} alkyloxyalkoxy wherein alkyloxy is C_1-C_4 alkyloxy and alkoxy is C_1-C_6 alkoxy;

R_5 and R_6 each independently represent hydrogen; OH; C_1-C_6 alkoxy; C_1-C_6 alkyl; hydroxyalkyl wherein the alkyl is C_1-C_6 alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO_2H; CO_2(C_1-C_6 alkyl); $CONH_2$; CONH(C_1-C_6 alkyl); CON(C_1-C_6 alkyl)$_2$; amino; C_1-C_6 monoalkyl amino; C_1-C_6 dialkyl amino; C_5-C_6 cycloalkyl-amino; SH; SO_3H; SO_3(C_1-C_6 alkyl); SO_2(C_1-C_6 alkyl); SO_2NH_2; SO_2NH(C_1-C_6alkyl); SO_2NH (C_7-C_{20} arylalkyl); SO(C_1-C_6 alkyl); or R_5 and R_6 together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C_1-C_6 alkyl; trifluoromethyl; C_1-C_6 alkoxy, CO_2H, CO(C_1-C_6 alkyl), amino, C_1-C_6 monoalkylamino, C_1-C_6 dialkylamino, SH; SO_3H;SO_3 (C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), SO(C_1-C_6 alkyl), and

X represents oxygen; sulfur; CH = CH or NR_9 wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl;

AUSTRALIAN PATENT OFFICE

and wherein

aryl is unsubstituted or mono- or di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CO_2H, CO_2 (C_1-C_3)alkyl, $CONH_2$, $CONH(C_1$-C_3 alkyl), $CON(C_1$-C_3 alkyl), $CO(C_1$-C_3 alkyl), amino, (C_1-C_3 monoalkyl)amino, (C_1-C_3 dialkyl)amino, C_5-C_6 cyhloalkylamino (C_1-C_3 alkanoyl)amino, SH, SO_3H, SO_3 (C_1-C_3 alkyl), SO_2 (C_1-C_3 alkyl), $SO(C_1$-C_3 alkyl), C_1-C_3 alkylthio or C_1-C_3 alkanoylthio; and

with the following provisos:

(i) when R_2 is hydroxy, R_3 may only be hydrogen when R_4 is hydrogen, OCH_2OCH_3, $OCH_2OC_2H_5$ or $OC(Ph)_3$; or

(ii) R_3 may only be hydrogen when R_4 is C_2-C_{10} alkyloxyalkoxy, and/or when R_2 is C_7-C_{16} arylalkenyloxy or C_1-C_6 alkenyloxy;

as well as pharmacologically acceptable salts thereof.

2. A compound or pharmacologically acceptable salt according to claim 1, wherein R_1 is selected from allyl, cinnamyl, cyclopropylmethyl or cyclobutylmethyl;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy, benzyloxy substituted in the aromatic ring with F, Cl, NO_2, CN, CF_3, CH_3 or OCH_3; allyloxy, cinnamyloxy or 3-phenylpropyloxy;

R_3 is selected from hydrogen, methyl, ethyl, benzyl or allyl;

AUSTRALIAN PATENT OFFICE

R_4 is selected from hydroxy, methoxy, methoxymethoxy or acetyloxy;

R_5 and R_6 are each and independently selected from hydrogen; nitro; cyano; chloro, fluoro, bromo trifluoromethyl; CO_2H; CO_2 CH_3; $CONH_2$; CONH CH_3; SH; SO_2NH_2; $N(CH_3)_2$; SO_2CH_3;

X is selected from oxygen; NH or N CH_3, N-benzyl, N-allyl.

3. A compound according to claim 1, in form of a pharmaceutically acceptable salt.

4. A compound according to claim 1, wherein the salt is an inorganic salt.

5. A compound according to claim 1, wherein the salt is an organic salt.

6. A compound or pharmacologically acceptable salt according to claim 1, being :

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2´,3´-indolomorphinan x HCl; or

17-allyl-6,7-dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2´,3´-indolomorphinan x HCl; or

6,7-dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-17-(2-phenyl)ethyl-6,7-2´,3´-indolomorphinan x HCl; or

17-allyl-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2´,3´-indolomorphinan x HCl; or

AUSTRALIAN PATENT OFFICE

6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-17-(2-phenyl)ethyl-6,7-2´,3´-indolomorphinan x HCl; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2´,3´-indolomorphinan x HCl; or

17-allyl-6,7-dehydro-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2´,3´-indolomorphinan x CH_3SO_3H; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2´,3´-indolomorphinan x CH_3SO_3H; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-3-(methoxymethoxy)-6,7-2´,3´-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-3-(methoxymethoxy)-6,7-2´,3´-(N-methoxymethylindolo)morphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-14-(2´,6´-dichlorobenzyloxy)-4,5α-epoxy-3-(methoxymethoxy)-6,7-2´,3´-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-14-(2´,6´-dichlorobenzyloxy)-4,5α-epoxy-3-hydroxy-6,7-2´,3´-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-14-(3´-nitrobenzyloxy)-6,7-2´,3´-benzo[b]furanomorphinan; or

AUSTRALIAN PATENT OFFICE

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(3′-nitrobenzyloxy)-6,7-2′,3′-benzo[b]furanomorphinan x HCl; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-14-(2′-naphthylmethoxy)-6,7-2′,3′-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(2′-naphtylmethoxy)-6,7-2′,3′-benzo[b]furanomorphinan x HCl; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-(2′-fluorobenzyloxy)-3-(methoxymethoxy)- 6,7-2′,3′-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-(2′-fluorobenzyloxy)-3-hydroxy-6,7-2′,3′-benzo[b]furanomorphinan x HCl; or

14-cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-6,7-2′,3′-benzo[b]furanomorphinan; or

14-cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7-2′,3′-benzo[b]furanomorphinan salicylate; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-methoxy-3-(methoxymethoxy)-6,7-2′,3′-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-14-(2′-chlorobenzyloxy)-6,7-dehydro-4,5α-epoxy-3-(methoxymethoxy)-6,7-2′,3′-(N-methoxymethylindolo)morphinan; or

17-(cyclopropylmethyl)-14-(2′-chlorobenzyloxy)-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7-2′,3′-indolomorphinan x HCl; or

30 AUSTRALIAN PATENT OFFICE ML

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-6,7-2´,3´-benzo[b]furanomorphinan; or

17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-6,7-2´,3´-indolomorphinan x HCl; or

17-(cyclopropypmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(3´-chlorobenzyloxy)-6,7-2´,3´- benzo[b]furanomorphinan x HCl; or

17-(cyclopropypmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(2´-chlorobenzyloxy)-6,7-2´,3´- benzo[b]furanomorphinan x HCl; or

14-allyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-1´-allyl-6,7-2´,3´-indolomorphinan x HCl.

7. A compound or pharmacologically acceptable salt according to claim 1, which compound or salt is:

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5-methyl-6,7-2',3'-indolomorphinan hydrochloride; or

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'indolomorphinan hydrochloride; or

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-5-methyl-14-n-propyloxy-6,7-2,3'-indolomorphinan CH_3SO_3H; or

17-(Cyclopropylmethyl)-6,7-dehydro-14-(2',6'-dichlorobenzyloxy)-4,5α-epoxy-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan; or

AUSTRALIAN PATENT OFFICE

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(3'-nitrobenzyloxy)-6,7-2',3'-benzo[b]furanomorphinan hydrochloride; or

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(2'-naphtylmethoxy)-6,7-2',3'-benzo[b]furanomorphinan hydrochloride; or

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-(2'-fluoro benzyloxy)-3-hydroxy-6,7-2',3'-benzo[b]furanomorphinan hydrochloride; or

14-Cinnamyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7-2'-3'-benzo[b]furanomorphinan salicylate; or

17-(Cyclopropylmethyl)-14-(2'-chlorobenzyloxy)-6,7-dehydro-4,5α-epoxy-3-hydroxy-6,7-2'-3'-indolomorphinan hydrochloride; or

17-Cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-14-hydroxy-6,7-2',3'-benzo[b]furanomorphinan; or

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-14-hydroxy-6,7-2'-3'-indolomorphinan hydrochloride; or

17(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(3'-chlorobenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan hydrochloride; or

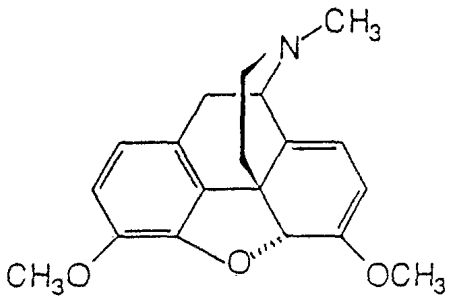
17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-14-(2'-chlorobenzyloxy)-6,7,2',3'-benzo[b]furanomorphinan hydrochloride; or

14-Allyloxy-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3-hydroxy-1'-allyl-6,7-2',3'-indolomorphinan hydrochloride.

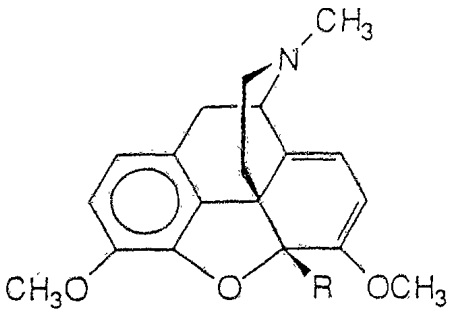
AUSTRALIAN PATENT OFFICE

8. A process for the preparation of a compound of the formula I according to claim 1, or a pharmacologically acceptable salt thereof, wherein:

i) thebaine of the formula



is treated with dialkylsulfates, fluorosulfonic acid alkyl esters, alkylsulfonic acid alkyl esters, arylsulfonic acid alkylesters, alkyl halides, aralkyl halides, alkylsulfonic acid aralkyl esters, arylsulfonic acid aralkyl esters, arylalkenyl halides, or chloroformates, giving compounds according to formula (II)

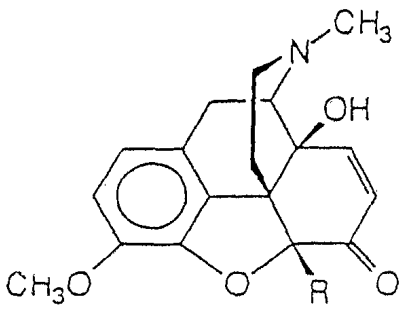


(II)

wherein R is C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} aralkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

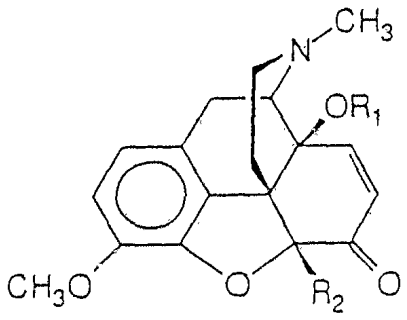
AUSTRALIAN PATENT OFFICE

ii) Compound (II) is reacted with performic acid or m-chloroperbenzoic acid at a temperature in the range 0-60 °C yielding



(III)

iii) Compound (III) is treated with dialkyl sulfates, alkyl halides, alkenyl halides, aralkyl halides, arylalkenyl halides, chloroformates, using a strong base giving compounds according to formula (IV)



(IV)

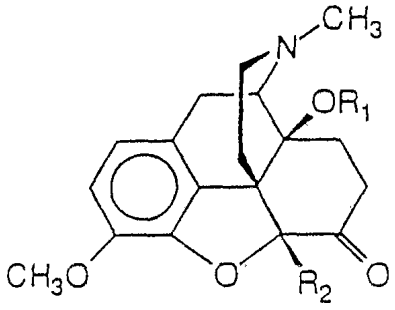
wherein

R_1 is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C1-C_6 alkenyl, C_1-C_6 alkanoyl, C_7-C_{20} arylalkanoyl wherein the aryl is C_6-C_{14} aryl and the alkyl is C_1-C6 alkyl, C_7-C_{20} arylalkenoyl wherein the aryl is C_6-C_{14} aryl and the alkyl is C_1-C_6 alkenoyl;

R_2 is C_1-C_6 alkyl; C_1-C_6 alkenyl C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

AUSTRALIAN PATENT OFFICE

iv) catalytic hydrogenation of compound (IV) yields compounds according to formula (V)

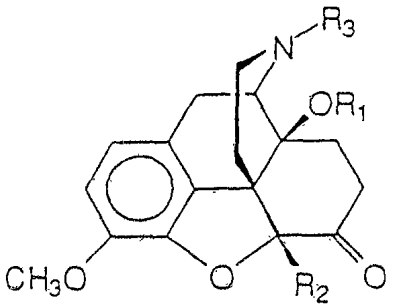


(V)

wherein

R_1 and R_2 are as defined above in formula (IV);

v) Compound (V) is *N*-demethylated, giving compounds according to formula (VI)



(VI)

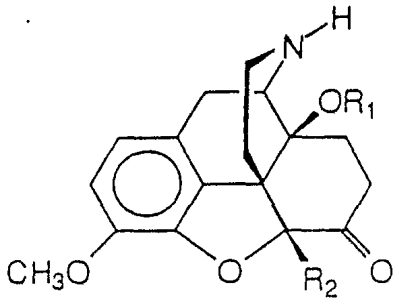
wherein

R_1 and R_2 are as defined above; and

R_3 is $CO_2CHClCH_3$, $CO_2CH{=}CH_2$, $CO_2CH_2CCl_3$, $CO_2CH_2CH_3$, CO_2Ph or CN;

vi) Compound (VI) is cleaved giving compounds according to formula (VII)

AUSTRALIAN PATENT OFFICE ML

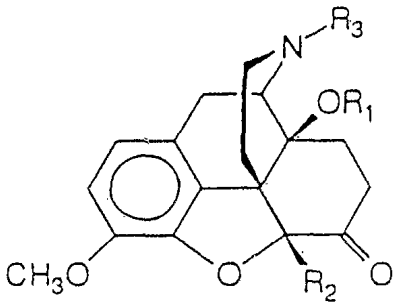


(VII)

wherein

R_1 and R_2 are as defined above in formula (V);

vii) Compounds (VII) are alkylated, yielding compounds according to formula (VIII)



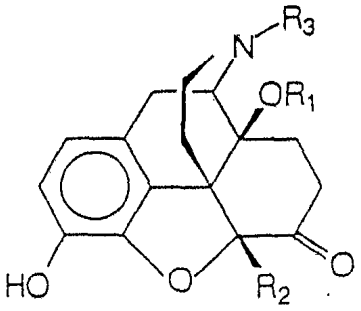
(VIII)

wherein R_1 and R_2 are as defined above in formula (V); and

R_3 represents C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_4-C_{10} cycloalkylalkyl wherein the cycloalkyl is C_3-C_6 cycloalkyl and the alkyl is C_1-C_4 alkyl; alkyl; C_4-C_{10} cycloalkylalkenyl wherein the cycloalkenyl is C_3-C_6 cycloalkenyl and the alkyl is C_1-C_4 alkyl;

viii) ether cleavage of compound (VIII) is performed, giving compounds according to formula (IX)

AUSTRALIAN PATENT OFFICE

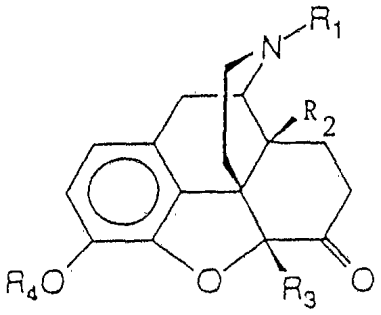


(IX)

wherein

R_1, R_2 and R_3 are as defined above;

ix) Compound (IX) is alkylated or acetylated, giving compounds according to formula (X)



(X)

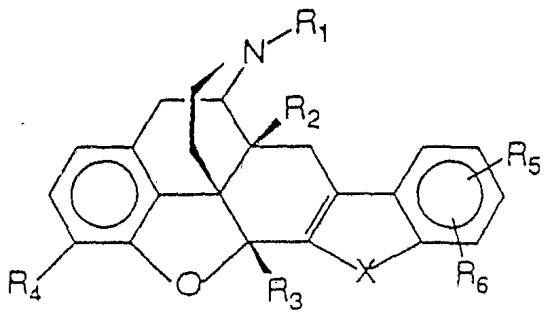
wherein

R_1, R_2 and R_3 are as defined in formula I of claim 1, excepting that R_2 may not be hydrogen or hydroxy, and that R_3 may not be hydrogen; and

R_4 is hydrogen, C_1-C_6 alkyl, C_7-C_{16} aralkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1C_6 alkanoyl; C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{14} aryl and the alkanoyl is C_1-C_6 alkanoyl, C_2-C_{10} alkyloxyalkyl wherein alkyloxy is C_1-C_4 alkyloxy and alkyl is C_1-C_6 alkyl,

x) Compound (IX) or (X) is reacted with phenylhydrazine or substituted phenylhydrazine giving compounds according to formula (I)

AUSTRALIAN PATENT OFFICE



(I)

wherein

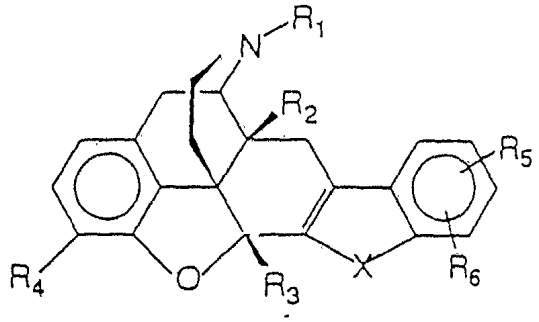
R_1, R_2, R_3 and R_4 are as defined in formula I of claim 1, excepting that R_2 may not be hydrogen or hydroxy, and that R_3 may not be hydrogen;

R_5 and R_6 each independently represent hydrogen; OH; C_1-C_6 alkoxy; C_1-C_6 alkyl; hydroxyalkyl wherein the alkyl is C1-C6 alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO_2H; $CO_2(C_1$-C_6 alkyl); $CONH_2$; $CONH(C_1$-C_6 alkyl); $CON(C_1$-C_6 alkyl)$_2$; amino; C_1-C_6 monoalkyl amino; C_1-C_6 dialkyl amino; C_5-C_6 cycloalkylamino; SH; SO_3H; $SO_3(C_1$-C_6 alkyl); $SO_2(C_1$-C_6 alkyl); SO_2NH_2; $SO_2NH(C_1$-C_6 alkyl); SO_2NH (C_7-C_{20} arylalkyl); $SO(C_1$-C_6 alkyl); or R_5 and R_6 together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C_1-C_6 alkyl; trifluoromethyl; C_1-C_6 alkoxy, CO_2H, $CO(C_1$-C_6 alkyl), amino, C_1-C_6 monoalkylamino, C_1-C_6 dialkylamino, SH; SO_3H; $SO_3(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), $SO(C_1$-C_6 alkyl), and

X represents NR_9 wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl,

AUSTRALIAN PATENT OFFICE

xi) Compound (IX) or (X) is reacted with O-phenylhydroxylamine or substituted O-phenylhydroxylamine, giving compounds according to formula (I)

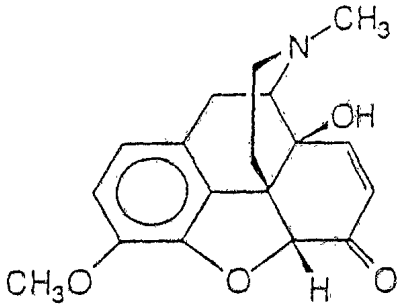


(I)

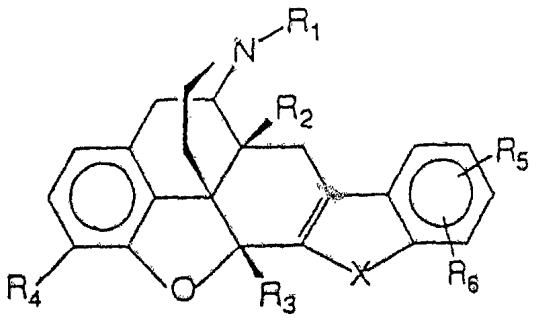
wherein

R_1, R_2, R_3, R_4, R_5 and R_6 are as defined in formula I of claim 1, excepting that R_2 may not be hydrogen or hydroxy, and that R_3 may not be hydrogen; and X is O;

xii) thebaine is converted to 14-hydroxy codeinone formula



which in turn is converted to compounds according to formula (I)



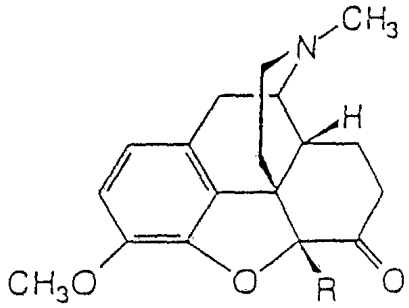
(I)

AUSTRALIAN PATENT OFFICE ML

wherein

R_3 is H and R_1, R_2, R_4, R_5, R_6 and X are as defined above, in essentially the same way (analogous to steps iii, iv, v, vi, vii, viii, ix, x and xi above) as described for the 5-substituted series of compounds;

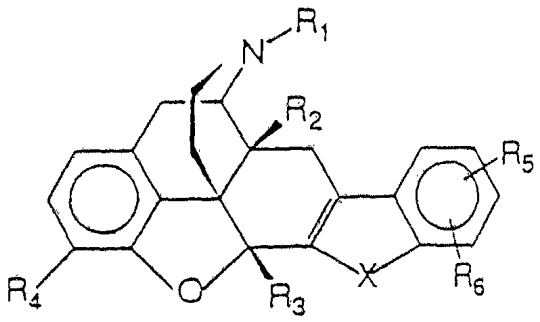
xiii) Compounds of the formula (II) wherein R is as defined above or hydrogen are reduced by catalytic hydrogenation followed by acid hydrolysis (s. Boden et al., J. Org. Chem., Vol. 47: 1347-1349, 1982) to give compounds of formula (XI)



(XI)

wherein R is as defined above in formula (II) or hydrogen,

which in turn is converted to compounds according to formula (I)



(I)

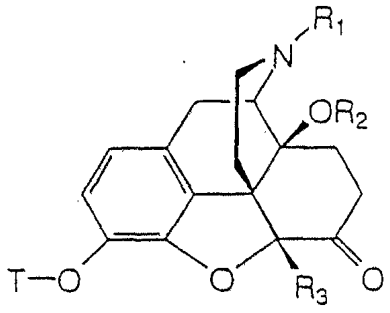
wherein

R_2 is H, and R_1, R_3, R_4, R_5, R_6 and X are as defined above,

AUSTRALIAN PATENT OFFICE ML

in essentially the same way (analogous to steps v, vi, vii, viii, ix, x and xi above) as described for the 14-substituted series of compounds;

xiv) Compounds of the formula (I) wherein R_4 is hydrogen are prepared from compounds of the formula (IX) by alkylation with 5-chloro-1-phenyl-1H-tetrazole, giving phenyltetrazolyl ethers of the formula (XII)

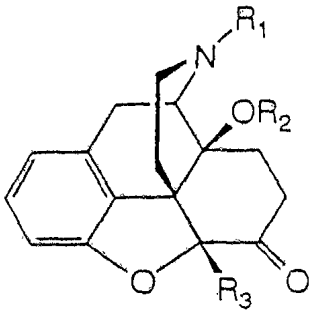


(XII)

wherein,

R_1, R_2 and R_3 are as defined in formula I of claim 1, and R_1 also can be CH_3, and T is phenyltetrazolyl;

xv) catalytic hydrogenation of compound (XII) affords compounds of the formula (XIII)



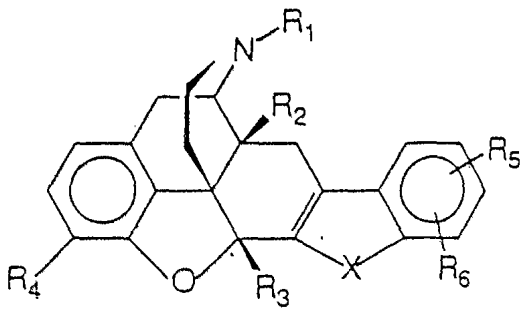
(XIII)

wherein

R_1, R_2 and R_3 are as defined above, or R_1 can also be CH_3, with the proviso that when R_3 is CH_3 the N-methyl group is removed and the nitrogen alkylated as described above;

AUSTRALIAN PATENT OFFICE

xvi) compound (XIII) is converted to compounds according to formula (I)

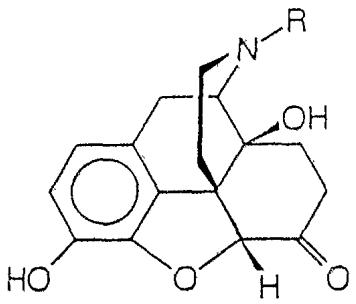


(I)

wherein

R_4 is hydrogen and R_1, R_2, R_3, R_5, R_6 and X are as defined above, in the same manner as described for 3-substituted derivatives above;

xvii) Compounds of formula (I) wherein R_1 represents allyl or cyclopropylmethyl and R_3 represents H are obtained starting either from naloxone (XIVa) or naltrexone (XIVa):



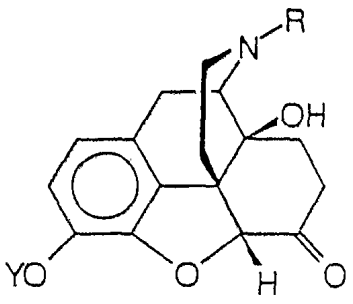
(XIV)

(XIVa): Naloxone - R is allyl

(XIVb): Naltrexone - R is cyclopropylmethyl,

wherein the 3-hydroxy group of compounds of formula (XIV) is protected by alkylation with benzyl bromide, methoxymethyl bromide, ethoxymethyl bromide or trityl chloride (triphenylmethyl chloride) in a solvent such as N,N-dimethyl formamide or dichloromethane in the presence of a base to yield compounds of formula (XV)

AUSTRALIAN PATENT OFFICE

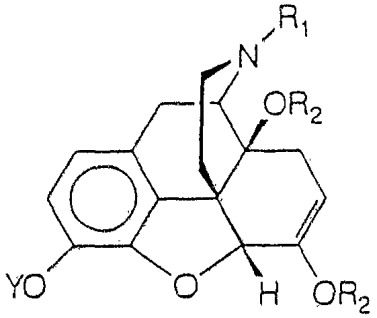


(XV)

wherein

R is allyl or cyclopropylmethyl and Y = CH_2Ph, CH_2OCH_3, $CH_2OC_2H_5$ or $C(Ph)_3$;

when said compounds are alkylated, alkenylated, cycloalkylalkylated, arylalkylated or arylalkenylated with dialkyl sulfates, alkyl halides, alkenyl halides, arylalkyl halides or arylalkenyl halides in solvents using a strong base such as sodium hydride, potassium hydride or sodium amide are formed 6-0,14-0-dialkylated compounds of formula (XVI)



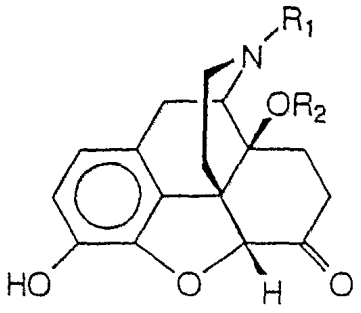
(XVI)

wherein

R_1 is allyl or cyclopropylmethyl; and

R_2 is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkoxy, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and alkenyl is C_1-C_6 alkenyl; and Y as defined above; said compounds, can be hydrolized in diluted acids like hydrochloric acid or sulfuric acid to afford compounds or formula (XVII)

AUSTRALIAN PATENT OFFICE



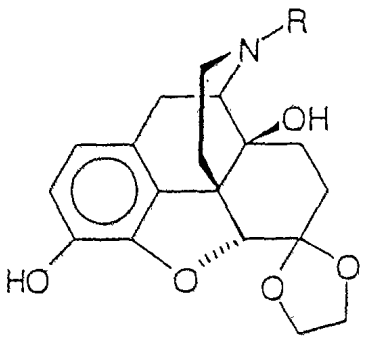
(XVII)

wherein

R_1 is allyl or cyclopropylmethyl; and

R_2 is as defined above (formula XVI);

xviii) the carbonyl group in 6-position of naloxone of the formula (XIVa) and naltrexone of the formula (XIVb), respectively, is protected at a temperature between 20 and 200 °C, giving ketals of the formula (XVIII)



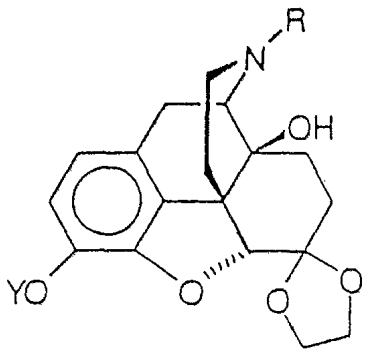
(XVIII)

wherein

R is allyl or cyclopropylmethyl;

xviii) the 3-hydroxy group in (XVIII) is protected by alkylation with benzyl bromide, methoxymethyl bromide, ethoxy methyl bromide or trityl chloride, giving compounds according to formula (XIX)

AUSTRALIAN PATENT OFFICE

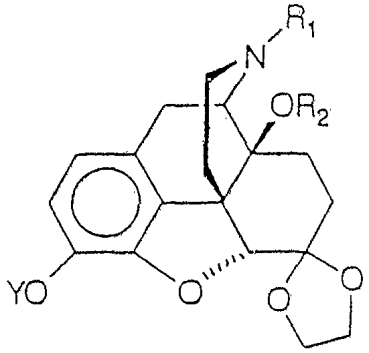


(XIX)

wherein

R is allyl or cyclopropylmethyl, and Y is as defined above;

xix) Compound (XIX) is alkylated, alkenylated, arylalkylated or arylalkenylated, giving compounds according to formula (XX)



(XX)

wherein

R_1 is allyl or cyclopropylmethyl, R_2 is as defined above in formula (XVI) and Y is also as defined above; or

xx) Compound (XX) is hydrolized giving compounds according to formula (XVII), which in turn is converted to compounds according to formula (I) wherein R_1 is allyl or cyclopropylmethyl, R_3 is H, exactly as described for the 5-substituted analogues.

9. A compound of the formula I according to claim 1, or a pharmacologically acceptable salt thereof, when obtained by the process according to claim 8.

AUSTRALIAN PATENT OFFICE

10. Use of a compound of the formula I or a pharmacologically acceptable salt thereof according to any one of claims 1 to 7 and 9, in the manufacture of a medicament.

11. Use of a compound or salt according to claim 10, wherein said medicament is formulated so as to be in a form suitable for the treatment of rheumatic diseases, in particular for the treatment of rheumatoid arthritis.

12. Use of a compound or salt according to claim 10, wherein said medicament is formulated so as to be in a form suitable for suppressing the rejection of transplants after organ transplantations.

13. Use of a compound or salt according to claim 10, wherein said medicament is formulated so as to be in a form suitable for the treatment of pain.

14. A pharmaceutical composition comprising a compound or a pharmacologically acceptable salt thereof according to any one of claims 1 to 7 and 9, as an active ingredient, together with a pharmaceutically acceptable carrier.

15. A method for the treatment of a subject suffering from a rheumatic disease, wherein an effective amount of a compound or a pharmacologically acceptable salt according to any one of claims 1 to 7 and 9, or a pharmaceutical composition according to claim 14, is administered to a subject suffering from a rheumatic disease.

AUSTRALIAN PATENT OFFICE

16. A method according to claim 15, wherein the rheumatic disease is rheumatoid arthritis.

17. A method for the treatment of a subject requiring suppression of rejection of transplants after organ transplantations, wherein an effective amount of a compound or a pharmacologically acceptable salt according to any one of claims 1 to 7 and 9, or a pharmaceutical composition according to claim 14, is administered to a subject requiring suppression of rejection of transplants after organ transplantations.

18. A method for the treatment of a subject suffering from pain, wherein an effective amount of a compound or a pharmacologically acceptable salt according to any one of claims 1 to 7 and 9, or a pharmaceutical composition according to claim 14, is administered to a subject suffering from pain.

DATED this 12th day of March 1998

ASTRA AKTIEBOLAG,
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

(Bruce Wellington)

A/PM/4380/8

AUSTRALIAN PATENT OFFICE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00503

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 489/09, C07D 491/18, A61K 31/485
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0456833 A1 (TORAY INDUSTRIES, INC.), 21 November 1991 (21.11.91), see especially table 2, test compounds no:s 11, 12 and 19 --	1-9,12-13, 16-17
X	J.Med.Chem., Volume 33, 1990, P.S. Portoghese et al, "Disign of Peptidomimetic & Opioid Receptor Antagonists Using the Message-Address Concept", page 1714 - page 1720, see especially compound 17 --	1-9,12-13, 16-17
X	J.Med.Chem., Volume 35, 1992, P.S. Portoghese et al, "Opioid Agonist and Antagonist Activities of Morphindoles Related to Naltrindole", page 4325 - page 4329, see especially compounds 7-9 --	1-9,12-13, 16-17

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 Sept 1995	08 -09- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00503

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0614898 A1 (TORAY INDUSTRIES, INC.), 14 Sept 1994 (14.09.94), see the whole document ---	1-9,12-13, 16-17
X	US 5225417 A (MICHAEL S. DAPPEN ET AL), 6 July 1993 (06.07.93), see the whole document ---	1-9,12-13, 16-17
X	Chemical Abstracts, Volume 119, No 9, 30 August 1993 (30.08.93), (Columbus, Ohio, USA), page 1096, THE ABSTRACT No 95503d, JP, 4342529, A, (Nagase, Hiroshi et al) 30 November 1992 (30.11.92) --- --------	1-9,12-13, 16-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00503

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14-15
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

31/07/95

International application No.
PCT/SE 95/00503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0456833	21/11/91	DE-D,T- 69017434	29/06/95
		KR-B- 9408032	01/09/94
		AT-T- 119039	15/03/95
		AU-B- 639053	15/07/93
		AU-A- 6876891	26/06/91
		ES-T- 2069100	01/05/95
		JP-A- 3223288	02/10/91
		US-A- 5332818	26/07/94
		WO-A- 9107966	13/06/91
EP-A1- 0614898	14/09/94	NONE	
US-A- 5225417	06/07/93	US-A- 5354863	11/10/94
JP-A- 4342529	30/11/92	NONE	