SYNTHESIS OF 9-AMINO-6,7-BENZOMORPHAN AS A POTENTIAL ANALGESIC

BY

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A THESIS SUBMITTED TO THE POSTGRADUATE SCHOOL, AHMADU BELLO UNIVERSITY, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICAL CHEMISTRY

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DECLARATION

I hereby certify that the work reported in this thesis was carried out by me under the supervision of Dr. S. A. Ansari and Dr. I. Abdu-Aguye of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria. The works of other investigators are acknowledged and referred to accordingly. I declare that no part of this thesis has been submitted elsewhere for a degree.

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CERTIFICATION

This thesis entitled 'SYNTHESIS OF 9-AMINO-6,7-BENZOMORPHAN AS A POTENTIAL ANALGESIC' by TERRUMUN AMOM TOR-ANYIIN meets the regulations governing the award of the degree of MASTER OF SCIENCE (M.Sc.) of Ahmadu Bello University, and is approved for its contribution to scientific knowledge and literary presentation.

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DEDICATION

To: Ukanmba,
Sedoo,
Torkaa,
Sewuese and
Serumun.

"For all you have done.....
For the love you have shown
in the life we are living.
I thank you with the whole of
my heart."

Laine Parsons.

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ABSTRACT

6,7-Benzomorphans have been reported to show pronounce narcotic analgesic activities. In preceeding years several compounds comprising 6,7-benzomorphan nucleus have been synthesized. Previous works were centred mainly on structure-activity relationship to the effect of oxygen, hydroxyl, alkyl or aryl substituents on various positions of the molecule and variation of N-substituents.

The present work is concerned with the synthesis of 6,7-benzomorphan having an amino group at C-9 of the molecule. The synthesis of the title compound involved bromination and rearrangement of heterocyclic enamines, followed by aqueous basic hydrolysis to give 9-oxobenzo-morphan. Conversion of 9-oxo compound to the oxime followed by catalytic reduction afforded the desired 9o(-amino-6,7-benzomorphan. Its pharmacology demonstrated a dose-dependent inhibition analgesia.

The product obtained as well as the intermediates have been analysed and characterized on the basis of their spectral and chemical properties.

TABLE OF CONTENTS

Page

Title Page.....i

Declaration.....ii

Certification.....iii

Copyright Statement.....iv

Dedication.....v

Acknowledgements.....vi

Abstract vii

Table of Contents.....ix

List of Tables.....xii

List of Figures.....xiii

List of Appendices.....xiv

Abbreviations and Symbols.....xv

CHAPTER ONE - INTRODUCTION

1.1 Analgesics and pain.....1

1.2 Morphine and related analgesics.....3

1.3 Morphinans.....9

1.4 6,7-Benzomorphans.....10

1.5 Opiates Receptors.....26

CHAPTER TWO - CHEMISTRY OF BENZOMORPHANS

2.1 Nomenclature.....39

2.2 Stereochemical conventions.....40

2.3 Synthetic routes to the benzomorphan ring systems.....41

2.4 Reactions of benzomorphanones.....49

Page

CHAPTER THREE - DISCUSSION :

SYNTHESIS OF 9-AMINO-6,7-BENZOMORPHAN

3.0 Introduction.....62

3.1 Synthetic route to 9-amino-6,7-benzomorphan.....65

3.2 Synthesis of 2-tetralone.....66

3.3 Synthesis of 1-methyl-2-tetralone.....73

3.4 Synthesis of ethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-1-naphthalene acetate...78

3.5 Synthesis of 3,9b-dimethyl-3a-hydroxy-2-oxo-2,3,3a,4,5,9b-hexahydro-1H-benz(e)-indole.....82

3.6 Synthesis of 3,9b-dimethyl-2-oxo-2,3,5,9b-tetrahydro-1H-benz(e)indole.....84

3.7 Synthesis of 3,9b-dimethyl-5,9b-dihydrobenz(e)indole.....87

3.8 Synthesis of 4-bromo-9b-methyl-2,4,5,9b-tetrahydro-1H-benz(e)indole methobromide...90

3.9 Synthesis of 2,5-dimethyl-9-oxo-6,7-benzomorphan.....93

3.10 Synthesis of 2,5-dimethyl-9-oxo-6,7-benzomorphan oxime.....96

3.11 Synthesis of 9 -amino-2,5-dimethyl-6,7-benzomorphan.....100

CHAPTER FOUR: BIOLOGICAL EVALUATION OF 9α-AMINO-6,7-BENZOMORPHAN

4.0 Introduction.....103

4.1 Materials.....106

4.2 Method of evaluation of analgesic activity.....106

4.3 Results and discussion.....108

4.4 Conclusion.....114

Page

CHAPTER FIVE: EXPERIMENTAL

5.1 Synthesis of 2-tetralone.....118

5.2 Synthesis of 3,4-dihydro-1-methyl-2(1H)-naphthalenone.....121

5.3 Synthesis of ethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-1-naphthalene acetate.....122

5.4 Synthesis of 3,9b-dimethyl-3a-hydroxy-2-oxo-2,3,3a,4,5-9b-hexahydro-1H-benz(e)indole.....124

5.5 Synthesis of 3,9b-dimethyl-2-oxo-2,3,5,9b-tetrahydro-1H-benz(e)indole.....124

5.6 Synthesis of 3,9b-dimethyl-5,9b-dihydro-benz(e)indole.....125

5.7 Synthesis of 4-bromo-9b-methyl-2,4,5,9b-tetrahydro-1H-benz(e)indole methobromide....126

5.8 Synthesis of 2,5-dimethyl-9-oxo-6,7-benzomorphan.....127

5.9 Synthesis of 2,5-dimethyl-9-oxo-6,7-benzomorphan oxime.....128

5.10 Synthesis of 9α-amino-2,5-dimethyl-6,7-benzomorphan.....129

REFERENCES.....130

APPENDICES.....144

LIST OF TABLES

Page

Table 1.1 Effect of alkyl chain length at C-5 and C-9 on analgesic potencies of diastereoisomers of 5,9-dimethylbenzomorphans compared with morphine.....12

Table 1.2 Analgesic activity, physical dependence capacity and antagonistic potencies of some benzomorphan enantiomers compared to morphine.....15

Table 1.3 Analgesic activity of some 5-phenylbenzomorphans as compared to metazocine.....17

Table 1.4 Analgesic action of some C-5 non-quaternary carbon benzomorphans compared to morphine.....18

Table 1.5 Analgesic activity of some 8-alkyl-2,5,9-trimethylbenzomorphans compared to pentazocine.....20

Table 1.6 Agonist and antagonist actions of an 8-keto analogue of cyclazocine compared to cyclazocine and pentazocine.....21

Table 1.7 Analgesic activity of 8-hydroxy isomers of some benzomorphans.....22

Table 1.8 Analgesic activity of some 2-methyl-5-carboethoxy benzomorphans.....23

Table 1.9 Agonist and antagonist actions of a 2'-amino analogue of cyclazocine compared to cyclazocine.....24

LIST OF FIGURES

Page

Figure 1.1 Sketch of receptor model as proposed by Beckett and Casy.....28

Figure 1.2 Beckett's receptor model as modified by Lewis et al. 29

Figure 1.3 Galt's alternative modification of Beckett's receptor model.....29

Figure 1.4 Receptor model as proposed by Feinberg et al. 30

Figure 1.5 Receptor binding sites as postulated by Portoghese et al. 33

Figure 4.1 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 1mg/kg.....109

Figure 4.2 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 2mg/kg.....110

Figure 4.3 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 4mg/kg.....111

Figure 4.4 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 8mg/kg.....112

LIST OF APPENDICES

		Page
Appendix	4.1	P value of benzomorphan and morphine obtained by comparing each with saline at various doses..... 144
Appendix	4.2	P values of benzomorphan and morphine obtained by comparing each with saline at various times at a dose of 1mg/kg..... 145
Appendix	4.3	P values obtained by comparing benzomorphan and morphine at various doses and times..... 146

ABBREVIATIONS AND SYMBOLS

CBM	-	Cyclobutylmethyl
CPM	-	Cyclopropylmethyl
N.M.R. or n.m.r.	-	Nuclear magnetic resonance
I.R. or i.r.	-	Infrared
Et	-	Ethyl
Pr	-	Propyl
ED_{50}	-	Effective dose - 50
AD_{50}	-	Antagonist dose - 50
Me	-	Methyl
PDC	-	Physical dependence capacity
Ph or C_6H_5	-	Phenyl
SC	-	Subcutaneous (subcutaneously)
C_3H_5	-	Allyl (CH_2-CH=CH_2)
*Phe^4	-	Phenylalanine
*Tyr^1	-	Tyrosine
HOAc or AcOH	-	Acetic acid
PPA	-	Polyphosphoric acid
LAH	-	Lithium aluminium hydride
MeOH	-	Methanol
AcO_2	-	Acetic anhydride
EtOH	-	Ethanol
DMF	-	N,N-Dimethylformamide
PTSA	-	Para toluene sulphonic acid
DCM	-	Dichloromethane
THF	-	Tetrahydrofuran
Hg	-	Mercury
δ	-	Delta (chemical shift)

Min	-	Minute
Sec or SEC	-	Second
hr(s)	-	Hour(s)
ml	-	Millilitre
g	-	Gram
mmol	-	Millimole
^{o}C	-	Degree centigrade
mp	-	Melting point
%	-	Percent
$\approx$	-	Approximately
M	-	Molar (molarity)
mg	-	Milligram
Kg	-	Kilogram
i.e	-	That is
cm^{-1}	-	Wavenumber (frequency unit)
Vs	-	Versus
S.e.m.	-	Standard error of mean

* The phenylalanine and tyrosine moieties of a mixture of two amino acids peptides. This mixture has been shown to be an endogeneous morphine-like substance.

..... Sense of pleasure we may well spare
out of life perhaps, and not repine, ...
But pain is perfect misery, the worst of evils;
And excessive, over turns all patience.

John Milton: Paradise Lost,
Book 6, pp. 456-464.

CHAPTER ONE

INTRODUCTION

1.1 ANALGESICS AND PAIN

The problems of prolonged physical pain and mental anguish, the efficacy of opiates in ameliorating these experiences, and the consequent difficulties of physical dependence and addiction associated with opiate use have been the subject of extensive study by chemists, biochemists, pharmacologists, and physicians for many decades. The problems of opiate addiction and the associated social trauma have served in part to intensify efforts directed toward understanding the basic mechanism of the action of these drugs and to intensify the search for a better analgesic which has no harmful side effects and does not induce physical dependence. The detailed mechanisms of action are still in large part unknown and the ideal analgesic has not yet been found (Palmer and Strauss, 1977).

Analgesics act centrally to increase the capacity to tolerate pain. They are characterized by altered behavioural responses to pain and by diminished ability to perceive pain impulses, without loss of consciousness.

It is however generally accepted that the narcotic analgesics do not in fact interfere with the pain as such; rather, these compounds change the perception of the pain - the patient comes to regard pain with detachment (Lednicer and Mitscher, 1977).

A widely recognized medical need exists for an analgesic useful in the long-term treatment of chronic pain that is both safe and effective, with minimum respiratory depression and dependence properties.

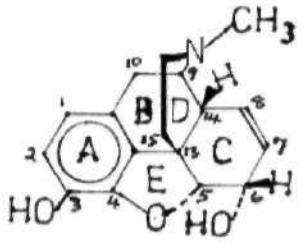
Morphine is the prototype of analgesic compounds and is still in many cases, a preferred drug for pain relief. Its use, however, is restricted by its side effects, the most serious of which are respiratory depression and development of tolerance and physiological and psychological dependence. In an attempt to overcome these side effects, a considerable number of analogues of varying structure have been prepared, some of which have proved useful substitutes for morphine. Despite the substantial progress made, there remains a serious problem with analgesics in so far as analgesics, euphoric effects and dependence remain largely unseparated properties. Thus the goal of an ideal analgesic still awaits achievements.

The enormous benefit in the discovery of better analgesic is obvious. Lack of knowledge of the fundamental physiology of pain and the subcellular mechanisms by which the analgesic drugs exert their pharmaceutical effects has hampered progress towards this goal. The pharmacological effects of opiates have been linked with interactions with central nervous system neurotransmitters-acetylcholine, dopamine, noradrenaline and 5-hydroxytryptamine. The discovery of the opioid peptides now provides a new concept in the study and design of analgesic agents.

The search for a better analgesic, is therefore, a search for a better morphine; a substance with morphine's beneficial properties and with attenuated or no harmful side effects including tolerance and dependence (Eddy and May, 1973).

1.2 MORPHINE AND RELATED ANALGESICS

The extract of the latex from opium poppy seed capsule is reported to be the oldest material employed for medicinal purpose. The major component of the extract was found to be morphine (1) to which significant biological activities are attached. Morphine (I), was isolated from the poppy latex of Papaver somniferum by a German pharmacist, Sertuner, in 1806; and its structure was only confirmed in 1952 by synthesis (Gates and Tshudi, 1952; 1956). Morphine is the prototype of analgesic compounds and is still in many cases a preferred drug for pain relief, primarily because of confidence and experience gained during many years of use (Mellet and Woods, 1963).



(I)

Morphine produces a large variety of pharmacological responses, the most important of which are analgesia, euphoria, respiratory depression and dependence. It has a retarding action upon the digestive system and is an effective antidiarrhoeal agent. Its effect on depressing the cough reflex has been clinically utilized. But its principal effect has been in decreasing awareness and reaction to pain. The euphoric effect, and reduction in anxiety and fatigue which are caused by it, is of importance in the alleviation of pain (Foldes et al., 1964; de Stevens, 1965; Goodman and Gilman, 1965).

It relieves the effects of mental and physical shocks, promote sleep, and evokes a general feeling of peace and well-being (Eddy and May, 1973). It controls pain caused by serious injuries, neoplasm, migraines.

Unfortunately morphine's use is accompanied by several serious side-effects which pose a major drawback to its exploitation. In particular the effect of morphine decreases with each successive dose; the presence of drug becomes more and more tolerated and progressively larger doses are required for a given effect. After continued exposure to the drug, the body becomes dependent upon it for normal function. If the administration of the drug is terminated at this stage, severe withdrawal symptoms develop. The symptoms are generally opposite to the

original effects of morphine and vary from stomach cramps, diarrhoea, insomnia, nervous excitation with dilated pupil, increase of respiratory rate to respiratory failure and ultimately death. The need for ever-increasing doses to maintain the analgesia and prevent withdrawal symptoms also increases the degree of side-effects such as nausea and constipation (Foldes et al., 1964).

The mechanism involved in tolerance and physical dependence remains largely unknown, inspite of intense biochemical investigation (Reynolds and Rendall, 1957; Parkhouse et al., 1979). Feinberg and co-workers (1976) have proposed a model, in the light of the discovery of opioid peptide, which involves adenylate cyclase in the mechanism of analgesia, tolerance and physical dependence.

Respiratory depression is another undesirable effect and this depressant effect is the prime cause of death with higher doses. At the therapeutic levels of morphine administration, other side-effects include vomiting, mental confusion, nausea, miosis, hypermotility, hyperglycaemia, antidiuresis and depression of the spinal reflexes.

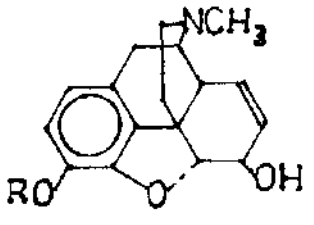
Morphine is promptly absorbed after parenteral administration but absorption by oral route is poor. It rapidly leaves the blood stream and is concentrated in parenchymatous tissue. The major pathway of

metabolism of morphine is conjugation with glucuronic acid and elimination is by glomerular filtration.

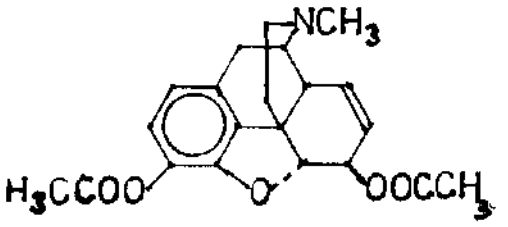
Numerous modifications of the morphine skeleton have been undertaken to produce analgesics without morphine's harmful side-effects. Many morphine derivatives have been prepared and some of them have proved to be very potent but, they all produce side-effects similar to morphine (Beckett and Casy, 1954a; Braenden et al., 1957).

Manipulation of the free phenolic hydroxyl group gives compounds with less analgesic activity but increased antitussive; larger the substituent, the more selective is the antitussive. Alkylation or acylation of the alcoholic hydroxyl group increases analgesic activity (Casy, 1970) with increased addiction and dependence liability.

Codeine (IIa), the phenolic ether of morphine, retains a useful degree of analgesic activity, and is widely used as an oral analgesic and antitussive agent. The abuse potential of codeine is lower than most other narcotic analgesics (Eddy et al., 1969). The ethyl (IIb), benzyl (IIc) and 4-morpholinoethyl (pholocodeine, IId) ethers have a similar clinical utility. Heroin or diacetylmorphine (III), is more potent and shorter acting than morphine, but has a higher addiction liability. The pharmacological action of heroin is attributed to its hydrolysis products (6-monoacetylmorphine and morphine (Casy, 1970).



(II)

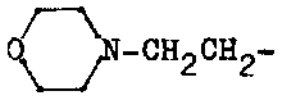


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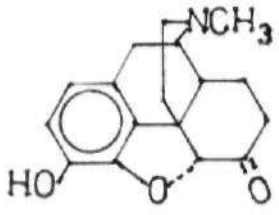
(a) R = CH_3-

(b) R = CH_3CH_2-

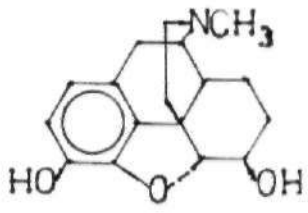
(c) R = Ph-CH_2-

(d) R = 

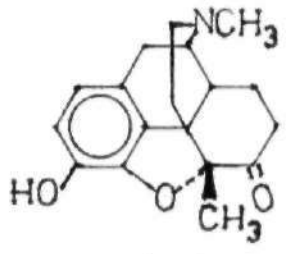
The chemical modification of ring C of morphine has led to several drugs that are clinically important (Eddy et al., 1969). These include dihydromorphinone (IV), dihydromorphine (V) and metopon (VI). Metopon is about three times as potent as morphine and shows lower addiction liability, but has not been promoted for general use. Desmorphine (VII) is a fast acting, powerful analgesic with little emetic or gastrointestinal effects. The 14-hydroxy-7,8-dihydro compounds, oxymorphone (VIIIa) and oxycodone (VIIIb), are also marketed, and are very potent drugs. The 14-hydroxy derivatives, naloxone (IXa) and naltrexone (IXb), are potent pure antagonists opposing the actions of morphine and are used as antidotes in narcotic analgesic overdose (Casy, 1970).



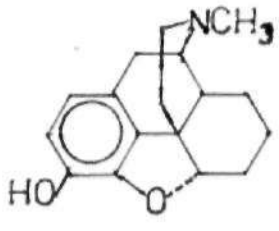
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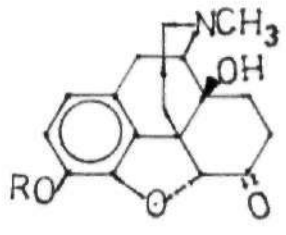
(V)



(VI)

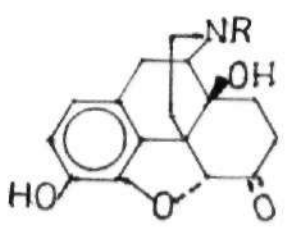


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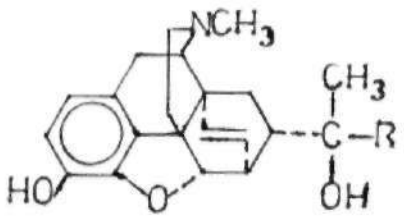
(VIII)

(a) R = H
(b) R = CH_3

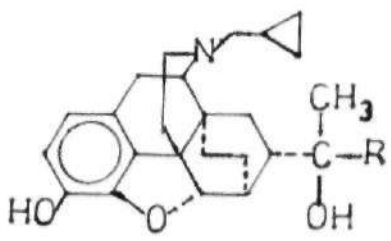


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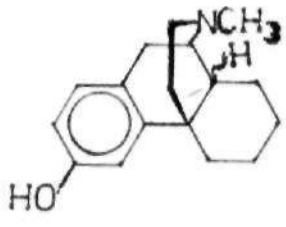
(a) R = CH_2-CH=CH_2
(b) R = CPM



(X)

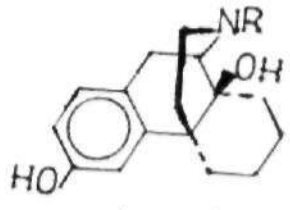


(XI)



(XII)

± Racemorphan



(XIII)

(a) R = CPM
(b) R = CBM

Many 6,14-endoethenotetrahydrothebaine derivatives (X) have extremely high potencies (Lewis et al., 1971). Etorphine (X, R = C_3H_7) for example, is 8,600 times as active as morphine in guinea pigs, and is used for immobilizing large animals for veterinary purposes and for game conservation. Diprenorphine (XI, R = CH_3) is a potent antagonist with very little analgesic activity and is used for the reversal of etorphine actions. Burprenorphine (Cowan et al., 1977) (XI, R = t - Bu) is a very potent mixed antagonist-agonist (0.6mg ≡ 15mg morphine).

1.3 MORPHINANS

After elucidation of morphine's structure, attempts were made to synthesize several modified compounds. The German chemist, Rudolph Grewe (1946) has contributed much regarding the total synthesis of morphine. His investigations revealed morphinans (XII), a class of compounds possessing the main structural skeleton of morphine (I), without 4,5-oxygen bridge. Schnider and Grussner (1949) and Grewe (1949) soon after described racemorphan, (±)-3-hydroxy-N-methylmorphinan (XII), as an analgesic more potent than morphine with no greater harmful side-effects. The laevo enantiomorph (levophanol) which possesses the same absolute configuration as natural morphine was found responsible for the analgesic activity.

A literature survey reveals that hundreds (Hellerbach et al., 1966) of morphinans have been evaluated for analgesic activity, acute toxicity, and some for addiction liability, and cough suppression. Although the side-effects in these compounds are not as severe as those found in morphine, all of them do show the deficiencies of the parent alkaloid (I) i.e. its dependence liability and respiratory depressant properties.

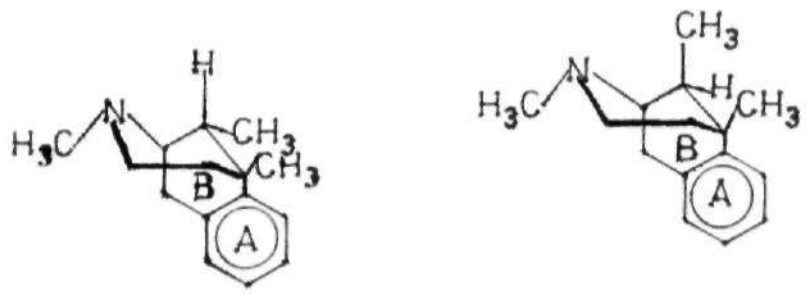
Recently, morphinan derivatives with 14-hydroxyl groups have been prepared (Monkovic et al., 1973) which could not be obtained by Grewe synthesis. The N-cyclopropylmethyl and N-cyclobutylmethyl derivatives (XIIIa and b) represent two of the more interesting compounds to emerge from these studies.

1.4 6,7-BENZOMORPHANS

The 6,7-benzomorphans are one of the most extensively investigated morphine analogues, first prepared and studied in detail by May and Murphy (1955). These compounds retain chemical features considered at one time essential for strong analgesic activity, namely, an aromatic ring attached to a quaternary carbon atom and two carbon atoms removed from a tertiary amine function (Eddy and May, 1973). These compounds are essentially three ring segments of the morphine nucleus. The two pairs are the α - and β - diastereoisomers which differ in

configuration at C-9. In α-isomers 5,9-dialkyl substituents are cis with respect to the hydroaromatic ring B (XIV) while in β-form the groups are trans (XV) (Casy, 1970; 1978).

The stereochemistry of the 9-substituent was initially determined by the rate of quaternization (Fullerton et al., 1962) and by nuclear magnetic

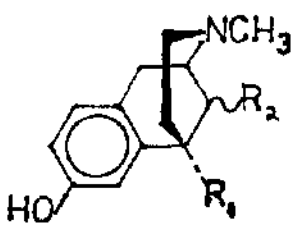


(XIV) (XV)

resonance (NMR) studies (Eddy and May, 1966; Casy et al., 1969; Fullerton et al., 1962). The rates of quaternization of α-isomer are faster than those of β - ones. The reaction in the latter is hindered by the 9-alkyl group (Fullerton et al., 1962; Palmer and Strauss, 1977). The C-9 methyl group in the α-isomer is upfield over 20 cycles from that of β-and was interpreted in terms of a diamagnetic shielding of the α-methyl but not the β - C-9 methyl, by the fused benzene ring (Casy, 1970). The geometry of the 9-position has considerable influence upon the analgesic activity. Without exception, β-diastereoisomers are substantially more potent

than the α -forms (Fullerton et al., 1962; Ager et al., 1963; Ager et al., 1965) inspite of their stereochemistry differing from that of morphine (Casy, 1970).

Eddy and May (1966) prepared a number of 5-monoalkyl- and 5,9-dialkyl substituted benzomorphans, many of them possessed moderate to strong analgesic activity and low or no physical dependence capacity in monkeys. The effect of alkyl chain length at C-5 and C-9 differs in diastereoisomers (Table 1.1).



(XVI)

R_1	R_2	Isomer	ED_{50}, mg/kg SC mice hot plate
Me	Me	α	3.0
		β	0.44
Et	Me	α	4.90
		β	0.07
Pr	Pr	α	71.20
		β	0.87

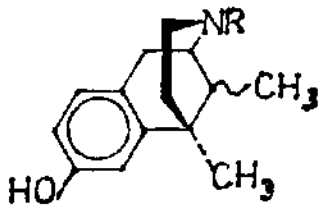
Morphine = 2.90 ED_{50}, mg/kg SC.

Table 1.1: Effect of alkyl chain length at C-5 and C-9 on analgesic potencies of diastereoisomers of 5,9-dimethylbenzomorphans compared with morphine.

For example, the β-dipropyl derivative (XVI, R_1=R_2=Pr) is a potent analgesic whereas the corresponding α-isomer is essentially inactive.

The β-derivatives with a C-5 ethyl or propyl groups are particularly potent even without a phenolic hydroxyl function (Ager et al., 1965; Casy, 1970) which is a pre-requisite for high activity. Omission of a 9-methyl group is detrimental to activity, suggesting it to be an important pharmacodynamic feature of the molecule (Chignelli and May, 1965; Casy, 1970).

The effect of substitution at the nitrogen in the benzomorphan series has been studied extensively (Archer et al., 1964; Tuller et al., 1967); leading to the development and promotion of the agonist-antagonist concept, which is very prominent in present day analgesic research rationale. Pentazocine (XVII, R = $CH_2CH = CMe_2$) is a moderately strong agonist with weak antagonist activity and is now in clinical use in a wide range of pain situations (Casy, 1978). Full reviews of its use are available (Goodman and Gilman, 1965; Martindale, 1977). Cyclazocine (XVII, R = CPM) is a powerful morphine antagonist (7 times nalorphine) with equally powerful



(a) R = CH_2–(2′-furyl) , 9α-Me

(b) R = CH_2–(2″-furyl) , 9β-Me

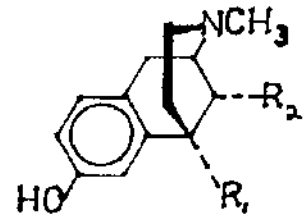
(XVII)

pain relieving qualities (0.25mg = 10mg morphine), and has proved to be a good research tool. Phenazocine (XVII, R = CH_2-CH_2Ph; ED_{50}, 0.25mg/kg SC, mice) is almost about 5-10 times more powerful than the parent member of the series, metazocine (XVII, R = Me; ED_{50}, 3.0mg/kg SC, mice hot plate) as an analgesic (Fullerton et al., 1962).

The two isomers (XVIIa and XVIIb) (Merz et al., 1975) are powerful non-morphine-like analgesic with potencies of more than 100 times that of morphine. These compounds did not show a positive straub tail test in mice and failed to suppress the abstinence sign in dependent monkeys deprived of morphine, and hence are potential non-addicting analgesics.

An interesting aspect of the benzomorphan compounds is the study of the antagonist-agonist profiles of pairs of optical isomers (Ager et al., 1969),(Table 1.2). The laevo isomers are more potent than the corresponding racemates and, like racemates, would not support morphine-dependent monkeys. Surprisingly, leavo-isomers in some cases, showed antagonistic action in precipitating the morphine abstinence signs in these morphine-dependent animals. The laevo-isomer of 5-methyl 9α-propyl-6,7-benzomorphan (Table 1.2; XVIIId) is one-fifth as potent as nalorphine as an antagonist but stronger than morphine as an analgesic. Some dextro-isomers are also active, and surprisingly show some capacity to substitute for morphine. However this phenomenon of separation of morphine-like effects in enantiomers is not general for

this series (May and Takeda, 1970). For instance both isomers of 5-methyl-9α-ethyl-6,7-benzomorphan (Table 1.2; XVIIIc) are active and neither show the capacity to substitute for morphine, nor do they manifest any antagonist effect.



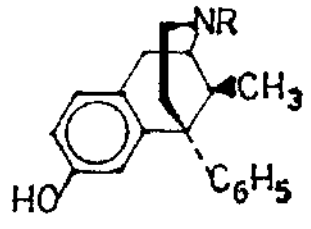
(XVIII)

	R_1	R_2	Enantiomer	ED_{50} mg/kg	PDC	Antagonist potency
(a)	Me	Me	(-)	0.9	No	1/50 - 1/10 nalorphine
			(+)	Inactive	No	No
(b)	Et	Et	(-)	1.2	No	1/10 nalorphine
			(+)	7.9	Intermediate	No
(c)	Me	Et	(-)	0.7	No	No
			(+)	17.7	No	No
(d)	Me	Pr	(-)	0.8	No	1/5 nalorphine
			(+)	12.3	High	No
	Morphine			1.2	High	No

Table 1.2 Analgesic activity, physical dependence capacity (PDC) and antagonistic potency of some benzomorphan enantiomers.

The work on synthesis, analgesic activity and physical dependence capacity (PDC) of various 5-phenyl benzomorphan derivatives have been reported (Block and Clarke, 1969; Yokoyama et al., 1970; Yokoyama et al., 1979). Such compounds provide a structural link between the benzomorphans and the 4-phenylpiperidines and diphenylpropylamine analgesics. The 9-methyl-5-phenyl derivative (XIX; R = Me) was obtained by an adaptation of the Grewe-type synthesis. Only one diastereoisomer resulted and, unexpectedly, this had a β-configuration (Block and Clarke, 1969; Yokoyama et al., 1970). The laevo isomer of XIX (R = Me) is twice as potent as morphine as an analgesic, with morphine-like properties in precipitating the morphine abstinence in non-withdrawn, dependent monkeys. The laevo-isomers of the N-dimethyl allyl- and N-cyclobutylmethyl analogues of XIX are both mixed agonist-antagonists but are less potent than the corresponding 5,9-diakyl-6,7-benzomorphan derivatives either as analgesics or as antagonists. The N-propargyl analogue ((-), XIX; R = $CH_2C \equiv CH$) is a pure, long acting antagonist in the guinea pig ileum (Yokoyama et al., 1979). Most of the dextro-isomers XIX with antagonist-like substituents are inactive or very weak as analgesics.

The preparation of 2-methyl-6,7-benzomorphan and 2,9-dimethyl-6,7-benzomorphan to ascertain the importance of the quaternary carbon in rigid structures has been reported (Kanematsu et al., 1968; Kanematsu et al., 1969; May and Takeda, 1970; Inoue et al., 1975; Inoue and May, 1976).



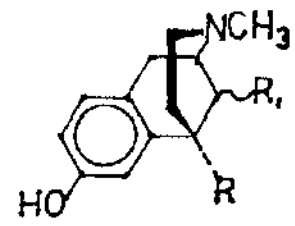
(XIX)

R	Isomer	ED_{50}, mg/kg SC
Me	(-)	0.18
Me	(+)	3.4
CH_2CH_2Ph	(±)	Inactive
Metazocine	(±)	0.44

mice hot plate test.

Table 1.3: Analgesic activity of some 5-phenyl-benzomorphans as compared to metazocine.

Compounds (Table 1.4) with H at position 5, although somewhat reduced in potency from corresponding 5-methyl relatives, are nevertheless moderately to strongly active. All the nonquaternary-carbon compounds as racemates show mixed agonist-antagonist action in morphine-dependent monkey, similar to <u>leavo</u> isomers in the 5-alkyl series. Surprisingly, a secondary amine analogue (XVIb; R = R_1 = H) without quaternary carbon is codeine-like in analgesic activity (ED_{50}, 10.2mg/kg SC) as determined by the mouse hot plate (Fauley and Lapidus, 1973).



(XVI)

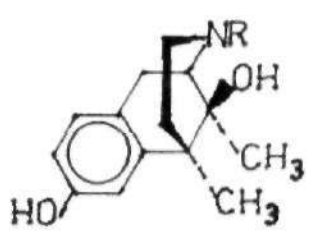
		ED_{50}, mg/kg SC
(a)	R = Me, R_1 = H	3.2
(b)	R = R_1 = H	4.5
(c)	R = Me, R_1 = 9α-Me	1.2
(d)	R = H, R_1 = 9α-Me	4.3
(e)	R = Me, R_1 = 9β-Me	0.1
(f)	R = H, R_1 = 9β-Me	1.1
	Morphine	2.1

Determined by hot plate method in mice.

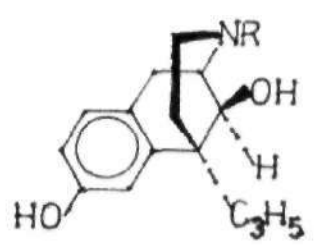
Table 1.4: Analgesic action of some C-5 non-quaternary carbon benzomorphans compared to morphine.

The effect of introduction of a 9-hydroxyl group (equivalent to the 14-hydroxyl of the morphine analogues) has been examined in the benzomorphan series (May et al., 1961; Casy, 1970). A 9-hydroxyl substituent reduces the analgesic activity of metazocine (XX; R = Me), the influence of the β-positioned group being more detrimental (Grewe et al., 1949; Casy, 1970). Introduction of a 9β-hydroxy group onto the benzomorphan bearing an

allyl or cyclopropylmethyl group on nitrogen (XX; R = CH_2-CH = CH_2 or CPM) increased antagonist activity but decreased agonist activity. In case of cyclazocine, a 9β-hydroxyl group raised the antagonist activity by ten fold, while agonist activity is decreased by 400 fold. On the other hand, introduction of an 9α-hydroxy group had no influence on the antagonist action of pentazocine or cyclazocine (Albertson, 1975).



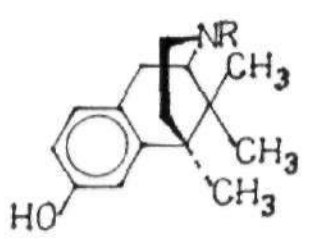
(XX)



(XXI)

Some potent analgesic with antagonist-agonist profiles have been derived from 5-allyl-9β-hydroxy - benzomorphan (XXI). The N-cyclopropylmethyl and N-cyclobutylmethyl derivatives of XXI were effective agonists in the mice writhing test; both effectively antagonised the action of oxymorphone. In both respects, the N-cyclopropylmethyl compound was more potent (Saucier et al., 1977). A 9α-methyl group abolished the analgesic properties of the N-cyclopropylmethyl derivative of XXI but enhanced its antagonist action, whereas it increased the potency of the N-cyclobutyl-methyl derivative of XXI both as agonist and antagonist.

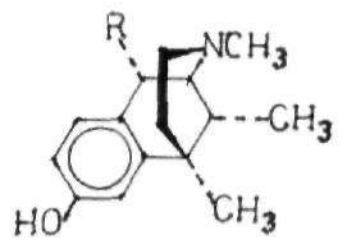
Introduction of another methyl group at C-9 in certain 5,9-dimethylbenzomorphan derivatives, as in XXII, gave a series of compounds which possessed pharmacological profiles similar to the 9-monomethyl series, but they were generally more potent and longer acting (Janssen, 1973).



(XXII)

(a) R = CPM

(b) R = CBM



(XXIII)

(a) R = Ph

(b) R = Me

	R	ED_{50}, mg/kg SC.
(a)	Ph	2.5
(b)	Me	0.6
	Pentazocine	20.4

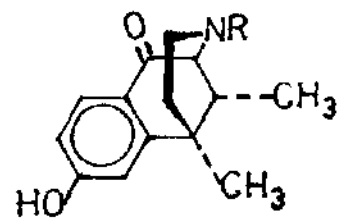
mice, tail flick antagonist of morphine.

Table 1.5: Analgesic activity of some 8-alkyl-2,5,9-trimethylbenzomorphans compared to pentazocine.

The structure-activity effects of altering the substituents at other positions on the ring system have been studied. Ziering et al. (1970) introduced alkyl or aryl groups into the 8α-position of the benzomorphan nucleus. The 8α-phenyl- and 8α-methylbenzomorphan

derivatives (Table 5; XXIIIa and b) are surprisingly active as antagonists for N-methylated 6,7-benzomorphan.

Michne and Albertson (1972) reported that the direct introduction of oxygen in the benzylic carbon provided another subseries with mixed agonist-antagonist properties (Table 1.6). Introduction of an 8-keto group in certain benzomorphan antagonists invariably reduced antagonist activity without appreciably effecting agonist activity. However, antagonist activity increases when such a change is made in nor base (XXIV; R = H). The 8-oxo analogue of cyclazocine (XXIV; R = CPM) possessed agonist activity similar to cyclazocine, and an antagonist activity similar to pentazocine.

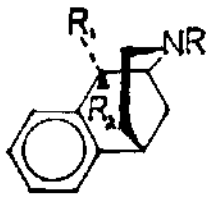


(XXIV)

	AD_{50}, mg/kg SC Antagonist	ED_{50}, mg/kg SC Agonist
R = CPM	7.2	0.16
Cyclazocine	0.02	0.15
Pentazocine	3.9	2.2

Table 1.6: Agonist and antagonist actions of an 8-keto analogue of cyclazocine compared to cyclazocine and pentazocine.

A few 8-hydroxy-6,7-benzomorphans (Michne and Albertson, 1972; Fauley and Lapidus, 1973) have also been reported. Unexpectedly, the N-methyl derivative of XXV was inactive. This is unexpected on the basis of classical structure-action relationship of analgesic 6,7-benzomorphan. The tertiary amine would be expected to be more potent analgesic than the secondary amine (Fauley and Lapidus, 1973).



(XXV)

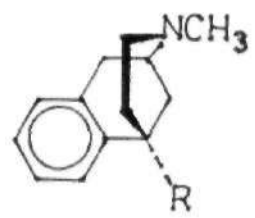
R	R_1	R_2	Isomer	ED_{50}, mg/kg SC
H	OH	H	α	56.5
H	H	OH	β	13.7
Me	H	OH	β	Inactive

mice hot plate

Table 1.7: Analgesic activity of 8-hydroxy isomers of some benzomorphans.

Kugita et al. (1962) prepared 2-methyl-5-carboethoxybenzomorphan (XXVIa) as a hybrid of both the benzomorphan and piperidine analgesics. The analgesic activity of XXVIa is comparable to meperidine, and it did not support morphine dependence in monkeys. The

benzomorphan-prodine hybrid (XXVIb), (Takeda and May, 1970) is about one quarter as active as morphine, and does support morphine dependence in monkeys.



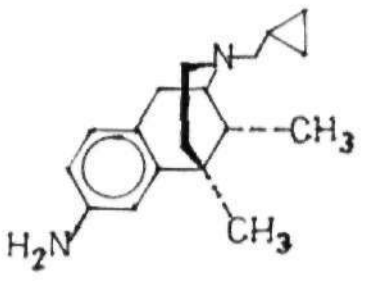
(XXVI)

	R	ED_{50}, mg/kg SC
(a)	$CO_2C_2H_5$	11.1
(b)	OCOMe	5.1

mice hot plate

Table 1.8: Analgesic activity of some 2-methyl-5-carboethoxy benzomorphans.

It was anticipated that replacement of the 2'-hydroxyl group in benzomorphans by an amino group would give an analgesic less subject to metabolic inactivation, and thus render it longer acting. The 2'-amino analogue (XXVII) of non-phenolic cyclazocine was found to be strong, active analgesic agonist with antagonist properties and had a favourable oral/parenteral ratio (Jacobson and May, 1965; Wentland et al., 1980).



(XXVII)

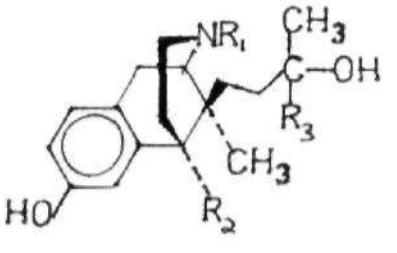
	ED_{50}, mg/kg SC[a]	AD_{50}, mg/kg SC[b]
(XXVII	0.8	2.7
Cyclazocine	0.15	0.028

(a) Acetylcholine writhing test

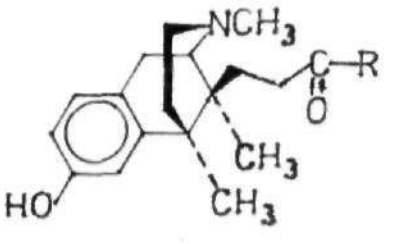
(b) Pentazocine antagonism

Table 1.9: Agonist and antagonist actions of a 2'-amino analogue of cyclazocine compared to cyclazocine.

Michne et al. (1977) reported the synthesis and analgesic activity of a large number of 9-propanol-6,7-benzomorphans (XXVIII). The structure activity profile of XXVIII analogues differs from the structurally similar bridged oripavine derivatives.



(XXVIII)

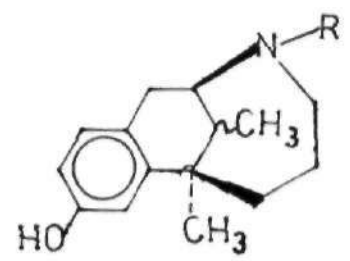


(XXIX)

In general, these variants had weak analgesic properties but were potent antagonists. The N-methyl derivative of XXVIII ($R_1 = R_2 = Me$, $R_3 = (CH_2)_2CH(CH_3)_2$) is five times as potent as nalorphine and represents the most potent N-methyl antagonist reported to date (Michne, 1978).

Michne et al. (1979) reported a series of 9-(3-oxo-alkyl)-6,7-benzomorphans (XXIX), where the alkyl group is a straight chain or terminally branched chains containing from one to six carbon atoms. The compounds (XXIX; R = C_3H_7, C_4H_9, $CH_2CH(CH_3)_2$, $(CH_2)_2$-$CH(CH_3)_2$) displayed activity up to 100 times that of morphine. Compound XXIX containing five to six carbon atoms of alkyl chain exhibited antagonist activity.

Various skeletal modification of the benzomorphan ring have been reported. These include C-ring expansion to form the homobenzomorphan, introduction of a second nitrogen, contraction of B or C ring and synthesis of the basic skeleton with nitrogen in different positions. The homobenzomorphans have significant agonist and antagonist activity depending on the nature of the N-substituent. The β-isomers with antagonist N-substituent (XXX; R = CPM or $CH_2CH = C(CH_3)_2$) may be classified as 'pure' antagonist while the corresponding α-isomers also display agonist properties.



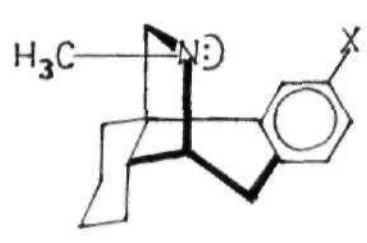
(XXX)

1.5 OPIATE RECEPTORS

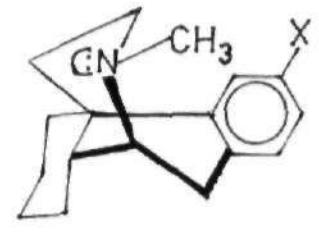
There are several structural features common to narcotic analgesic drugs (Feinberg et al., 1976). Many strong analgesics contain an aromatic ring bonded to a saturated two- or three- carbon chains terminating with an amine nitrogen. Other additional features are associated with strong analgesic activity (Braenden et al., 1955; Mellet and Woods, 1963). In morphine analogues, the presence of a phenolic hydroxyl, tertiary nitrogen, and quaternary benzylic carbon all enhance analgesic activity.

It is generally agreed that an essential feature of an analgesic drug is its basic nitrogen, which either forms part of an alicyclic ring structure or an acyclic chain. In most examples, the base is tertiary, but a number of secondary amines have also been reported by Eddy (1959); Bentley and Hardy (1967), with analgesic properties. The low analgesic potencies of nor-analogues is considered to be due to distribution factors and not to the failure of such derivatives to associate at the receptors (Beckett and Casy, 1954b; Casy, 1970; 1978).

The cationic (protonated) forms of the drug is generally accepted to be the active species and to interact with the receptor *via* ionic association (Beckett and Casy, 1954b; Portoghese, 1966; Feinberg *et al.*, 1976). Belleau *et al.* (1974), however, proposed that the nitrogen lone pair orientation is a key factor governing association of an opiate drug with its receptor, and ruled out the protonated form as the active species. This was postulated after comparison of the X-ray structure of *N*-methyl-D-normorphinan salt, which is devoid of analgesic or antagonist activity, with that of the morphinan salt. Belleau *et al.* (1974) pointed that the protonated nitrogen lone-electron pair of the D-normorphinan (XXXI) is directed towards the aromatic feature of the molecule, whereas the same feature points away from aryl in morphinan or benzomorphan salt (XXXII).



(XXXI)



(XXXII)

An objection to these views is the fact that morphine metho-salts (in which the lone-pair is not available and nitrogen atom carries a full positive charge) are similar in potency to morphine itself when administered directly into the brain (Casy, 1970; Albertson, 1975).

Opiate receptors are stereoselective towards a variety of narcotic analgesics and in all cases activity is distributed unevenly in enantiomeric forms. Beckett and Casy (1954b), formulated a receptor model on the basis of stereochemical evidence and structural features common to analgesics and their antagonists known at that time. It was postulated that the receptor possessed a flat surface, a cavity and an anionic site which were thought to accommodate an aromatic ring, hydrocarbon moiety and a protonated basic nitrogen respectively (Figure 1.1).

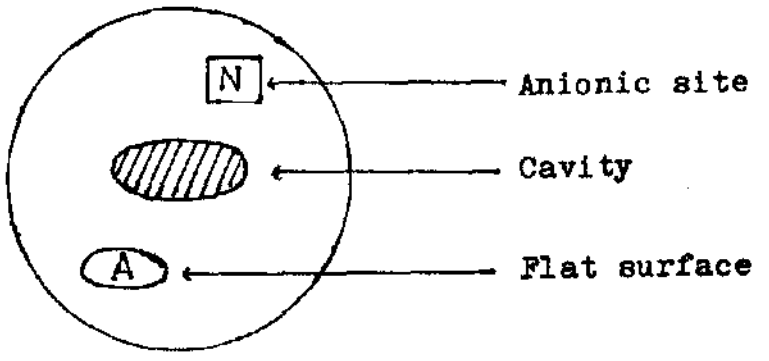


Figure 1.1: Sketch of receptor model as proposed by Beckett and Casy.

A number of proposals that update Beckett's receptor model have been made in the light of new information. Lewis et al. (1971) proposed an extension of the receptor (Figure 1.2)to include lipophilic site which would accommodate the very potent 6,14-endoethanotetrahydrothebaine and oripavine series. An alternative proposal, attempting to account for stereochemical anomalies among certain compounds

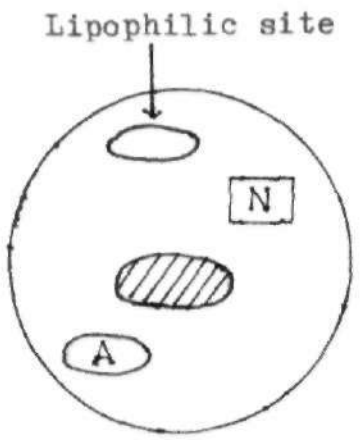


Figure 1.2

Beckett's receptor model as modified by Lewis et al.

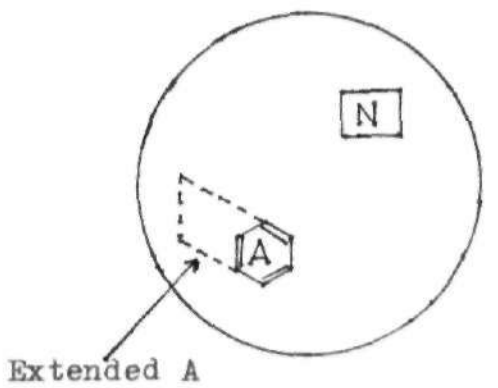


Figure 1.3

Galt's alternative modification of Beckett's receptor model.

where both members of an enantiomeric pair show significant pharmacological activity, for example, 5-phenyl-6,7-benzomorphan (XVIII) has been advanced by Galt (1977). Galt (1977) proposed an extension of the planar binding area (A) as shown in Figure 1.3. Any molecule, according to Galt (1977), which has, or can project a planar surface and cationic centre in the same juxtaposition in space as the model, could have opiate properties. Thus both enantiomeric forms of 5-phenyl-6,7-benzomorphan provides features required to fit the model; the nitrogen atom and phenolic hydroxyl superimpose, but the aromatic rings do not overlap.

Feinberg et al. (1976) proposed a model attempting to explain the structure-activity relationships of opiate agonists and antagonists, and the importance of sodium. They suggested the receptor exists in two conformations allosterically modulated by sodium ions, the agonist and antagonist (Figure 1.4). Two sites, one

of lipophilic and one of anionic character that interact with the aromatic ring and amine nitrogen respectively, are available in both conformations. In addition, the receptor has a specific agonist site (F), which is not available to the antagonist molecule, and binding of agonists to this site stabilises the agonist conformation. Antagonists also have a specific binding site capable of interaction with antagonist conformation. Normally, the receptor is in the antagonist conformation because of the prevailing brain sodium ion concentration.

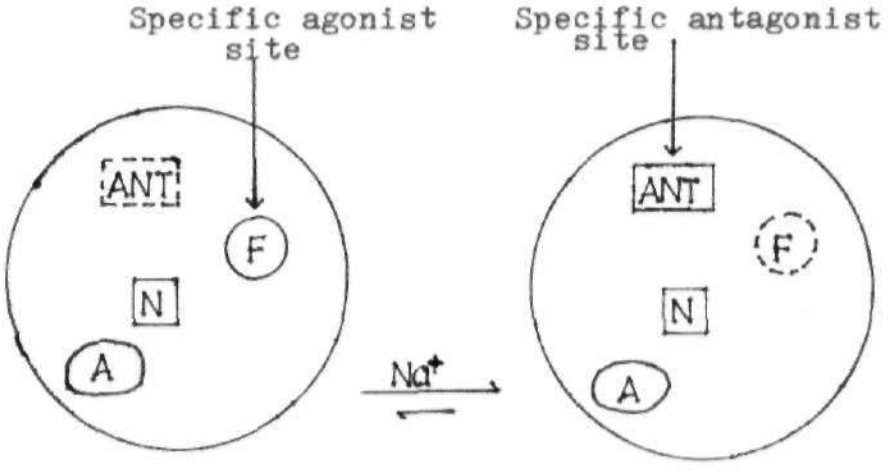


Figure 1.4: Receptor model as proposed by Feinberg et al.

The enhanced potency of phenazocine, fentanyl and the bridged thebaines is attributed to the fact that such molecules have aromatic features capable of bonding to both A and F sites. Mixed agonists-antagonists are considered to interact with both agonist and antagonist conformations. The failure to design narcotic analgesic antagonist based on phenylmorphinans by linking the basic centre to groups

such as allyl and cyclopropylmethyl is suggested to be due to aromatic rings of such compounds interacting with specific agonist site F rather than A site.

In this model, agonist and antagonist activities are associated with axial and equatorial N-substituents respectively and the effect of the C-14 hydroxyl group in enhancing antagonist activity is explained by assuming its presence is responsible for a shift from axial to equatorial N-substituent. Quantum chemical studies carried out by Loew and Berkowitz (1975), do not support this hypothesis. They found no correlation between agonist-antagonist potency variation and calculated axial-equatorial N-substituent characteristics. Loew and Berkowitz (1975) suggested that agonist-antagonist activity is regulated by two different low energy equatorial N-substituent conformers, and the C-14-hydroxyl group and N-substituent interact indirectly through a common anionic site (Loew and Berkowitz, 1976). Alternatively, Casy (1978) proposed that the hydroxyl group may exert its influence electronically by inducing an electron drift towards the $RN^{+}H$ feature *via* an $N^{+}H...OH$ hydrogen bonding mechanism.

A variant of the Feinberg *et al.* (1976) model in which only one conformation of the receptor is needed for both agonist and antagonist molecules was proposed by Kolb (1978). There are two different spatially fixed amine binding sites: one agonist and one antagonist.

The opiate undergoes binding to its amine sites *via* the lone-pair electrons on nitrogen. It is suggested that the primary action of antagonists at the receptor is through the interaction of the antagonist nitrogen lone-pair and its amine-site, and not through some lipophilic association of the *N*-allyl chain with a specific antagonist binding site. The main role of the *N*-allyl chain is to force the *N*-lone pair lobe of an antagonist molecule in the direction of its amine binding site (Scheinar and Kolb, 1980).

Each of the proposed models can account for some of the experimental observations but none is satisfactory. The concept of a single receptor at which all ligands associate by mechanisms that are essentially alike appears improbable. Binding interactions of so restricted a character are incompatible with present stereochemical and structure-activity data.

Portoghese (1965) introduced a new concept on the mode of interaction of ligands with opiate receptors. He proposed multiple modes of interaction which arises from association of different ligands with different recognition loci on either a single or a group of related receptors. A method of determining similarities or differences in molecular binding modes by comparing the variation of activity in different series of compounds when identical changes in the *N*-substituent are made, was proposed. Comparison of meperidine

derivatives with identically substituted benzomorphans showed no parallel relationship (Portoghese, 1965), and thus implies dissimilar modes of binding.

The loss of activity upon introduction of a meta phenolic OH in allyl prodine (XXXIII) which is in marked contrast to the enhancement of agonist potency conferred by this group in morphine is attributed to divergent binding modes. Portoghese *et al*. (1981) postulated that this difference arises from the recognition of the aromatic groups of morphine and allylprodine by different aromatic-binding subsites of the receptor. These subsites are suggested to be identical with those that recognise the aromatic rings of the Tyr^1 and Phe^4 of the enkephalins and endorphin (Figure 1.5).

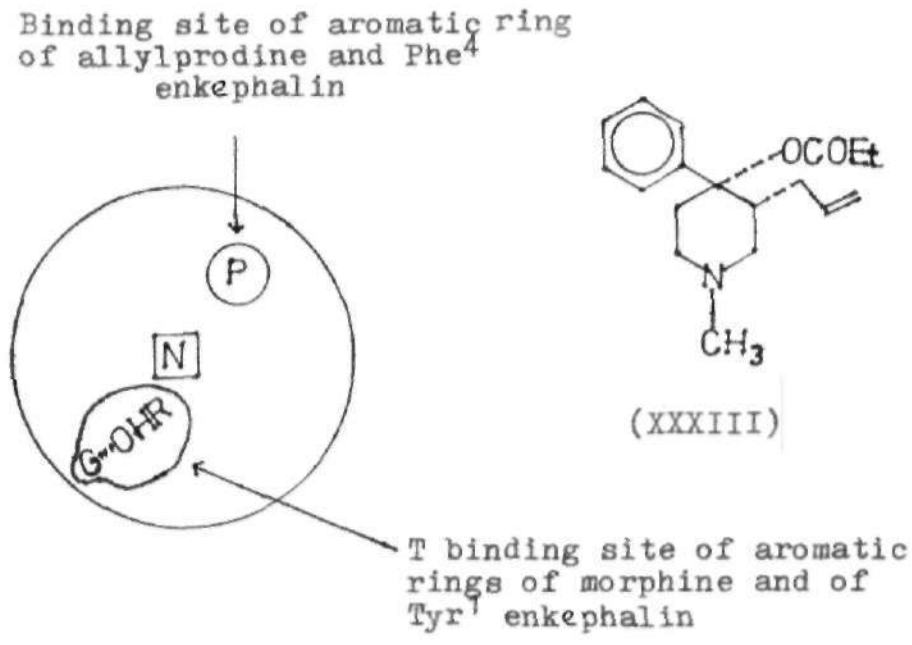


Figure 1.5: Receptor binding sites as postulated by Portoghese *et al*.

Evidence of competitive kinetics and the fact that antagonist molecules like nalorphine block a wide range of analgesics support the view of a single receptor species. However, the differential pharmacological responses seen with various opiates, and the differential competitive displacement of various opiates by narcotic agents from the receptors suggests that there are multiple receptors (Martin et al., 1976; Gilbert and Martin, 1976; Terenius, 1977; Audigier et al., 1977).

Martin et al. (1976); Gilbert and Martin (1976) have observed on the basis of different pharmacological responses a variety of narcotic analgesic in the non-dependent chronic spinal dog. Morphine was reported to be the prototype agonist of mu receptor, ketocyclazocine for kappa and SKF-10047 (N-allyl analogue of normetazocine) for delta receptor. The effect of these drugs are antagonised by naltrexone, indicating that they are agonists. Pentazocine is suggested to be a weak mu receptor antagonist and a moderate kappa and delta agonist. The antagonistic action of pentazocine at the mu receptor is the reason why pentazocine precipitates abstinence in persons dependent on morphine. Its agonistic action at the kappa receptor accounts for its analgesic activity and for the induction of the nalorphine-type of physical dependence. Agonistic effects at delta receptors account for the psychotomimetic effects. Cyclazocine is suggested to

have both kappa and delta agonistic activity but no activity at the mu receptor.

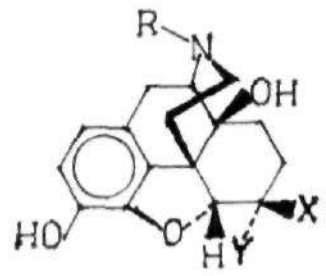
This hypothesis by Martin et al. (1976) and Gilbert and Martin (1976) has been confirmed biochemically by demonstrating the presence in brain as well as in isolated organs of at least two kinds of sites (Leslie et al., 1980) for radio-labelled analogues of enkephalins. These compounds bind to a low affinity site where they are readily displaced by natural and synthetic opiates, and to a high affinity site which exhibits a high preference for the peptide structures. A comparative study of the binding properties and the pharmacological potency on isolated organs showed that the low affinity site is related to the mu receptors (or morphine receptors) of the guinea pig ileum and the high affinity site is related to the delta receptors (or enkephalin receptors) of the mouse vas deferens (Lord et al., 1977; Childers et al., 1979; Kosterlitz et al., 1980; Leslie et al., 1980). Several biochemical differences between the binding sites exist. Sodium selectively inhibits opiate agonist binding by abolishing high affinity with minimum effects on the low affinity site (Pasternak et al., 1975). Structure-activity studies with selective enkephalin analogues have provided support for the hypothesis that analgesia is mediated by the mu receptors. The delta receptors are considered to be involved with behavioural effects (Gacel et al., 1981).

Studies on Stereostructure-Activity Relationship of opioid agonist and antagonist bivalent ligands have been carried out by Portoghese et al. (1985). Their results reflect possible differences between sites that bind agonists and those that bind antagonists (Portoghese and Takemori, 1983). Other reasons advanced for the discrepancy between binding and antagonist potency include differences between the organisation of the mu receptor system in the ileum and brain of guinea pigs and differences between the interaction of antagonists with intact cell membranes and membrane fragments (Portoghese et al., 1985).

The stereoselectivity of the potency enhancements supports the idea that vicinal opioid receptors are the recognition sites involved in the bridging of bivalent ligands. Thus a pharmacophore having the same absolute stereochemical configuration as morphine facilitates effective bridging. Such bridging should be manifested by a substantial increase in potency due to the high local concentration of the free pharmacophore in the vicinity of the proximal recognition site when the bivalent ligand is bound in a monovalent mode (Dwyer and Bloomfield, 1981; Erez et al., 1982).

The binding data obtained on the studies on opioid receptor interactions of 6α and 6β epimers of oxymorphamine show that 6α- (XXXIVa) and 6β- (XXXIVb) oxymorphamine are potent mu-selective ligands with affinities for mu receptors that are 19-fold and

12-fold greater, respectively, than their affinities for delta receptors (Lever Jr. et al., 1985).



(a) X = H; Y = NH_2; R = CH_3

(b) X = NH_2; Y = H; R = CH_3

(XXXIV)

The β epimer is however, slightly more potent than the α epimer in binding to each receptor.

The in vivo receptor occupancy of three benzomorphan drugs bremazocine (agonist); Win 44441-3 and MR 2266 (antagonists) and the oripavine antagonist diprenorphine, at the mu, delta and kappa sites, in comparison to their effects on urine flow has been reported (Richards and Sadee, 1985). The results indicate that the kappa receptors mediate the effects of benzomorphan opioid drugs on urine flow and the inhibition of bremazocine-associated diuresis correspond to a fractional kappa receptor occupancy of 0.5.

The actual structure and mechanism of action of opiate receptors must await the isolation of receptor material in a pure and viable state. Numerous attempts have been made to obtain an active solubilised receptor but with very limited success. Recently, successful solubilisation of receptor in a state that reversibly binds opiate ligands using new type of detergent has been reported (Simonds et al., 1980).

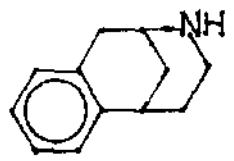
The concept of the analgesic receptor has been progressively modified with new experimental information. Casy (1978), concluded that the Portoghese hypothesis (Portoghese, 1965) of multiple modes of ligand-receptor interaction, whether at a single receptor or a variety of linked receptor sites, was a reasonable one in the light of present day stereochemical and other structure-activity data.

CHAPTER TWO

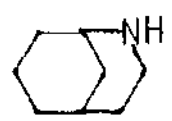
CHEMISTRY OF BENZOMORPHANS

2.1 NOMENCLATURE

The first compound containing the benzomorphan ring system (XXXVI), was reported by Barltrop (1947). The name is derived from the trivial name "Morphan", initially suggested to Barltrop by Sir Robert Robinson, for the simple azabicyclo (3:3:1) nonane (XXXV).

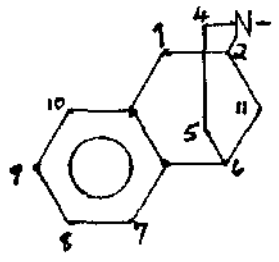


(XXXVI)
Benzomorphan

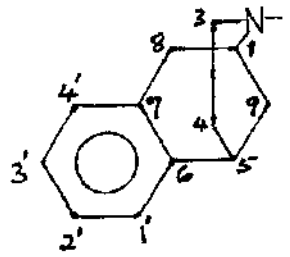


(XXXV)
Morphan

There are two common benzomorphan numbering systems (XXXVII) and (XXXVIII), now in use. The numbering system presently listed in the "Ring Index" and Chemical Abstracts is associated with the numbering system shown in XXXVII is 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine, but is better known as 6,7-benzomorphan, (XXXVIII); the numbering systems differ as shown.



(XXXVII)

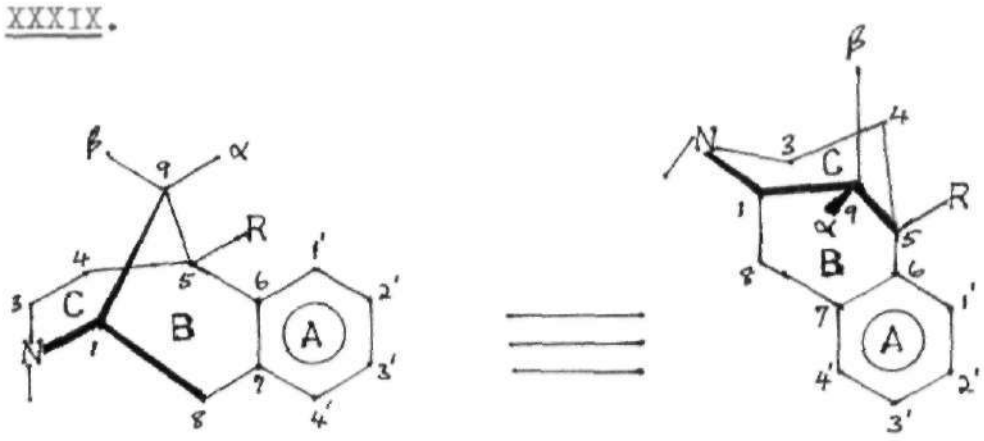


(XXXVIII)

The original nomenclature, as adopted by Eddy and May (1966), shown in (XXXVIII), will however, be employed in this work.

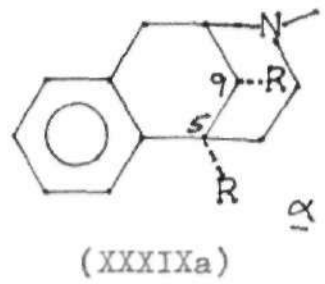
2.2 STEREOCHEMICAL CONVENTIONS

The stereochemical nomenclature of the benzomorphans has now been established. The general benzomorphan framework is represented by structure XXXIX.

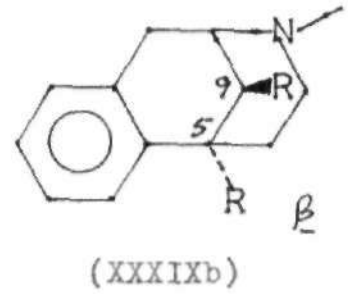


(XXXIX)

The stereochemistry at C-9 has been designated as α when the C-9 substituent and C-5 substituent are cis with respect to the B ring (Eddy and May, 1966). It is designated as β when the C-5 and C-9 substituents are trans with respect to the B ring (Casy, 1970; Palmer and Strauss, 1977; Casy, 1978).



(XXXIXa)

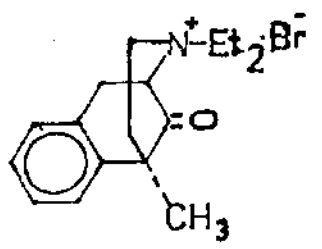


(XXXIXb)

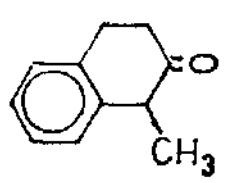
2.3 SYNTHETIC ROUTES TO THE BENZOMORPHAN RING SYSTEMS

The principal synthetic routes for constructing the ring system are shown schematically (Schemes 2.3-2.12). The Grewe and tetralone routes, as well as modification of these methods, are by far the most important synthetic routes.

The first compound containing the benzomorphan was ethobromide salt of 2-ethyl-5-methyl-9-oxo-6,7-benzomorphan, (XL), synthesized by Barltrop (1947), using the tetralone (XLI).

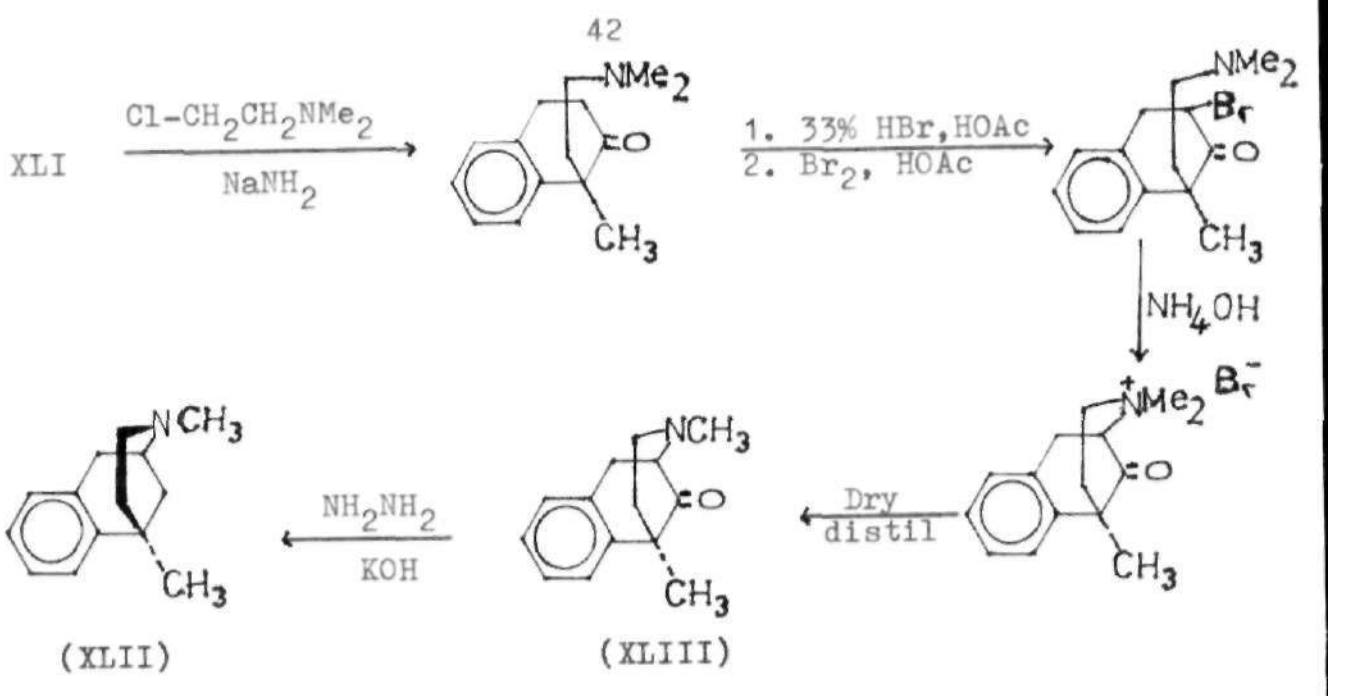


(XL)

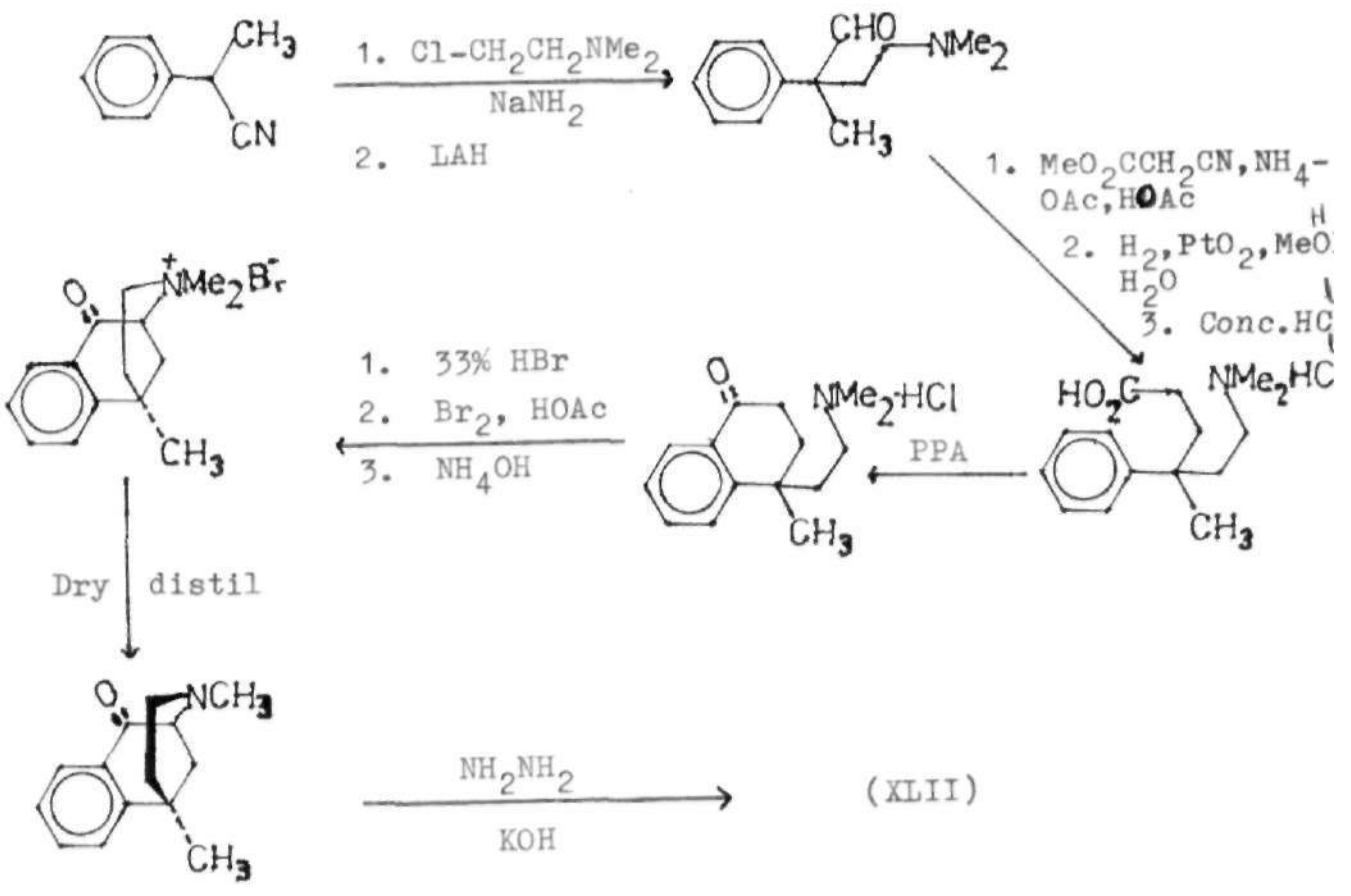


(XLI)

May and Murphy (1955) reported 2,5-dimethyl-6,7-benzomorphan (XLII) exploiting this route (Scheme 2.1) and by longer synthesis starting with hydratroponitrile (Scheme 2.2). β-Tetralone route has been widely used (Murphy et al., 1960 ; Saito and May, 1961; Chignelli and May, 1965) in the preparation of various 5-alkyl benzomorphan, and also in the preparation of homobenzomorphan (XXX).

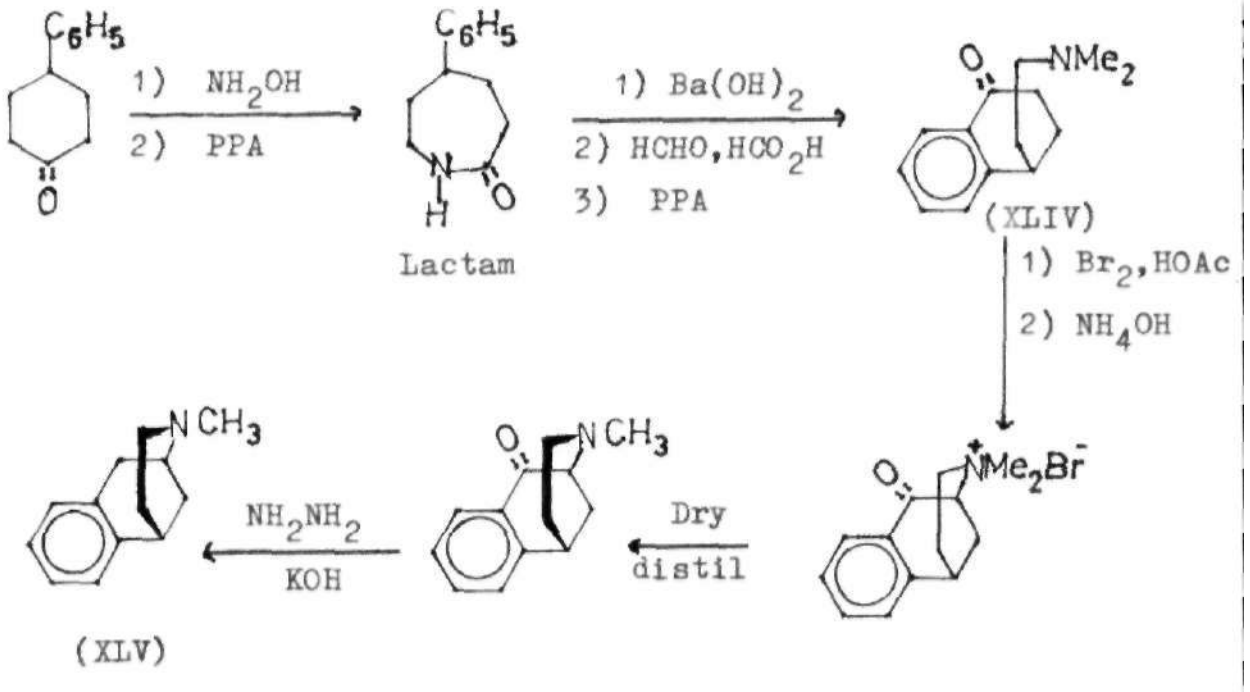


Scheme 2.1



Scheme 2.2

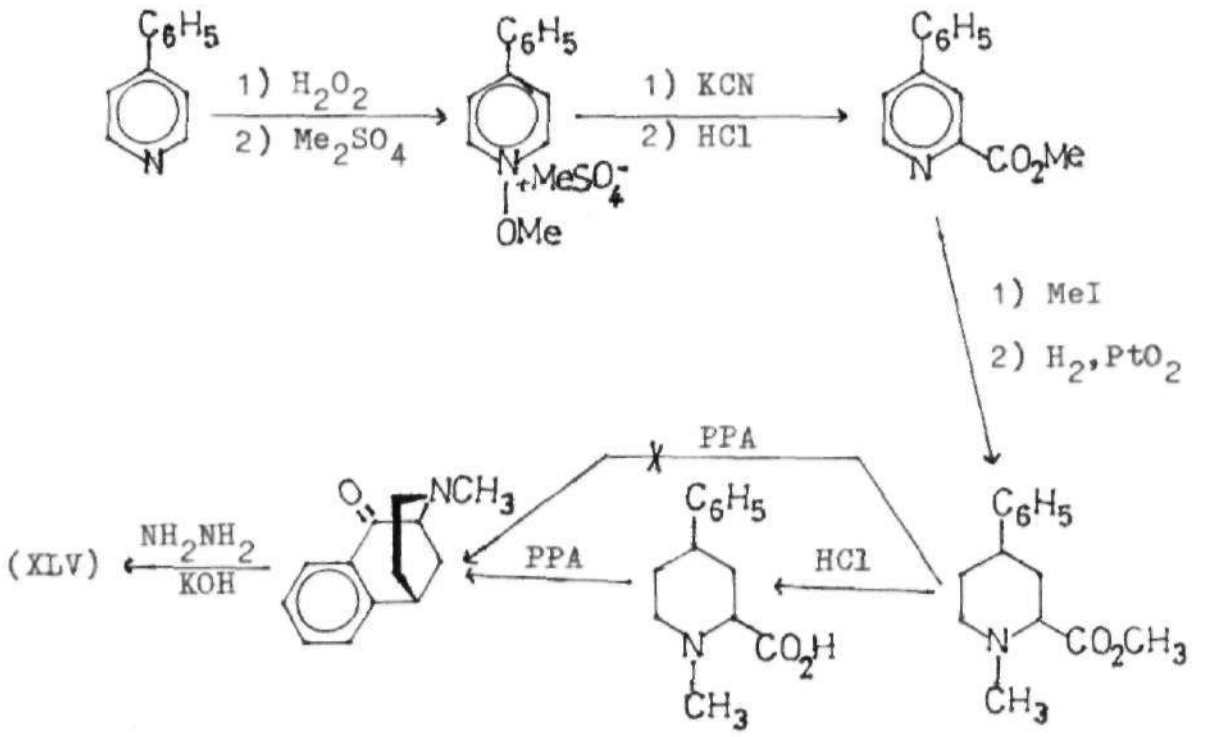
Mitsuhasi et al. (1969) employed tetralone route to prepare the nonquaternary carbon compound, 2-methyl benzomorphan (Scheme 2.3; XLV) which was previously prepared by Kanematsu et al. 1968; 1969) by an alternative route, (Scheme 2.4). The approach by Mitsuhasi et al. (1969) to the preparation of tetralone precursor (XLIV) involved conversion of 4-phenyl cyclohexanone to oxime followed by the Beckmann rearrangement to 5-phenyl caprolactam followed by hydrolysis with barium hydroxide,



Scheme 2.3

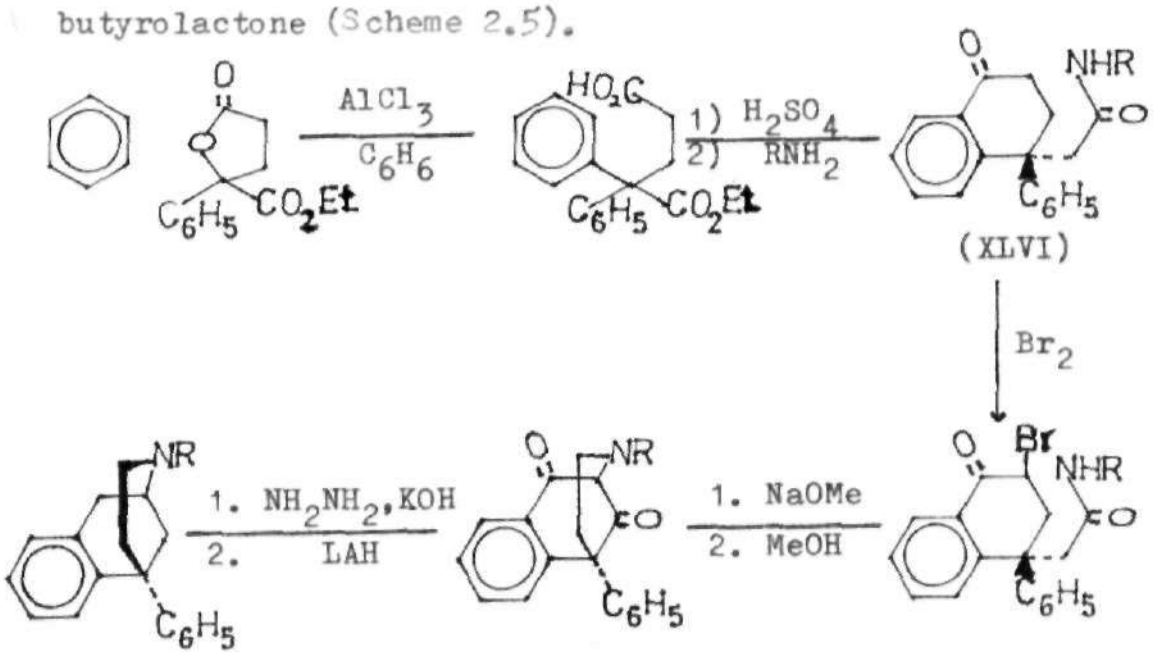
N-methylation, and cyclization with PPA to give XLIV. This was converted in usual manner to 2-methylbenzomorphan (XLV).

Kanematsu et al. (1968; 1969) also prepared 2-methylbenzomorphan (Scheme 2.4; XLV) starting from 4-phenyl pyridine.



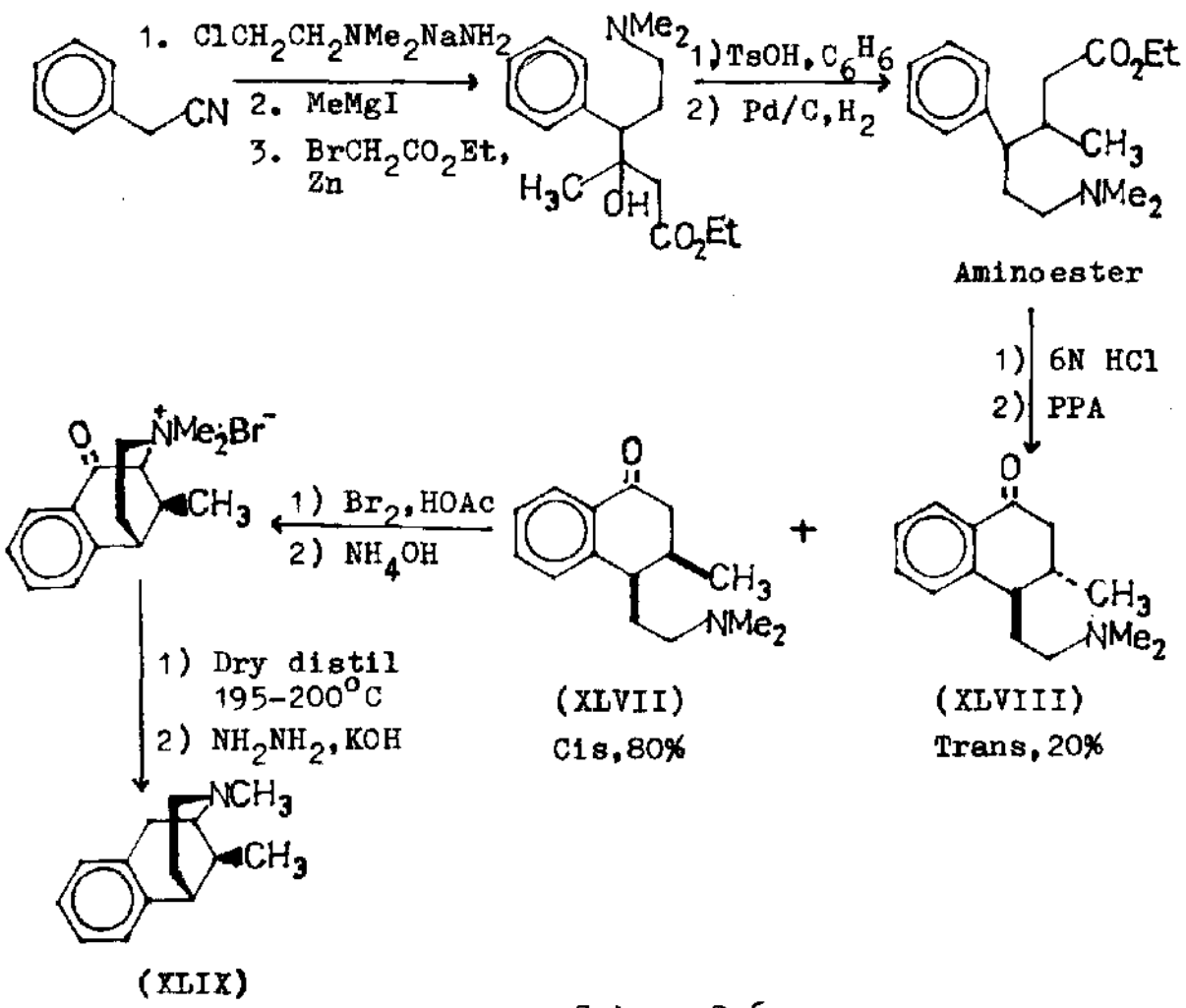
Scheme 2.4

The preparation of 5-phenyl-6,7-benzomorphan (Walker and Alkalay, 1966) involved the base catalysed cyclization of amido tetralone (XLVI), which was prepared by alkylation of benzene with γ-carboethoxy-γ-phenyl butyrolactone (Scheme 2.5).



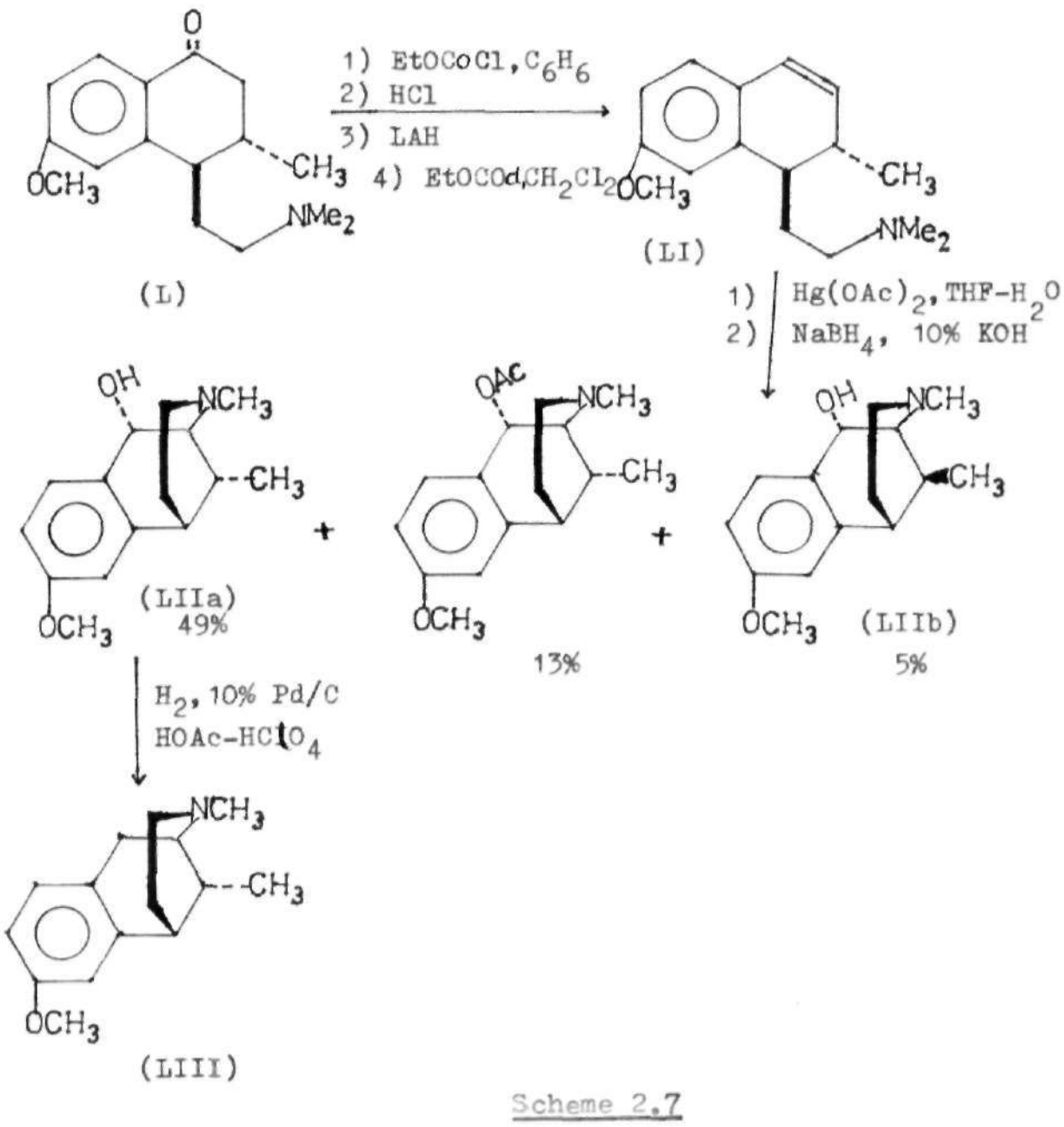
Scheme 2.5

Preparation of 2,9β-dimethyl-6,7-benzomorphan (Scheme 2.6; XLIX), unattainable by the usual Grewe cyclization, has been done utilizing tetralone route (Oh-ishi et al., 1974) starting from phenylacetonitrile to give the Reformatsky product, which was dehydrated and hydrogenated to afford amino ester. Hydrolysis followed by cyclization led to isomeric tetralone having cis isomer as major product which was converted to benzomorphan in the usual manner.



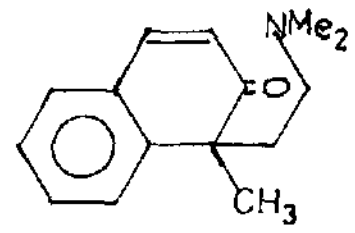
Scheme 2.6

A new modification of this synthesis has been reported in which cyclization is effected by mercuric acetate oxidation (Inoue and May, 1976) to prepare the 9α-methylbenzomorphans (Scheme 2.7; LIII) from the corresponding trans-3,4-disubstituted tetralone, (L). The formation of the 2,9β-dimethyl derivative (LIIb) was postulated to arise from inversion (by allylic rearrangement) at C-2 from intermediate LI.



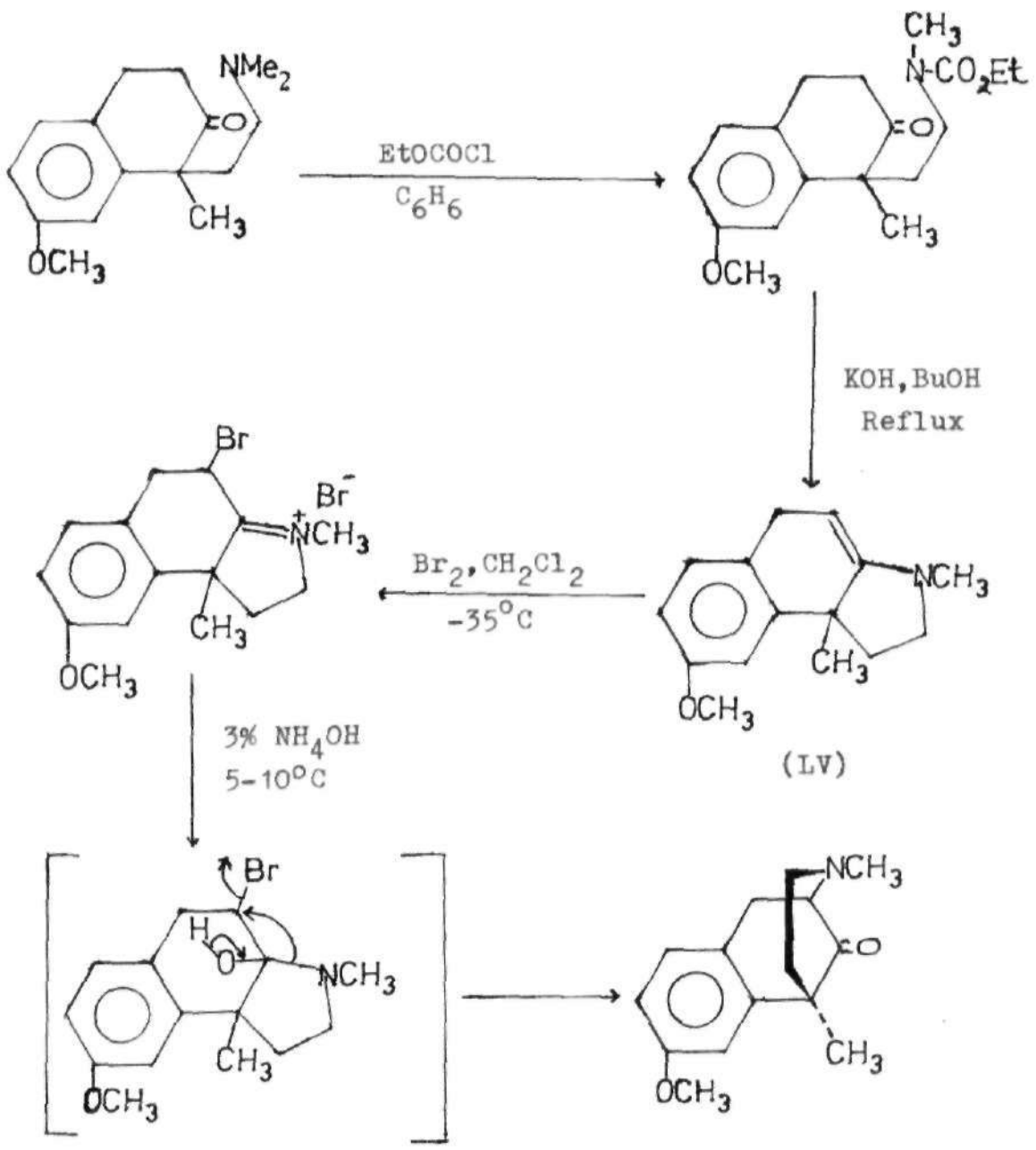
Scheme 2.7

The above β-tetralone synthesis suffer from low overall yield, and there are problems associated with cyclization and demethobromination (pyrolysis, therefore their application is limited to compounds that can survive the vigorous pyrolytic conditions) steps due to the formation of elimination products of type LIV.



(LIV)

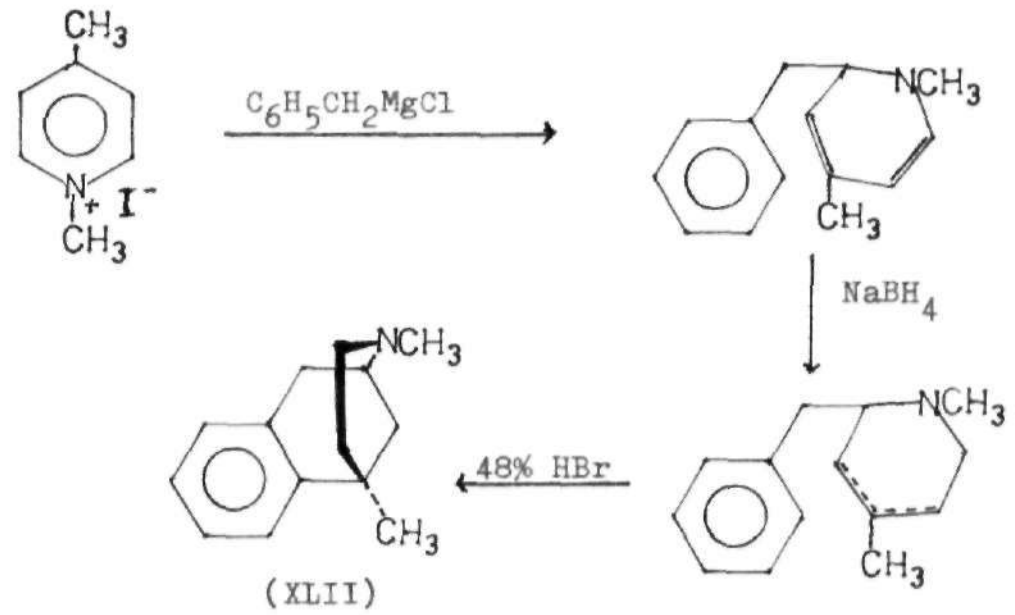
A novel synthesis to overcome these problems involves bromination and rearrangement of heterocyclic enamines (LV), (Takeda et al., 1972) (Scheme 2.8). Kavadias et al. (1979) synthesized 9-oxobenzomorphan with various substituents at the 2,2' and 5 positions in good yields by a modified process.



Scheme 2.8

8-oxo-6,7-benzomorphan (LXXV: Scheme 2.15) has been prepared by oxidation of previously prepared benzomorphan with chromic acid (Ziering et al., 1970; Fauley and Lapidus, 1973; Carr et al., 1980). The most widely used approach to benzomorphan synthesis is based on the Grewe cyclization of tetrahydropyridines (May and Fry, 1957; Fry and May, 1961; Fry, 1963; Joshi and May, 1965;

Eddy and May, 1966; Albertson and Walterau, 1970; Thyagarajan and May, 1971; Kametani et al., 1973) (Scheme 2.9). This method is analogous to Grewe's synthesis of morphine (Grewe and Mondon, 1948).



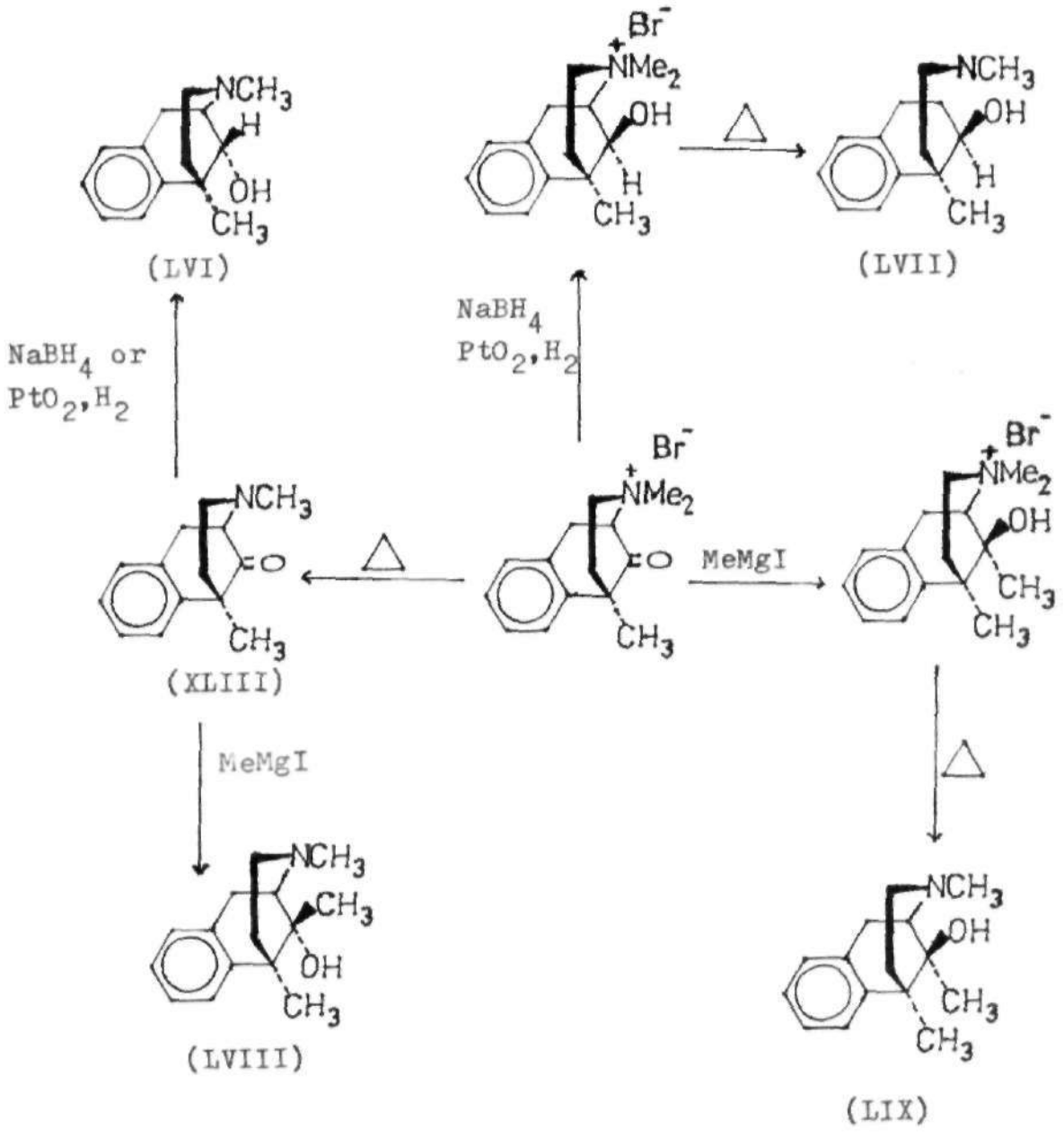
(XLII)

Scheme 2.9

2.4 REACTIONS OF BENZOPHANONES

Benzophanones provide useful intermediates which have been used for the synthesis of a variety of benzomorphan derivatives. Reduction of 9-oxobenzomorphan (XLIII) with platinum oxide (Kugita and May, 1961; May et al., 1961) or sodium borohydride (Carr et al., 1980) yielded 9α-hydroxybenzomorphan (LVI), whereas similar reduction of its methobromide gave, after thermal dequaternization, 9β-hydroxy benzomorphan (LVII) (Carr et al., 1980). Similar modes of addition occurred

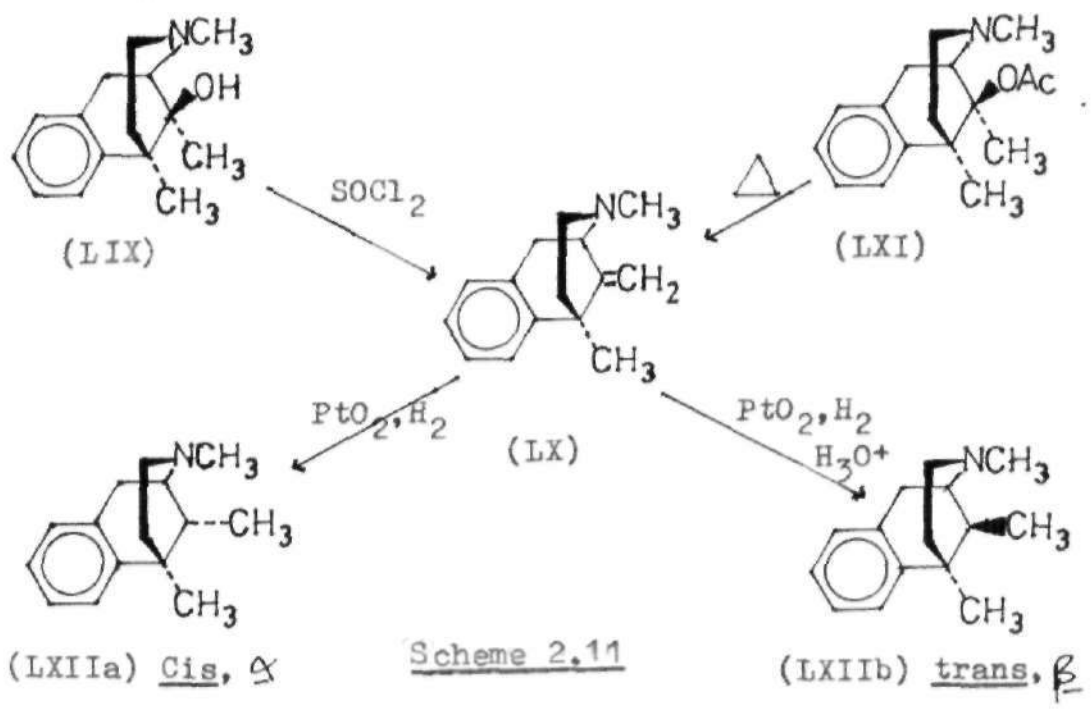
during Grignard or methyl lithium (May and Murphy, 1955; Carr et al., 1980) addition resulting in the formation of carbinol (LVIII) with hydroxyl cis to C-5 methyl and carbinol (LIX) with hydroxyl trans to C-5 methyl (Scheme 2.10).



Scheme 2.10

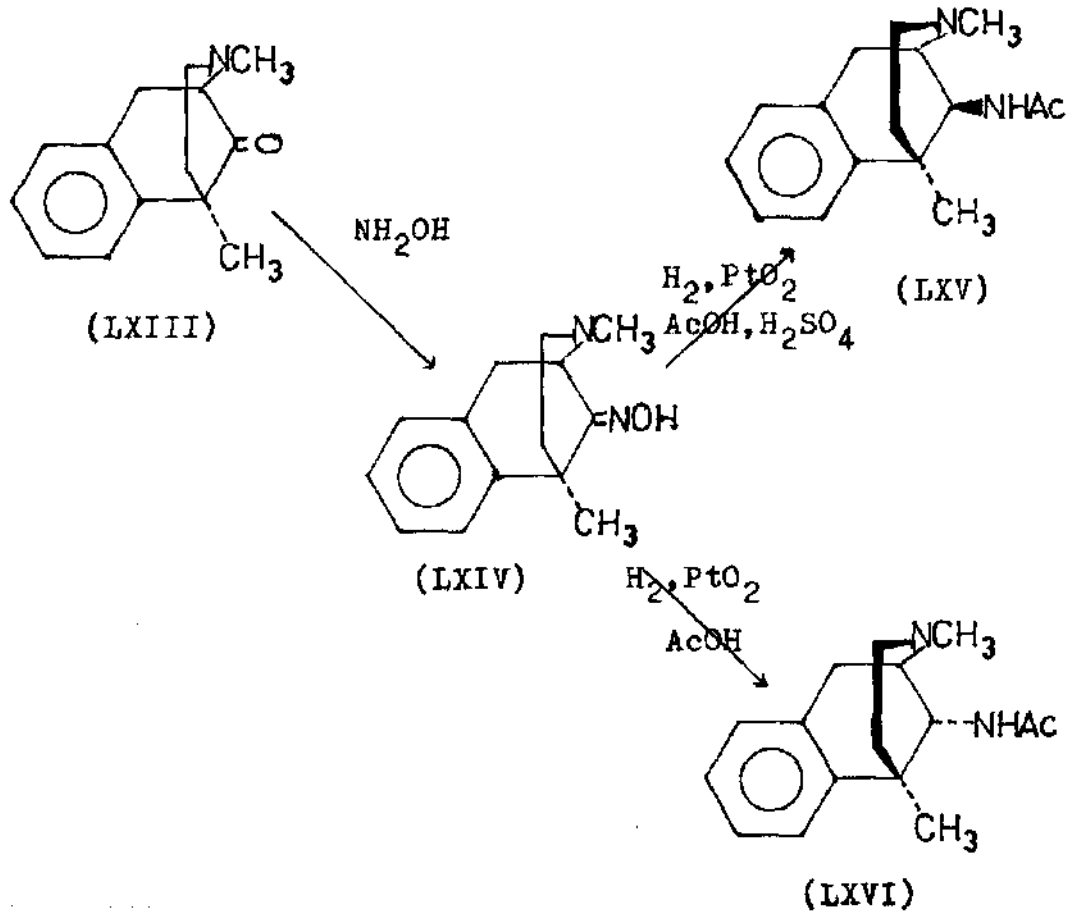
The mode of reaction was dependent on whether or not nitrogen was cationic. When nitrogen was cationic, addition to carbonyl compound occurred to yield alcohol with hydroxyl oriented towards nitrogen. With neutral tertiary nitrogen, the epimeric alcohol was formed (Saito and May, 1962).

Thionyl chloride dehydration of LIX gave 9-methylene-6,7-benzomorphan (LX) (Chignelli and May, 1965). Pyrolysis of 9-acetyl-9-methylbenzomorphan (LXI) also gave 9-methylene product (LX). Hydrogenation of 9-methylene benzomorphan was stereoselective depending again upon the condition of nitrogen atom (Saito and May, 1962); (Scheme 2.11; LXIIa and LXIIb). The α- and β-isomers of 9-hydroxymethyl-6,7-benzomorphan have been synthesized from the corresponding 9-methylene-6,7-benzomorphan (LX) by hydroboration under controlled conditions (Kugita and Takeda, 1963), followed by peroxide oxidation.



Scheme 2.11

Shiotani and Mitsuhasi (1972) converted 9-oxo-6,7-benzomorphan (LXIII) into oxime (LXIV), reduction of which demonstrated stereochemistry (Scheme 2.12). Hydrogenation of oxime LXIV) in the presence of acetic acid and sulphuric acid gave 9β-acetamide (LXV), but in presence of acetic acid it yielded only 9α-acetamide (LXVI).

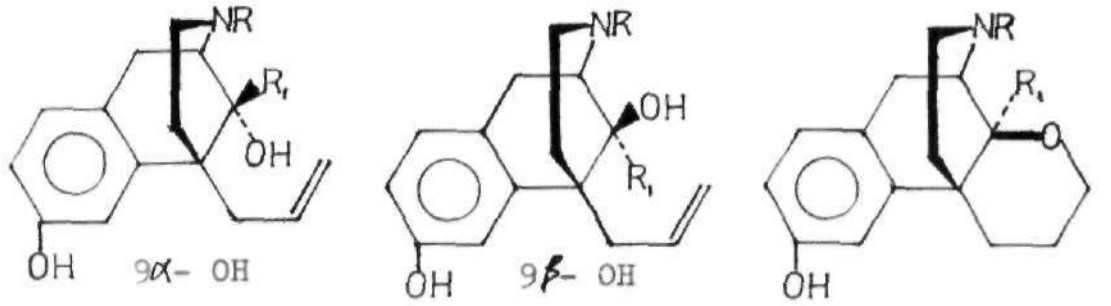


Scheme 2.12

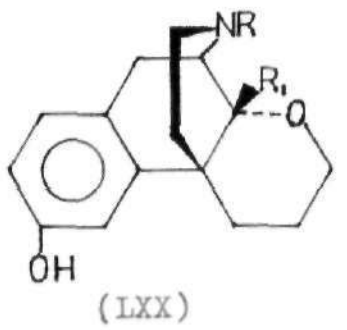
5-Allyl-9-oxo-6,7-benzomorphan and its methiodide salt were stereoselectively reduced to the corresponding 9α- and 9β-hydroxy compounds (LXVII, LXVIII) respectively (Lambert et al. 1978) which in turn were transformed to a number of 2-substituted-5-allyl-9-hydroxy-6,7-benzomorphans (Scheme 2.13).

A series of 3-hydroxy-8-oxaisomorphinans (LXIX) and 3-hydroxy-8-oxamorphinans (LXX) were derived from corresponding 9β- and 9α-hydroxybenzomorphans (LXVIII, LXVII) respectively (Scheme 2.13).

8-Oxobenzomorphans have provided a means of access to 8-hydroxy-6,7-benzomorphans and thence the acetyl derivatives. Catalytic reduction of the 8-oxo compound (LXXI) with palladium-charcoal or platinum oxide gave only one and the same diastereoisomer(LXXII) (May and Murphy, 1955). Reduction of the ketone (LXXI)



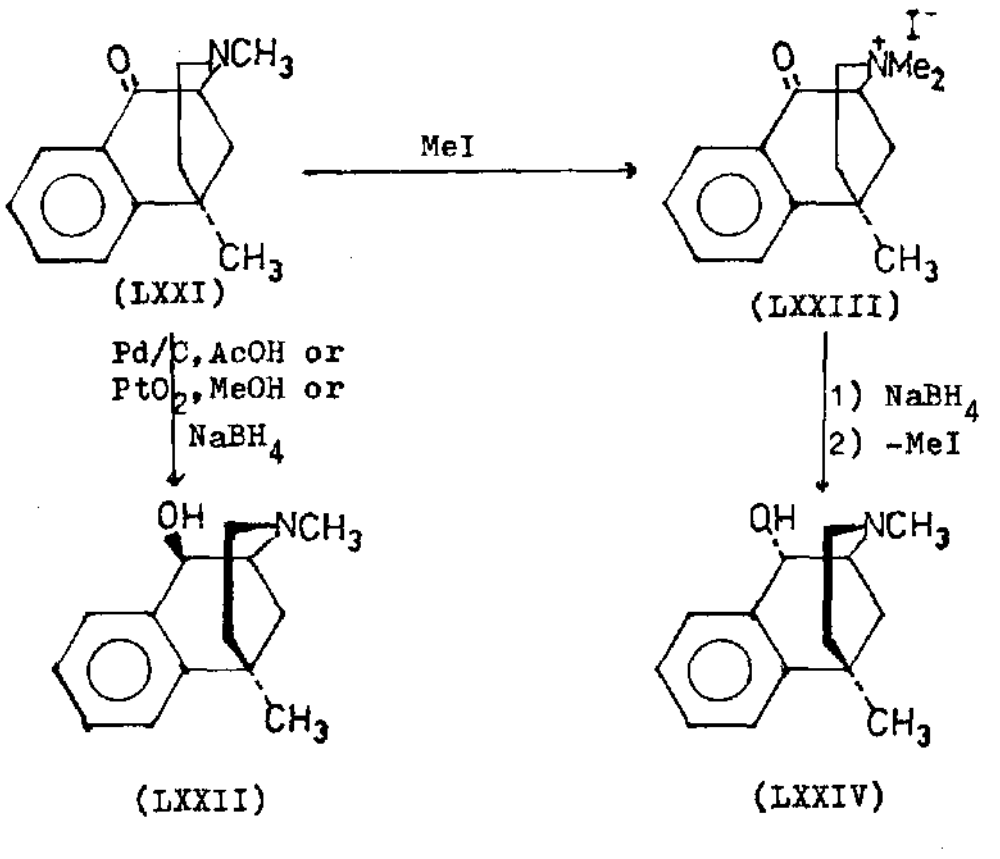
(LXVII) (LXVIII) (LXIX)



(LXX)

(Scheme 2.13

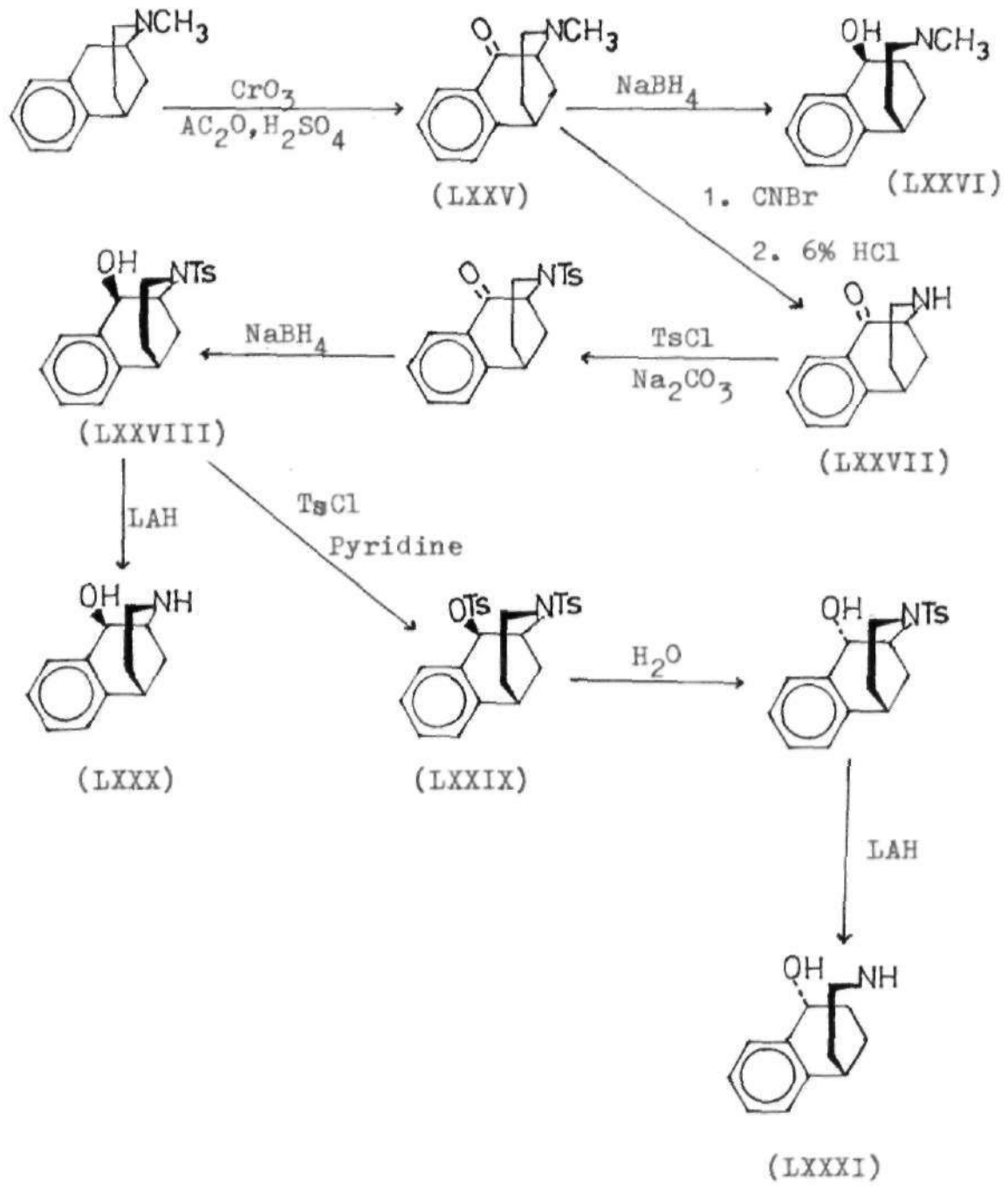
with $NaBH_4$ also gave 8β-hydroxy-6,7-benzomorphan (LXXII) whereas similar reduction of its methiodide (LXXIII) gave the 8α-hydroxy compound (Scheme 2.14; LXXIV) (Parfitt et al., 1981).



Scheme 2.14

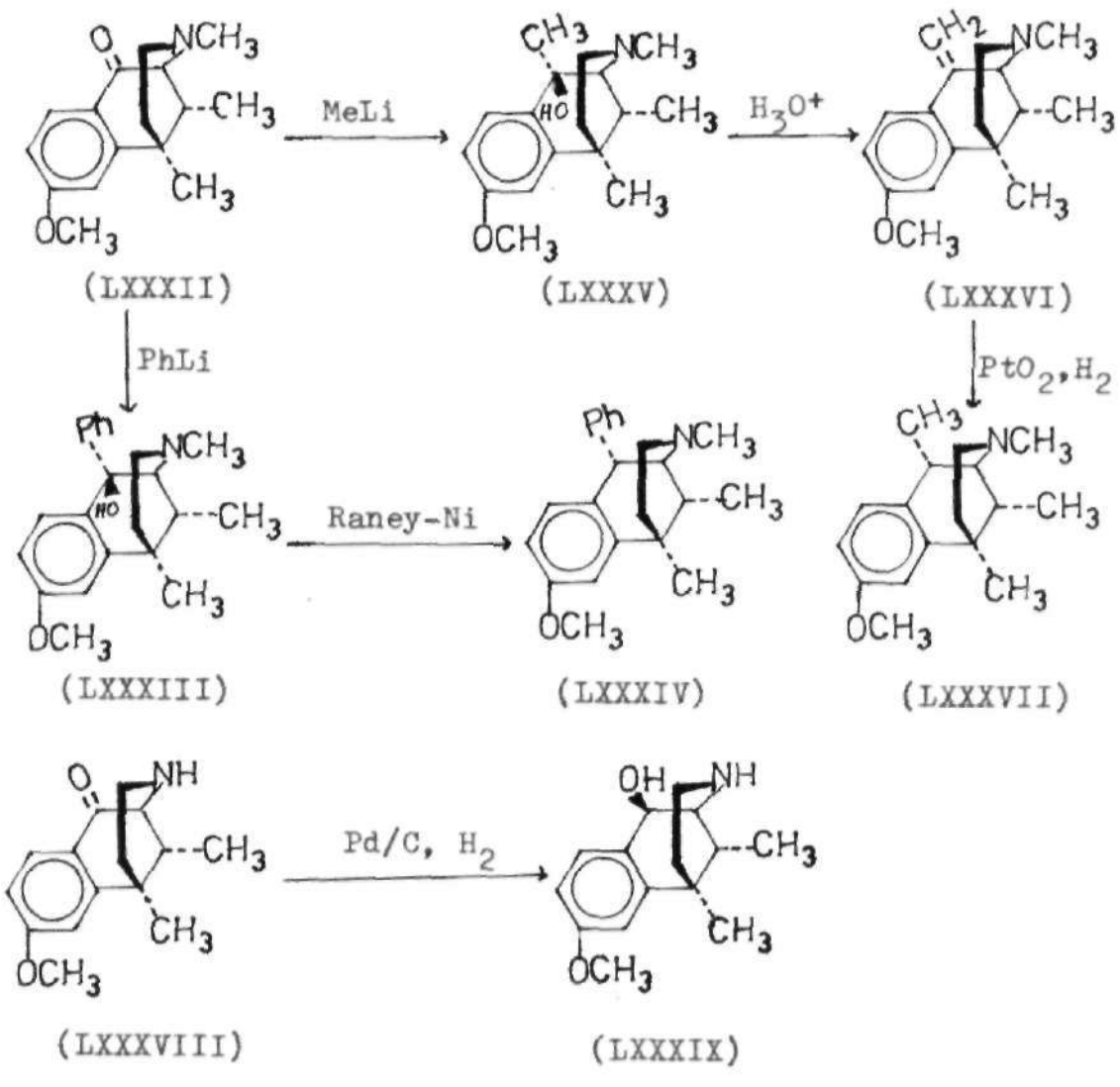
The diastereoisomerically related 8α- and 8β-hydroxy-6,7-benzomorphans (LXXX, LXXXI) were prepared from 8-oxobenzomorphan (LXXV) (Fauley and Lapidus, 1973). Reduction of 8-oxobenzomorphan (LXXV) with sodium borohydride yielded only 2-methyl-8β-hydroxydiastereoisomer (LXXVI). The N-demethylated compound (LXXVII) was converted to the 2-tosyl derivative, which upon reduction and detosylation afforded exclusively 8β-hydroxy-6,7-benzomorphan (LXXX). Conversion of 2-tosyl-8β-hydroxybenzomorphan (LXXVIII) to the 2-tosyl-8β-tosyl-derivative (LXXIX) followed by aqueous

solvolysis and detosylation of the later gave 8α-hydroxy-6,7-benzomorphan (Scheme 2.15; LXXXI).



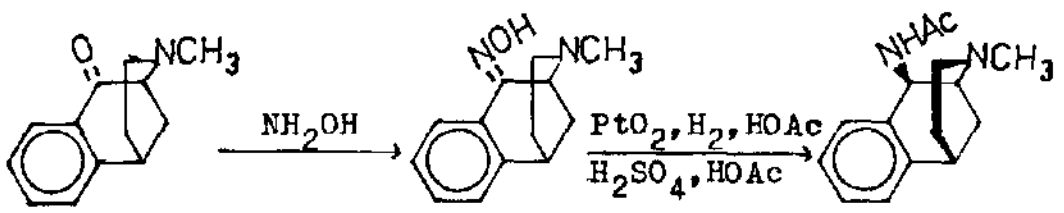
Scheme 2.15

Reaction of phenyl lithium with the 2,5,9-trimethyl-8-oxo-6,7-benzomorphan (LXXXII) gave 8,8-difunctionalized benzomorphan (LXXXIII) which on hydrogenolysis gave 8α-phenyl derivative (Scheme 2.16; LXXXIV). Treatment of LXXXII with methyl lithium afforded carbinol (LXXXV) which dehydrates with acid to give 8-methylene compound (LXXXVI). Catalytic reduction of LXXXVI gave 8β-methyl-6,7-benzomorphan (Ziering et al., 1970) (Scheme 2.16; LXXXVIII). Catalytic hydrogenation of N-demethylated compound (LXXXVIII) afforded 8β-hydroxy-6,7-benzomorphan (Michne and Albertson, 1972), (Scheme 2.16; LXXXIX).



Scheme 2.16

8-Oxobenzomorphan (LXXV) was converted to oxime (CXVI) which catalytically reduced in either acetic acid or acetic acid and sulphuric acid to give only 8β-acetamidobenzomorphan (Shiotani and Mitsuhashi, 1972)(Scheme 2.17;XC); this is in contrast to similar reduction of the oxime(LXIV)(Scheme 2.12).

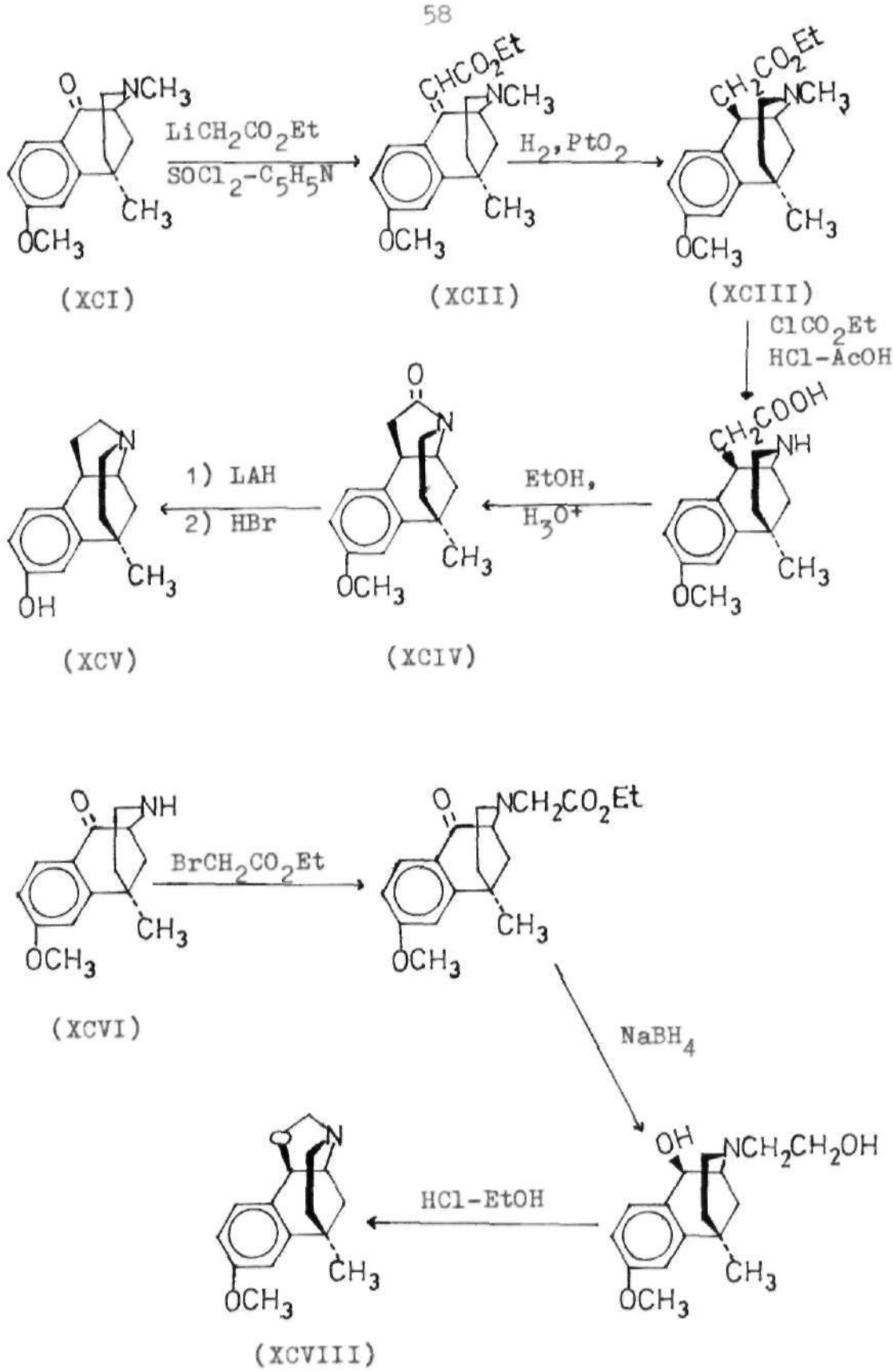


(LXXV) (CXVI) (XC)

Scheme 2.17

Treatment of 2,5-dimethyl-8-oxo-6,7-benzomorphan (Scheme 2.18;XCI) with lithium ethylacetate followed by dehydration with thionyl chloride-pyridine gave 8-ethoxycarbonyl methylene compound (XCII). Catalytic hydrogenation of XCII gave 8β-ethoxycarbonylmethylene isomer (XCIII) which, after N-demethylation, was cyclized to give lactam (XCIV). The lactam (XCIV) was reduced with lithium aluminium hydride, and O-demethylated to give 2,8-bridged benzomorphan (XCV).

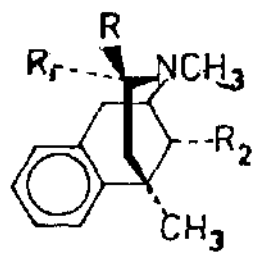
Treatment of ketone (XCVI) with ethylbromoacetate, followed by reduction with sodium borohydride yielded diol (XCVII), which cyclized by treatment with ethanol-hydrochloric acid to give morpholino compound (XCVIII) (Shiotani and Kometani, 1980).


LiCH2CO2Et
SOCl2-C5H5N
H2,PtO2
ClCO2Et
HCl-AcOH
EtOH,
H3O+
1) LAH
2) HBr
BrCH2CO2Et
NaBH4
HCl-EtOH
(XCI)
(XCII)
(XCIII)
(XCIV)
(XCV)
(XCVI)
(XCVIII)

Scheme 2.18

Reactions of 3-mono and 3,3-disubstituted benzomorphans have been reported by Ogundaini and Parfitt (1985). without C-9 methyl substituent, both α-cis (XCIXa) and β -trans (XCIXb) epimers were isolated. However, with C-9 methyl group present, only the predominant α-cis epimer (XCIXC) was formed.

The insertion of alkyl, aralkyl or alkenyl groups α- to nitrogen in (XCIXa,b,c) was effected through the intermediate(Scheme 2.19;C). Mercury II acetate



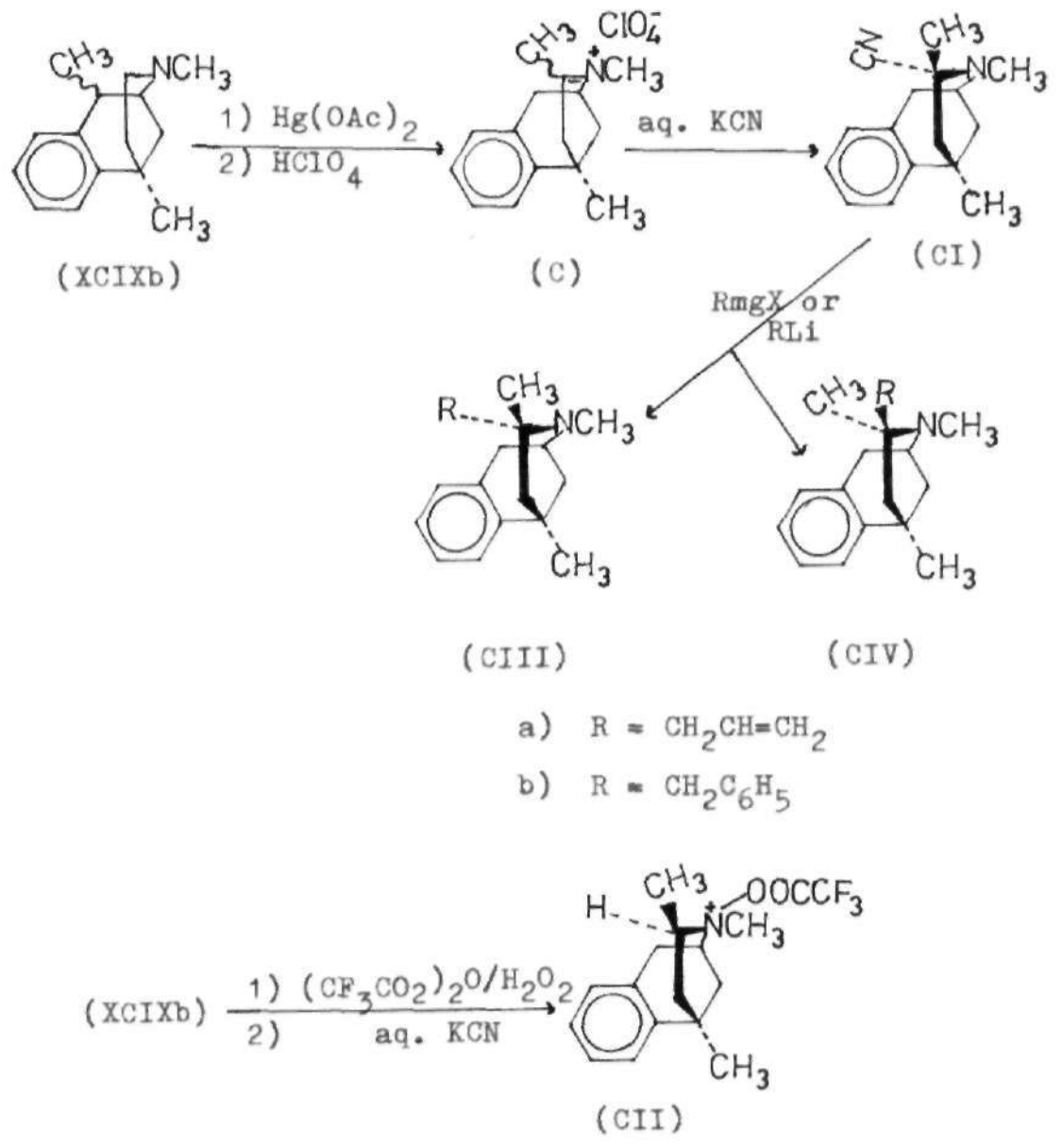
(a) $R = R_2 = H$; $R_1 = Me$
(b) $R_1 = R_2 = H$; $R = Me$
(c) $R_1 = R_2 = Me$ $R = H$

(XCIX)

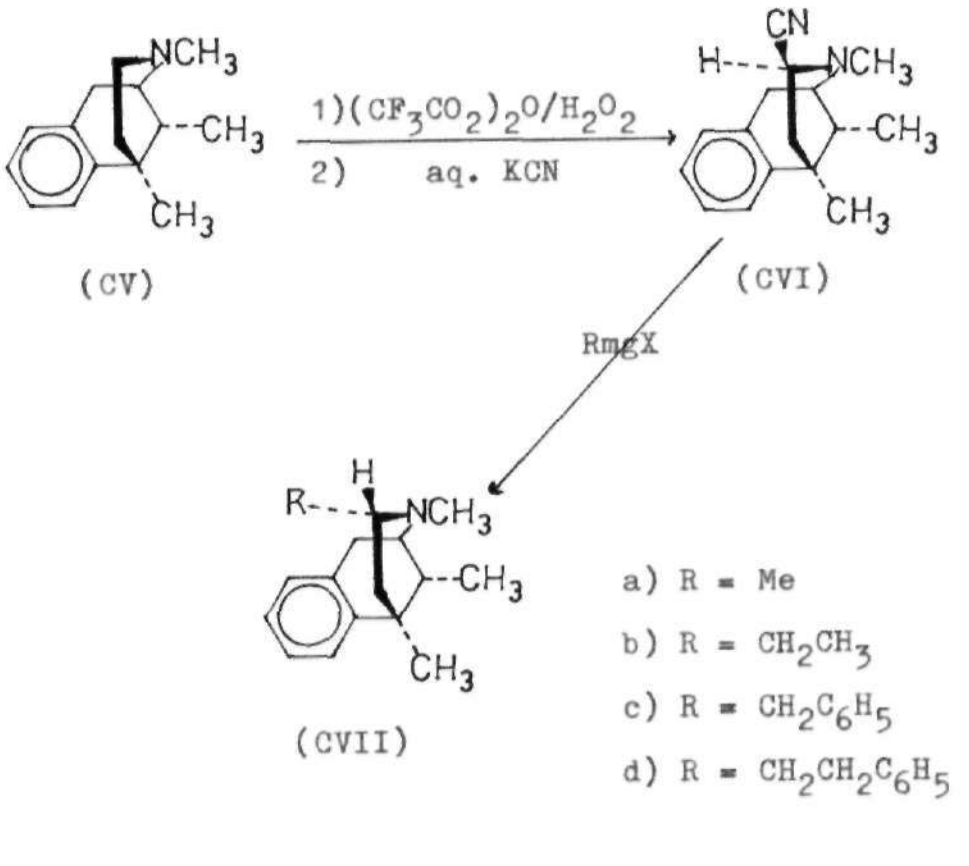
oxidation of XCIXa or XCIXb gave the perchlorate (C) which on treatment with aqueous potassium cyanide gave 3-cyano-3-methylbenzomorphan (CI). Reaction of 3-cyano benzomorphan (CI) with benzyl and allyl magnesium halides gave the corresponding diastereoisomers epimeric about 3-position(Scheme2.19; CIIIa and CIVa; CIIIb and CIVb) (Ogundaini and Parfitt, 1985).

An identical compound with higher yield was obtained by treating XCIXb with hydrogen peroxide and trifluoroacetic anhydride to afford (CII) which was then reacted with aqueous potassium cyanide. This method was employed for the conversion of compounds

lacking a 3-methyl substituent (CV) to the corresponding cyanobenzomorphans (Scheme 2.20; CVI). Insertion of appropriate substituents in the 3-position was by reacting CVI with lithium alkyl or Grignard reagents (Scheme 2.20; CVIIa,b,c,d) (Ogundaini and Parfitt, 1985).



Scheme 2.19


NCH3
CH3
CH3
1)(CF3CO2)2O/H2O2
2) aq. KCN
CN
H
NCH3
CH3
CH3
(CV)
(CVI)
RmgX
H
R
NCH3
CH3
CH3
(CVII)
a) R = Me
b) R = CH2CH3
c) R = CH2C6H5
d) R = CH2CH2C6H5

Scheme 2.20

CHAPTER THREE

D I S C U S S I O N :

SYNTHESIS OF 9-AMINO-6,7-BENZOMORPHAN

9-AMINO-6,7-BENZOMORPHANS

3.0 INTRODUCTION

The mechanism by which opiates elicit their biological responses is poorly understood but is known to involve principally interactions with one or more opiate receptors in the central nervous system. A necessary feature of an opiate molecule is its basic centre (Eddy et al., 1969; Thyagarajan and May, 1971). It is believed that the opiate nitrogen interacts with a receptor either via its lone electron pair (Balleau et al., 1974; Kolb, 1978) or its protonated form (Beckett and Casy, 1954b; Portoghese, 1966; Feinberg et al., 1976). In either case, the electron density on the nitrogen plays an important role in pharmacological activity.

The concept of a single receptor defined by a rigid morphine skeleton is incompatible with present-day stereochemical and structure-activity data. It is more likely that analgesics bind ionically with a relatively simple, identical anionic centre which acts as a pivot around which a variety of modes of binding may occur (Portoghese, 1965 and Portoghese et al., 1981). It is noteworthy that simple amines like β-phenylethylamine, 3-aminocyclohexene, 2-aminoindane fulfil the simple requirements for receptor binding in terms of structure and spacial configuration; these amines have

been reported to possess some analgesic activity (Avramaff, 1981).

6,7-Benzomorphans, which are semi-rigid, afford the most versatile series of synthetic compounds for investigating the nature of opiate receptors. Chemical modifications by altering the substituents at several positions of benzomorphan nucleus have been intensively studied (Ager et al., 1963; de Stevens, 1965; Ager et al., 1965; Archer et al., 1964; Tuller et al., 1967; Ager et al., 1969; Block and Clarke, 1969; May and Takeda, 1970; Yokoyama et al., 1970; Ziering et al., 1970; Yokoyama et al., 1979; Merz et al., 1979; Merz and Stockhaus, 1979; Martindle, 1977; Merz et al., 1975; Shiotani and Kometani, 1980), and these modifications have led to the discovery of a considerable number of compounds possessing interesting profiles with respect to analgesic activity. Several workers have proposed that the distance of the nitrogen atom relative to the aromatic ring is critical for interactions (Opheim and Cox, 1976; Schiller et al., 1977; Shiotani and Kometani, 1978; Kometani and Shiotani, 1978).

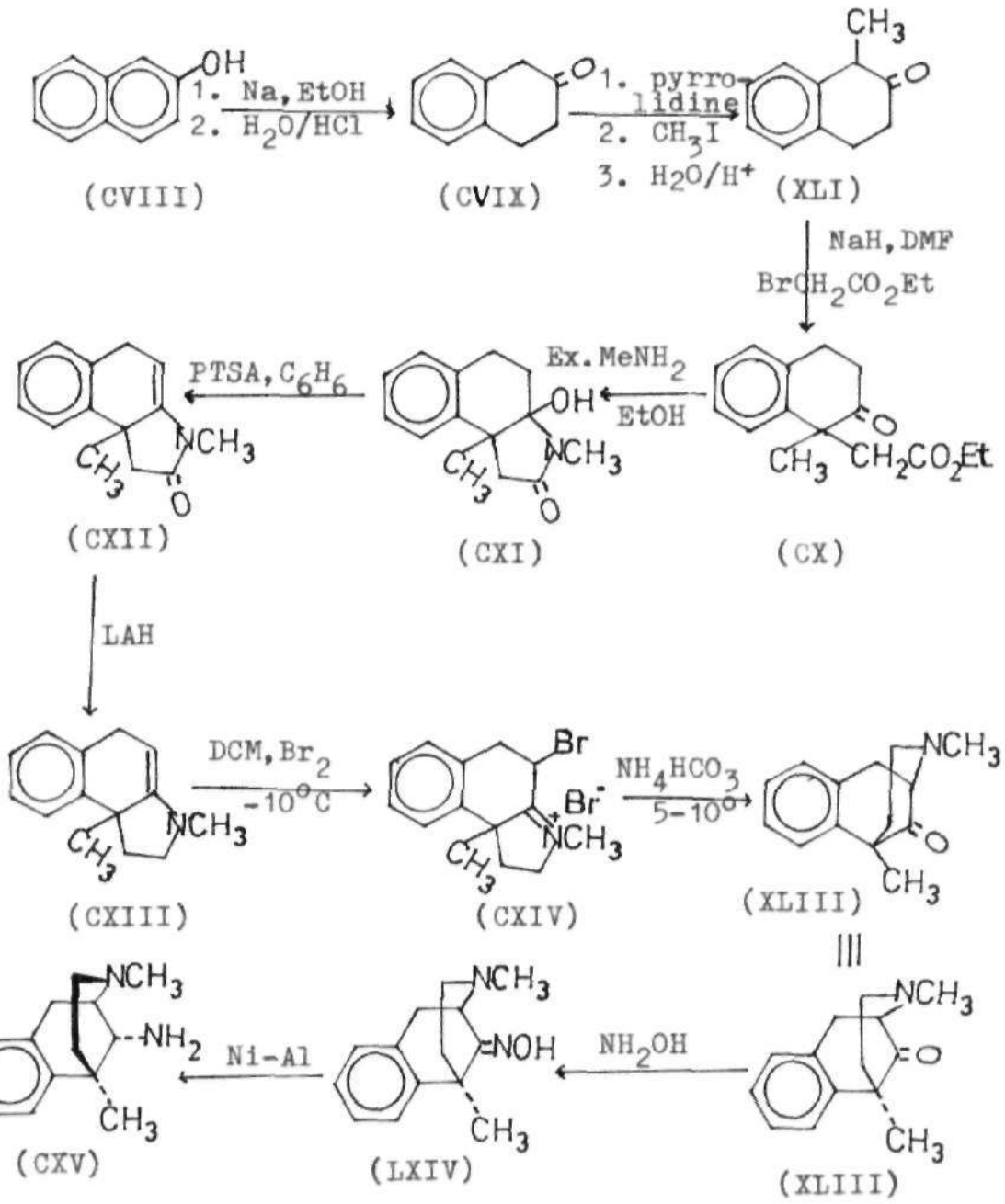
However, no compound which exhibits potent opiate analgesic activity with nitrogen at the 9-position has been reported in the literature - the effect on biological activity of placing a nitrogen atom at this apparently important position in the benzomorphan nucleus. In this

Chapter, the synthesis of 9α-amino-6,7-benzomorphan is described.

The introduction of a second nitrogen pharmacophore would affect pKa and electron density distribution of the benzomorphan, and thus should markedly influence opiate activity. It might also alter the fit between the opiate and its receptor(s), and thus may further define receptor requirements.

3.1 SYNTHETIC ROUTE TO 9-AMINO-6,7-BENZOMORPHAN

The synthetic route employed for 9α-amino-6,7-benzomorphan is shown schematically in Scheme 3.1. (Kavadias et al., 1979).



Scheme 3.1

3.2 SYNTHESIS OF 2-TETRALONE, (CVIX)

Various methods have been established for the oxidation of secondary alcohols to ketones. These include the use of aqueous potassium dichromate in glacial acetic acid; chromium trioxide in glacial acetic acid or in acetone, water and sulphuric acid (Jone's reagent) or in pyridine (Sarett's reagent); sodium dichromate in aqueous sulphuric acid and reflux; hot potassium permanganate (which is seldomly used because oxidation tends to go beyond the ketone stage, with breaking of carbon-carbon bonds).

Generally however, these processes are feasible with aliphatic or alicyclic secondary alcohols and, in some cases, unsaturated secondary alcohols may be oxidised without affecting a carbon-carbon double bond present in the same molecule (such as Jone's and Sarett's reagents). Since the conversion of 2-naphthol to 2-tetralone involves reduction and hydrolysis, these processes were therefore not suitable and had to be abandoned.

A literature survey revealed that several procedures existed for the conversion of substituted 2-naphthols to their corresponding 2-tetralones. These practical procedures include the ones involving the reduction of 2-naphthyl methyl ether with sodium and alcohol (Cornforth *et al.*, 1942) or with sodium and liquid ammonia (Birch, 1944; Barltrop *et al.*, 1952);

high pressure catalytic hydrogenation of 2-naphthol (Stork and Foreman, 1946); catalytic oxidation of 2-tetralol by hydrogen transfer with ethylene (Adkins et al, 1948), or the condensation of ethylene with phenylacetyl chloride in the presence of aluminium chloride (Burckhalter and Campbell, 1961).

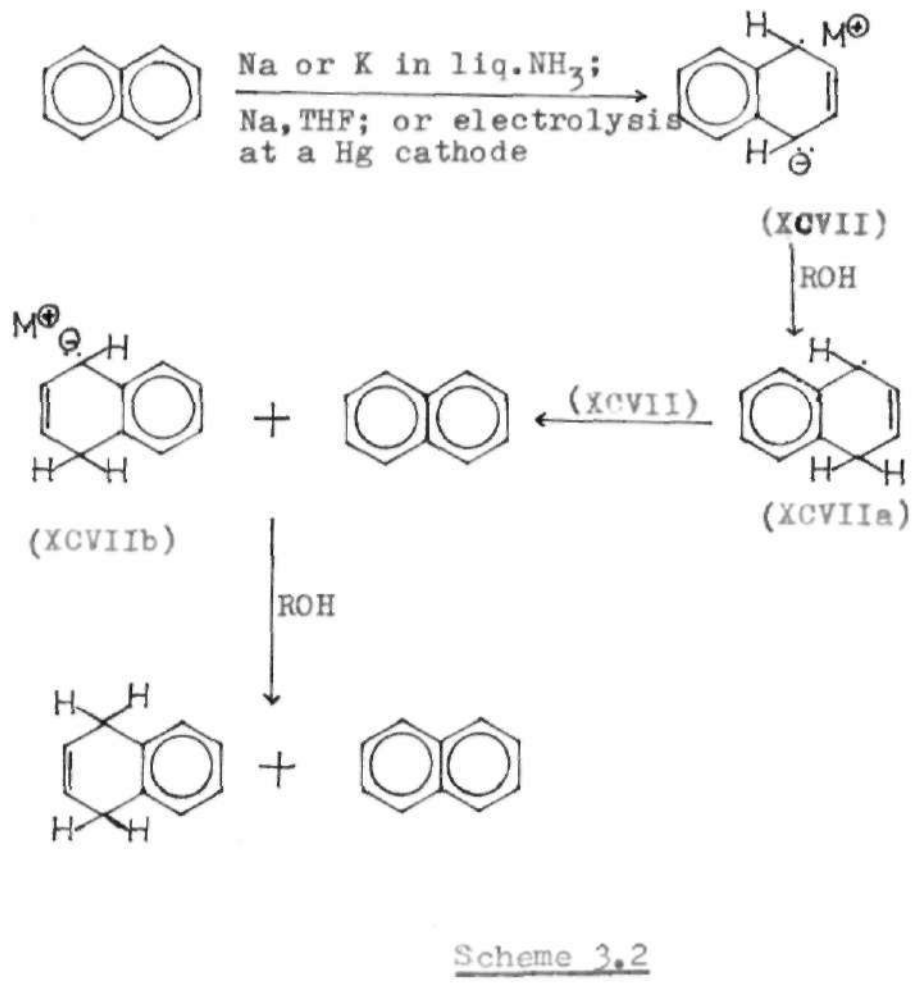
The method of Cornforth et al. (1942), initially chosen for its simplicity was abandoned because of negligible yield obtained. Thus the procedure described by Soffer et al. (1963) as an adaptation (Soffer et al., 1950) of the method of Cornforth et al. (1942) was used.

Various types of dissolving metal reductions of conjugated systems are available. These include the dissolving metal reductions of carbon-carbon double bonds conjugated with carbonyl groups, aromatic systems, or other carbon-carbon multiple bonds; and the dissolving metal reductions of aromatic systems to form dihydro or tetrahydro aromatic systems. Although α,β-unsaturated carbonyl compounds are initially reduced to saturated carbonyl compounds with zinc in acetic acid or zinc-amalgam in aqueous acid (Clemmensen reduction conditions), reduction with zinc or zinc-amalgam in acidic media may be complicated by olefin formation or by rearrangement (Mckenna et al., 1959; Davis and Woodgate, 1965; Buchanan and Woodgate, 1969).

Carbon-skeleton rearrangement is not observed (House et al., 1970) under more typical reduction conditions (Birch, 1950; Watt, 1950; Birch and Smith, 1958; Smith, 1968; Reusch, 1968) with an alkali metal (usually lithium or sodium) and a proton donor in liquid ammonia. This metal-ammonia reduction is characterized by its ability to selectively reduce conjugated carbon-carbon double bonds to form non-conjugated ketones (Halsall et al., 1964).

The nature of the reduction product of carbon-carbon double bonds conjugated with aromatic systems or with other multiple bonds using metals is dependent on the availability of a proton donor in the reaction medium. In the absence of an excess proton donor, dimerization of the initially formed anion radical (XCVII) is observed (Weyenberg, 1965).

The ability of alkali metals to partially reduce aromatic systems has proved especially useful in organic synthesis (Birch, 1950; Watt, 1950; Birch and Smith, 1958; Smith, 1968; Reusch, 1968). Among the reductions of polycyclic aromatic compounds, studies with naphthalene have been most extensive (Scheme 3.2)



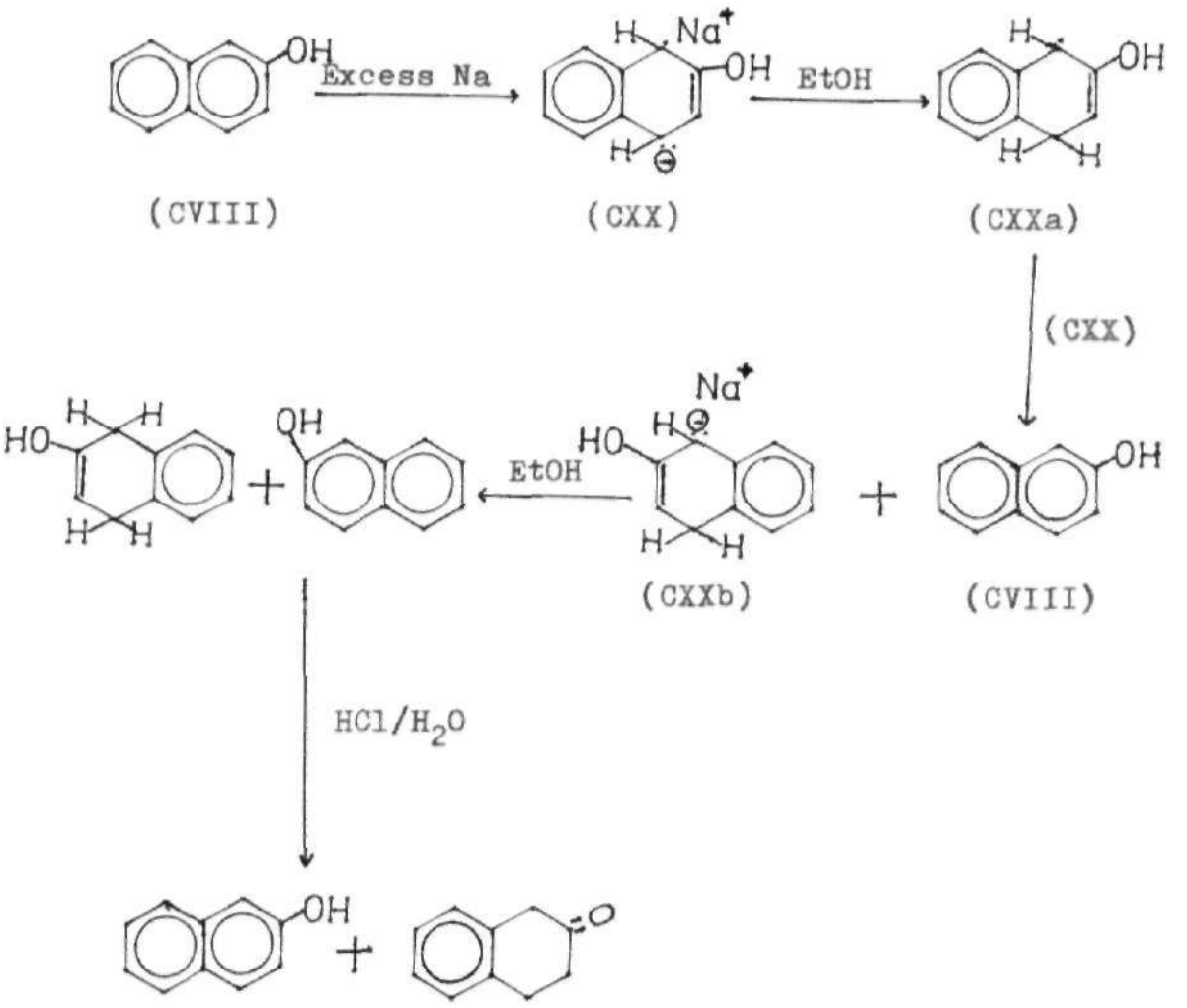
Scheme 3.2

In reductions of benzene derivatives, the anion radical (XCVII) is formed reversibly in low concentration and then reacts further with a proton solvent to form the radical (XCVIIa), and subsequently, the anion (XCVIIb) and the dihydro derivatives (Krapcho and Bothner-By, 1959; 1960; Eastham and Larkin, 1959; Krapcho and Nadel, 1964). Thus one important function of the alcohol in the reduction of benzene derivatives is to provide a proton source that is more acidic than ammonia. The difficulty involved in using liquid ammonia solution is the presence of iron compounds; common impurities in undistilled

liquid ammonia; which lowers the overall reducing ability of metal-ammonia solutions presumably by catalyzing the reaction of metal with ammonia to form hydrogen and metal amide.

The selective reduction of the non-substituted ring of 1-naphthol illustrates the deactivating influence of an electron-donating hydroxide substituent. However, the substituted ring can be reduced by the use of ammonia solutions containing higher (4 to 5M) than normal (1.5M) concentrations of lithium (Fried et al., 1967).

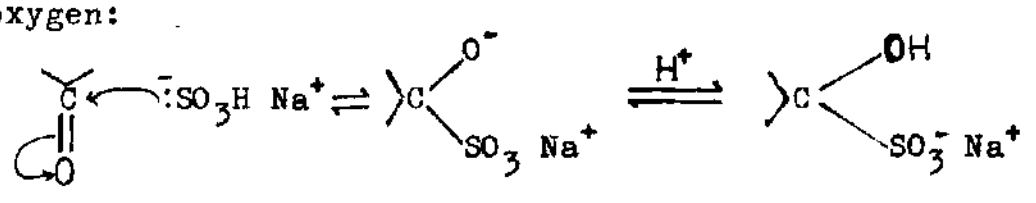
Although the relative rates of reduction of benzene with alkali metals and ethanol in liquid ammonia follow the order lithium > sodium > potassium, all three are sufficiently rapid to be synthetically useful. In certain cases, the selection of an alcohol of the correct acidity to serve as a proton donor may be important for successful reduction (Marvel and Lazier, 1944; Burgstahler and Worden, 1964). The possible mechanism of reduction of 2-naphthol has been suggested (Scheme 3.3).



Scheme 3.3

Sodium bisulphite undergoes nucleophilic addition to ketones (and in fact, all carbonyl compounds, where there is no steric hinderance) to form the bisulphite addition products. This reaction is carried out by mixing ketone with a concentrated aqueous solution of sodium bisulphite, the product separates as a crystalline solid. The addition involves nucleophilic attack by bisulphite ion on carbonyl carbon, followed

by attachment of a hydrogen ion to the carbonyl oxygen:



This addition reaction is reversible. Addition of warm acid or base destroys the bisulphite ion in equilibrium with the addition product, and regenerates the carbonyl compound, which is then extracted with ether.

Bisulphite addition products are generally prepared for the purpose of separating a carbonyl compound from non-carbonyl compounds. The carbonyl compound can be purified by conversion into its bisulphite addition product, separation of the crystalline addition product from the non-carbonyl impurities, and subsequent regeneration of the carbonyl compound by addition of base which destroys the hydrogen bisulphite ion, shifting the equilibrium to the left and regenerating the carbonyl compound. This addition product being somewhat soluble in water, dissolves in the aqueous layer.

The reduction of 2-naphthol in ethanol was carried out under mechanical stirring with sodium. Towards the end of the addition of sodium, the rate of the reaction decreased and heat was supplied by means of electric heating mantle to maintain the

reflux temperature. Heating continued until all the metal dissolved. This hot mixture was hydrolysed in aqueous hydrochloric acid and heated for further 30 minutes at reflux temperature before allowing to cool. Extraction with benzene and distillation gave an oily residue which was converted to the bisulphite addition product through the addition of the sodium bisulphite solution to the hot oily residue.

The oily residue thus obtained was crystallized through formation of bisulphite addition product, and regeneration of the carbonyl compound by addition of base afforded the ketone (CVIX) in 20% yield. Its i.r. spectrum showed bands at 1710 cm^{-1} ( )C = O). The n.m.r. spectrum displayed signals at δ 2.48 (triplet, C_4-benzylic protons) and at δ 7.12 (multiplet for aromatic protons). For further confirmation, its 2,4-dinitrophenylhydrazone derivative was prepared to show the presence of the carbonyl function.

3.3 SYNTHESIS OF 1-METHYL-2-TETRALONE (XLI)

The compound (CVIX) was treated with pyrrolidine and benzene (as carrier) and refluxed for 3 hours. Removal of the solvent by distillation gave a crystalline product, (Infra-red, 1570, 1620cm^{-1} unresolved benzene and enamine bands, melting point 80-82^{o}C), which was refluxed for further ten hours with methyl iodide in 1,4-dioxane. Hydrolysis with

aqueous acid followed by further heating for four hours. The reaction mixture was worked up and extracted with ether. The ethereal extract on distillation gave 1-methyl-2-tetralone in 72% yield.

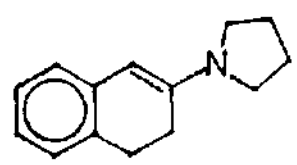
The infra red of the product showed a carbonyl stretching frequency at 1710cm^{-1}. Its n.m.r. absorption exhibited a doublet at δ 1.5 for C_1 methyl proton with J$\approx$6 Hz. The C_4 benzylic protons appeared at δ 2.3 as multiplet.

Enamines (α,β-unsaturated amines) are prepared by the reaction of secondary amine on an aldehyde or ketone in the presence of a dehydrating agent such as anhydrous potassium carbonate or para-toluene sulphonic acid (PTSA). However, superior yields of N-pyrrolidyl enamines of certain ketones may be obtained by azeotropic distillation with benzene.

The enamine reaction is a method for alkylating ketones and aldehydes with α-hydrogens, and a variety of substituents are readily introduced into the enamine. Readily ionizable halides such as allyl, benzyl, α-halo-substituted ethers, ketones, esters and nitriles, give good yield of the alkylated ketones. These products are the most difficult to prepare by the conventional β-ketoester path.

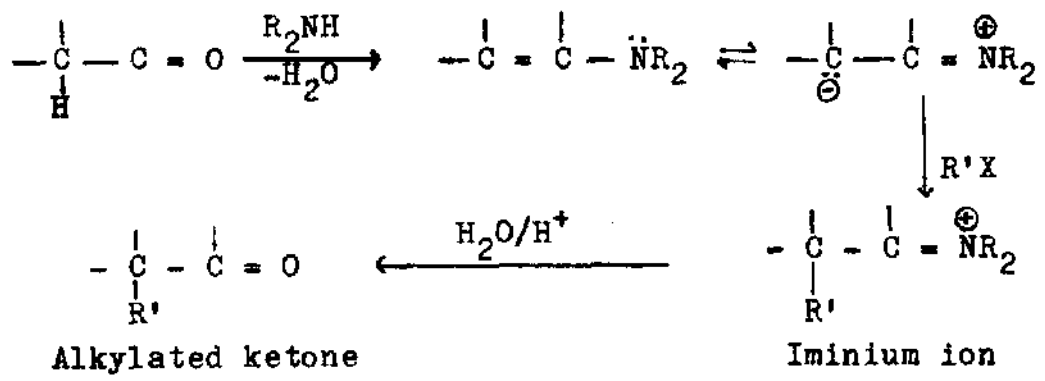
The reaction of ketone with pyrrolidine involves a nucleophilic attack (by the nucleophilic-lone pair on nitrogen) on the unsaturated carbonyl carbon

forming water and the enamine. The removal of water from product by azeotropic distillation (since the reaction is reversible) after the addition of a carrier such as benzene, toluene, xylene or a halogenated aliphatic solvent leads to rapid formation of the enamine (CXXI) and usually also to high yields.



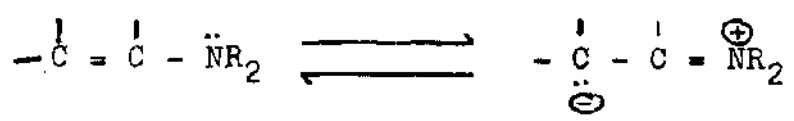
(CXXI)

The course of the reaction can be followed directly from the amount of water liberated. The addition of the alkylating agent leads to the iminium ion, which is hydrolysed to the ketone by an aqueous acid. The usefulness of the enamine system (C=C-N) stems from the fact that they form a conjugated system in which the carbon atom β to nitrogen has considerably higher electron density than the ordinary olefinic carbon and is therefore unusually nucleophilic. The electrons responsible for this nucleophilicity are the unshared pair on nitrogen; but they are available for nucleophilic attack on carbon of the enamine in alkylation (Scheme 3.4).

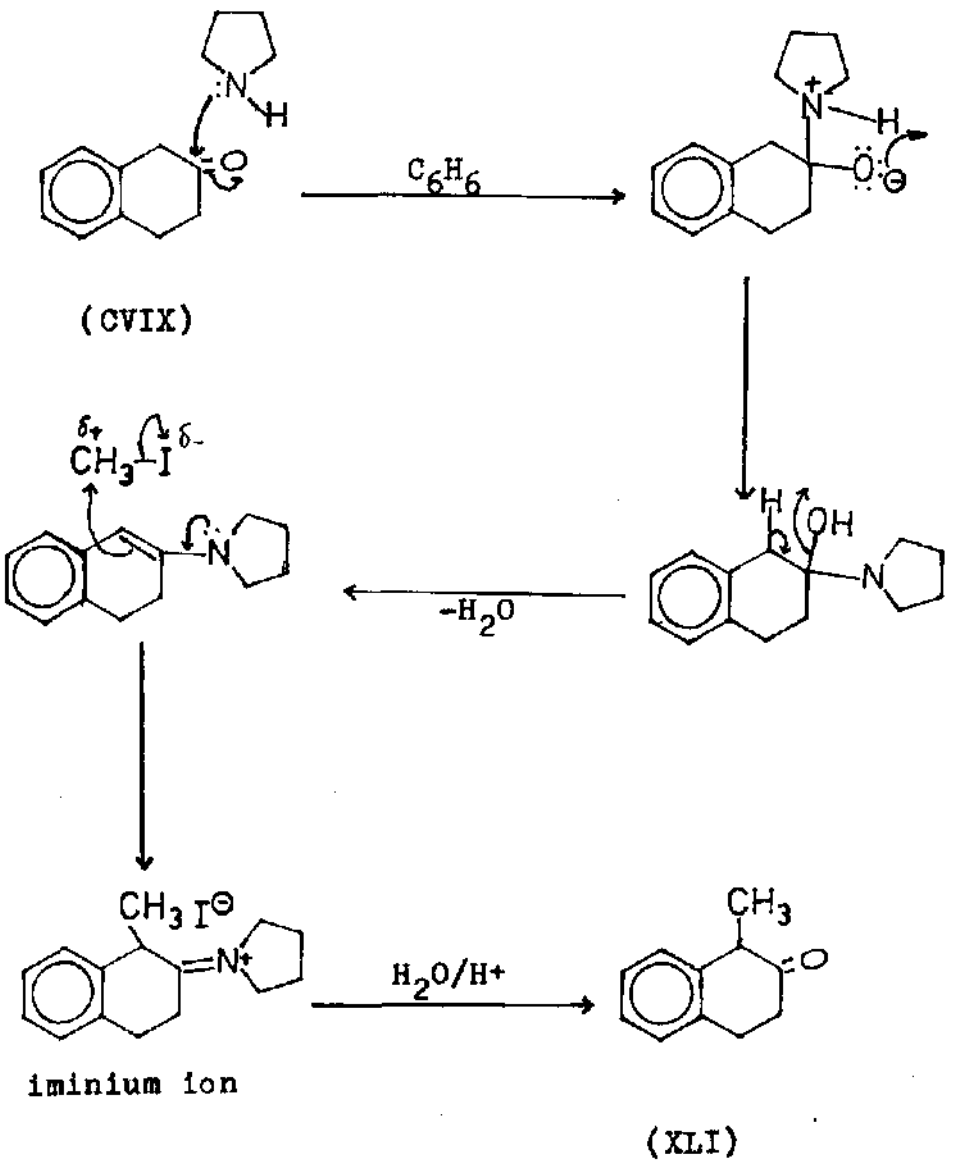


Scheme 3.4

The enamines are fairly stable to hydrolysis in the absence of acid but are hydrolysed readily by aqueous acid to carbonyl compounds and secondary amine salts. The product of alkylation, the iminium ion, is readily hydrolyzed to regenerate the carbonyl group. The equilibrium lies more to the left in 2-tetralone



pyrrolidine enamine because of stabilization due to resonance structures (i.e conjugation) with benzene ring. The proposed mechanism of the reaction of 2-tetralone and pyrrolidine followed by alkyl halide has been shown in Scheme 3.5.



Scheme 3.5

The advantages (Stork et al., 1963) of enamine alkylation method over other methods of alkylation, for example, Haller-Bauer reaction are that no catalyst is needed for the addition reaction; this means that base-catalysed polymerization (of the α,β-unsaturated ketone, nitrile, ester, etc) is not normally a factor to contend with, in contrast to the situation with the usual base-catalysed reactions of the Michael type. This means further that the carbonyl compound itself is not subject to aldol condensations which often preclude the use of base catalysis. Finally, monoalkylation is easily achieved in contrast to the results obtained, for instance, in the usual cyanoethylation procedures.

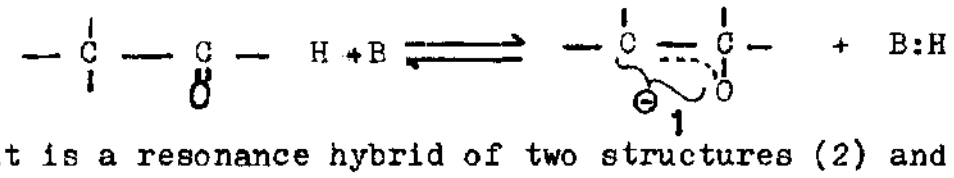
3.4 SYNTHESIS OF ETHYL-1-METHYL-2-OXO-1,2,3,4-TETRAHYDRO-1-NAPHTHALENE ACETATE,(CX)

Based on the Kavadias et al. (1979) procedure, to a suspension of sodium hydride in N,N-dimethyl-formamide (DMF) in ice-bath was added dropwise a solution of XLI in DMF. At the end of the gas evolution the flask was placed in an ice-bath and a solution of ethyl bromoacetate in DMF was added while maintaining the reaction temperature below 25°C, and then stirred over-night at room temperature. The excess sodium hydride was destroyed by addition of water. The product was extracted with ether, dried and

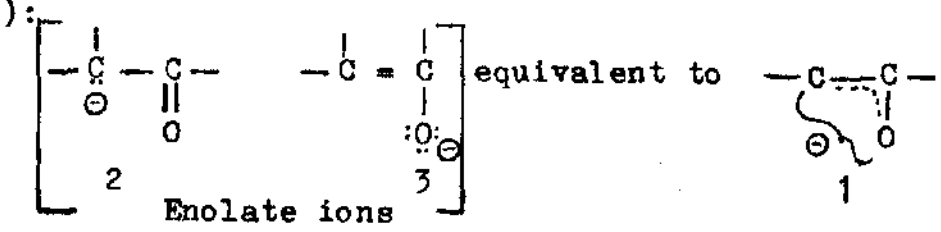
evaporated to give CI in 56% yield.

The i.r. spectrum of the product showed absorption at 1740cm^{-1} (unresolved) arising from the stretching vibrations of the ketone and ester bands. Its n.m.r. spectrum showed a triplet at δ1.2 and quartet at δ4.1 for methyl and methylene protons of the ethyl group respectively. The singlet at δ1.5 is due to C_1 methyl protons.

The presence of certain unsaturated functions as substituents at a saturated carbon atom - nitro carbonyl, cyano, phenyl groups for example - renders any alpha hydrogen atoms bonded to that carbon relatively acidic. The ionization (Morrison and Boyd, 1977) of an α-hydrogen in the presence of a base, B:, yields a cabanion (1):



that is a resonance hybrid of two structures (2) and (3):

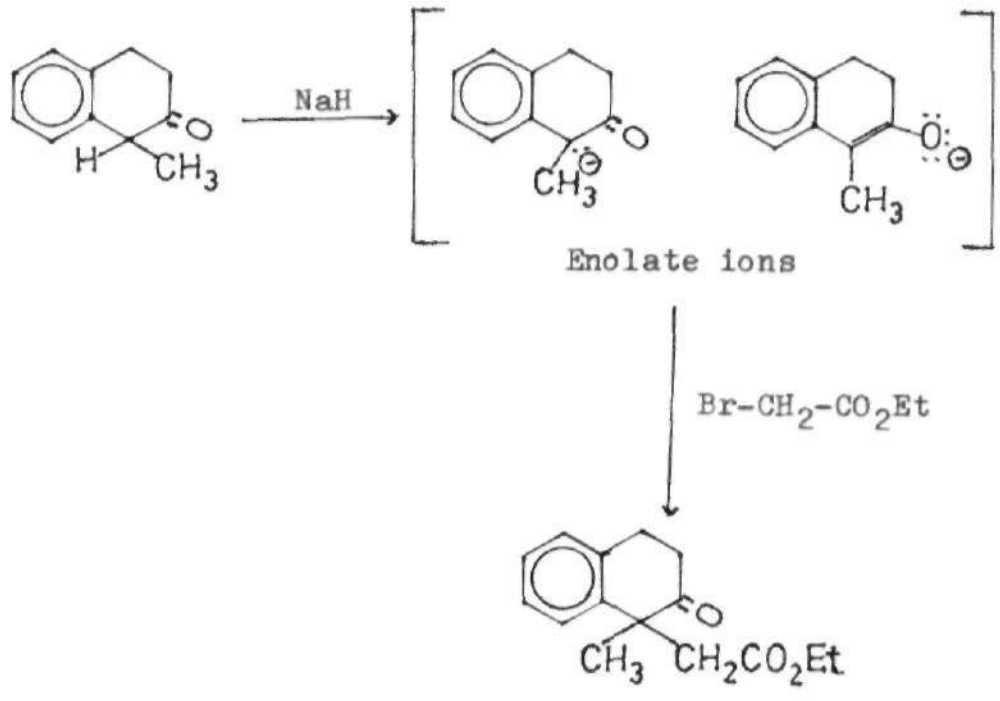


resonance that is possible only through participation by the carbonyl group. The carbonyl group thus affects the acidity of the α-hydrogens by helping to accommodate the negative charge on the anion.

The acidity of α-carbon-hydrogen bond in these substances is attributed to a combination of features that serve to stabilise the carbanions (Sykes, 1975). These features include the increase in S-character at the carbanion-carbon; through aromatization; conjugation of the carbanion lone pair with a multiple bond, and inductive-electron withdrawing ability of the unsaturated substituents i.e. the ability of these substituents to delocalize the negative charge remaining when a proton has been removed.

The Haller-Bauer reaction, common to ketones containing α-hydrogen atoms, are alkylated using strong base e.g. NaH, KH, KNH_2, $NaNH_2$, etc by forming carbanion which then attacks an alkyl as a nucleophile to give alkylated ketone. The result of reaction is to replace one or more of hydrogen atoms attached to the carbon adjacent to carbonyl group by alkyl groups. However, this has a limited use as a result of polyalkylation of carbonyl compound e.g 2-tetralone gives 1,1-dialkyl - 2-tetralone (Soffer et al., 1950), unless one of such position has been alkylated.

A mechanism for the formation of (CI) is proposed as shown in scheme 3.6.



(CX)

Scheme 3.6

Other methods of ketone alkylation such as Aldol or Claisen condensation, Reformatsky reaction are not possible in this case because they require two molecules of carbonyl compound to combine to form a β-hydroxy carbonyl compound in presence of base or dilute acid; dehydration of such compounds give α, β-unsaturated carbonyl compounds; or the reaction of two molecules of esters, which give rise to β-hydroxy esters and takes place only with esters containing bromine in the alpha position and a carbonyl compound. Others like free radical method, which involve heating at higher temperatures (130°C),

Michael condensation involving addition of an active methylene compound to α,β-unsaturated ketones or Mannich reaction giving rise to amino ketones too were not suitable.

3.5 SYNTHESIS OF 3,9b-DIMETHYL-3a-HYDROXY-2-OXO-2,3,3a,4,5,9b-HEXAHYDRO-1H-BENZ(e)INDOLE,(CXI)

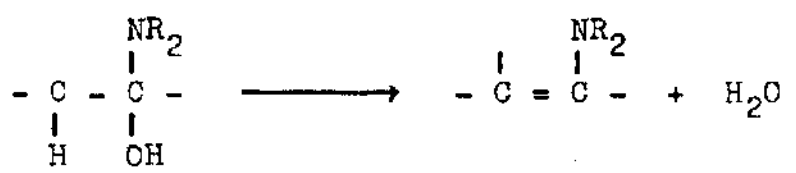
In accordance to the literature procedure (Kavadias et al., 1979) a solution of naphthalene acetate (CX) and methylamine in 95% ethanol was left at room temperature for 24 hr which afforded a crystalline precipitate in 54% yield (m.p 72-74°C).

The compound (CXI) was analysed for hydroxylactam. The i.r. spectrum of this compound showed absorption bands at 3500 - 3350 cm^{-1} (OH group) and 1650 - 1670cm^{-1} (lactam-carbonyl groups) but no absorption band for ketone carbonyl was observed. The n.m.r. spectrum indicated a singlet at δ 4.61 attributed to alcoholic proton while the methyl and NCH_3 protons appeared at δ 1.30 and δ 2.9 respectively.

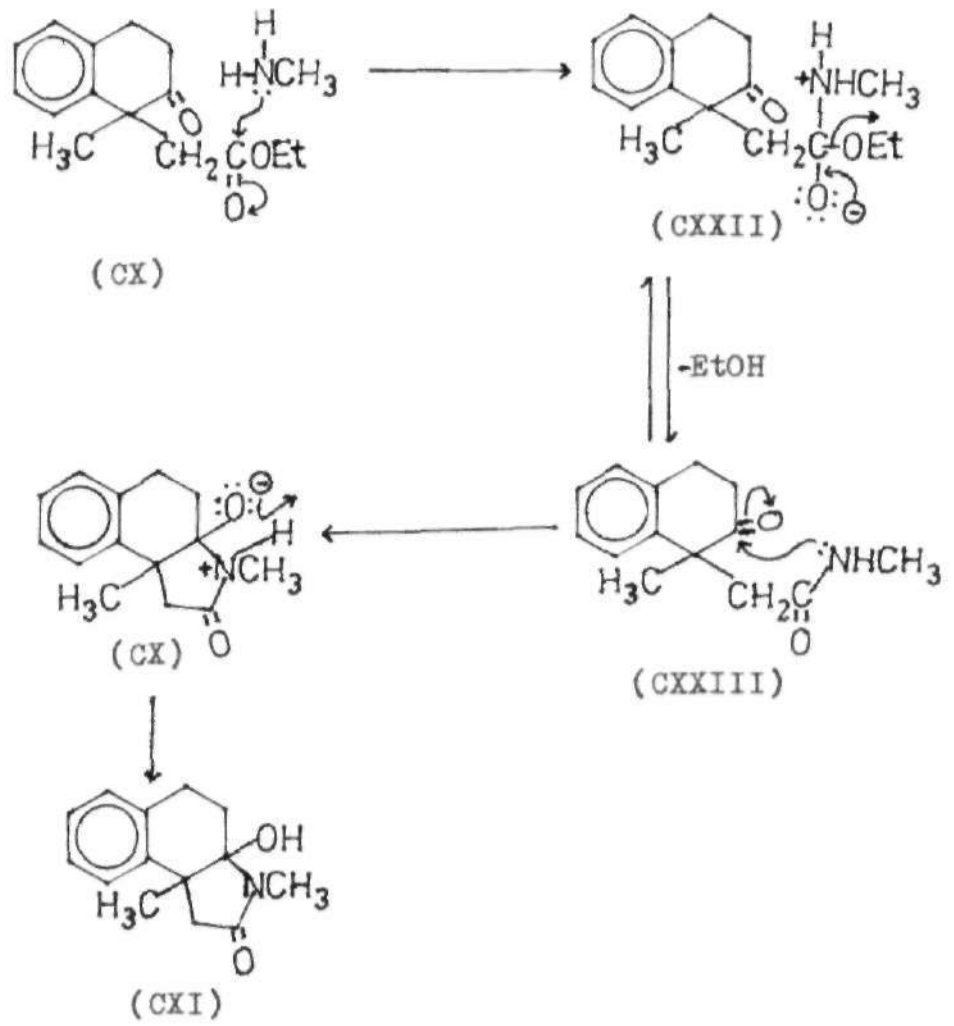
Primary, secondary and tertiary amines can add to carbonyl compounds to give different kinds of products. Primary amines give imines with ketones and aldehydes. These imines are stable enough for isolation, however, they rapidly decompose unless there is at least one aryl group on nitrogen or carbon.

The reaction is straight forward and proceeds in high yields. The initial N-substituted hemiaminals lose water to give stable schiff bases. The reaction is often used to effect ring closure.

Addition of primary amine (CH_3NH_2) to any carbonyl carbons, gives a secondary amine which reacts further with other carbonyl carbon to effect cyclization. The hydroxylactam (CXI) cannot lose water easily to give a carbon-nitrogen double bond as does other primary amines with carbonyl compounds. However, if there is an α-hydrogen, then water can be lost to give a carbon-carbon double bond, and the product would be an enamine (Morrison and Boyd, 1977):



Since the ethoxy group is an excellent leaving group, it is believed that nucleophilic reagent adds to ester carbonyl first, with the resultant release of ethanol to give secondary amine (CXXII, Scheme 3.7). The subsequent nucleophilic attack of the secondary amine (CXXII) on carbonyl ketone completes cyclization process to give the intermediate anion (CXXIII). The proton transfer from quaternary nitrogen (CXXIII) to negatively charged oxygen gives hydroxylactam.



Scheme 3.7

3.6 SYNTHESIS OF 3,9b-DIMETHYL-2-OXO-2,3,5,9b-TETRAHYDRO-1H-BENZ(e) INDOLE, (CXII)

The hydroxylactam (CXI) was refluxed for 2 hr in benzene with azeotropic removal of water, using catalytic amount of para-toluene sulphonic acid (PTSA). Ethereal treatment of the residue gave (CXII) as a crystalline product (m.p 83 -85^{o}C) in 50% yield.

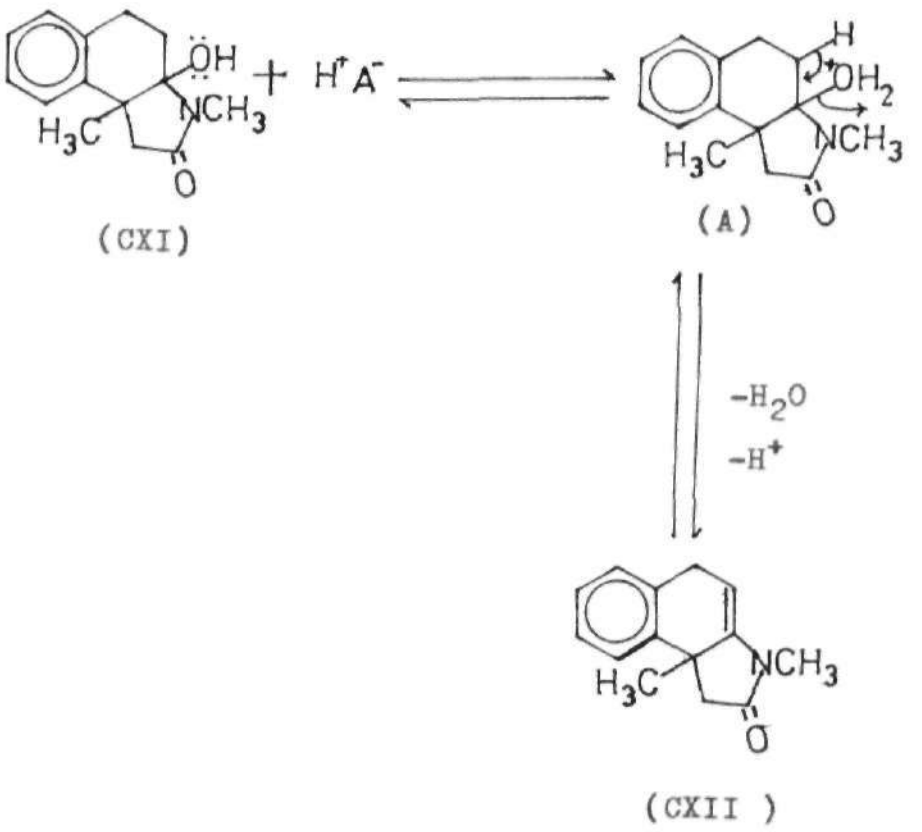
The i.r. spectrum of the product showed absorption at 1725, 1675 cm^{-1} (lactam moiety) and at 1600 cm^{-1} (carbon-carbon double bond). The absence of absorption bands in the region 3500 - 3200 showed the conversion of hydroxylactam (CXI) into extended conjugated lactam (CXII). The n.m.r. spectrum indicated a doublet at δ 3.35 (benzylic protons) and a triplet at δ 5.0 (NC = CH proton).

Nearly all olefin-forming reactions of any theoretical or synthetical importance are β-elimination, in which two groups are lost from adjacent carbon atoms. One of these groups is usually a hydrogen.

An alcohol is converted into an alkene by dehydration: elimination of a molecule of water. Dehydration requires the presence of an acid or application of heat.

For dehydration in the liqud phase, very many reagents have been used: H_2SO_4 has been employed extensively for preparation of alkenes. In most cases however, alkene produced contains ether and is contaminated by SO_2 and CO_2. Also, the temperature involved is very high that charing can easily occur or rearrangement products formed.

As dehydrating agents: P_2O_5, phthalic anhydride, $KHSO_4$, $ZnCl_2$, $Al_2(SO_4)_3$, aryl sulphonic acids have been used. A mechanism for dehydration reaction is shown in Scheme 3.8.



(CXI) (A) (CXII)

Scheme 3.8

The compound (A) formed is very liable to dehydration because of its nature (tertiary alcohol). After dehydration a more stable species (CXII) is formed. Now the compound (CXII) was subjected to further reaction.

3.7 SYNTHESIS OF 3,9b-DIMETHYL-5,9b-DIHYDROBENZ(e) INDOLE, (CXIII)

The crude compound (CXII) in ether was added to a suspension of lithium aluminium hydride (LAH) in ether and stirred at ambient temperature for 1½ hrs. Excess hydride was destroyed with aqueous sodium hydroxide solution and the resultant indoline obtained as a syrup in 53% yield. The infra red spectrum of the enamine (CXIII) showed stretching frequency at 1670 cm^{-1} (NC = CH), while the n.m.r. displayed signals for methylenic protons at δ 1·75 (multiplet); benzylic protons at δ 2.80 (doublet) and methine (NC = CH) protons at δ 4.15 (triplet).

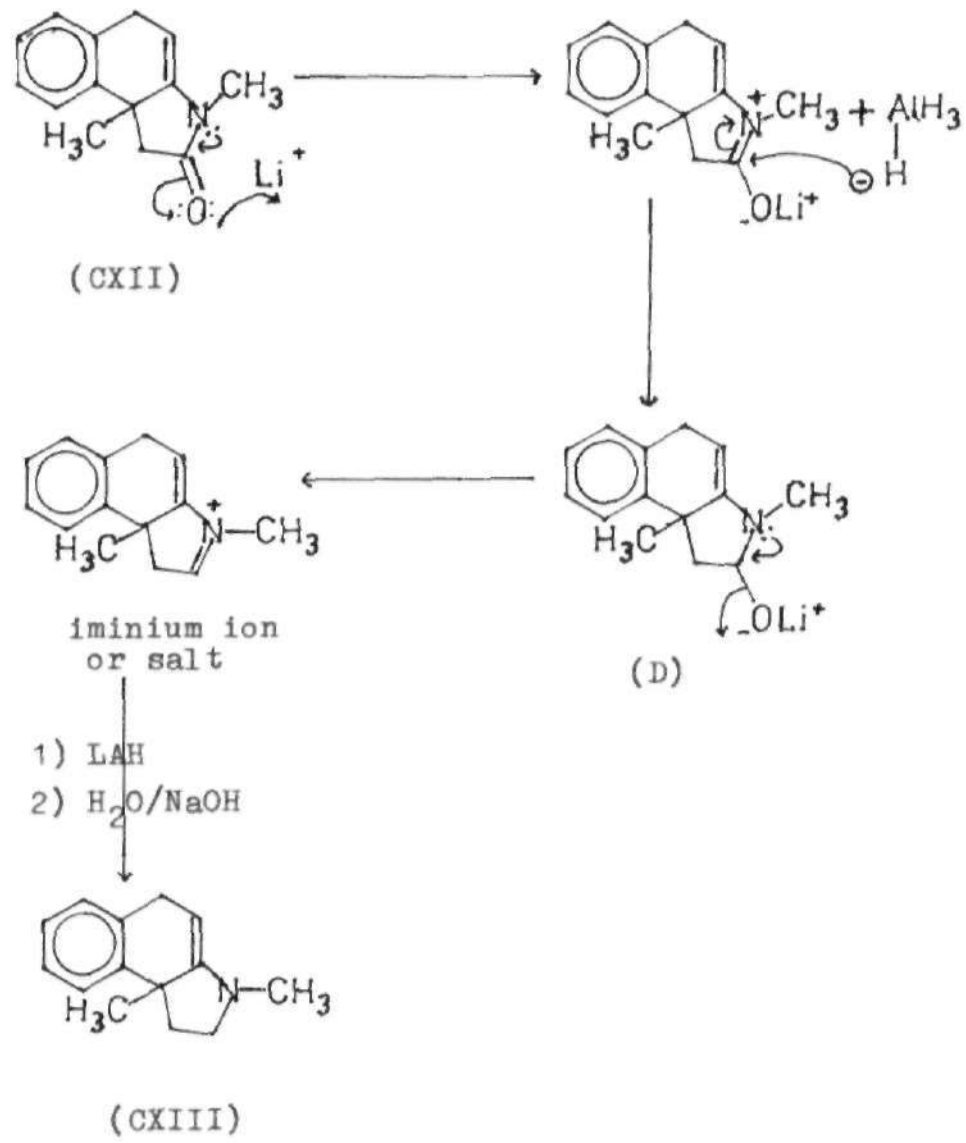
LAH is a useful and convenient reagent for the selective reduction of various polar functional groups. It is used in diethylether solution very commonly. Normally, the reactions proceed with extraordinary rapidity and are relatively free from side reactions. The reactions usually give rise to intermediate metal alkoxides from which the desired products are liberated by hydrolysis.

LAH in ether solutions exists largely as ionic aggregates of strongly solvated lithium ions and aluminohydride anions (ALH_4^-). Nearly all the normal reductions involve the displacement of a strongly electronegative atom (oxygen, nitrogen, halogen) and the addition of a hydrogen atom to the electron

deficient centre, usually a carbon atom. Hydrogen is transferred from reactive species, aluminohydride ion, as hydride in a bimolecular nucleophilic displacement type mechanism (Treyvoy and Brown, 1949). The steric course of the reduction is governed by a combination of steric interference, torsional strain and electrostatic effects in the transition state (Brown, 1951; Gaylord, 1956; Cherest and Felkin, 1968).

In general, the reduction of amides to amines is believed to proceed by an initial reduction to a geminal amino alcohol derivative. This reduction with LAH involves the transfer of a hydride anion from metal atom to carbonyl carbon atom; this transfer is presumably assisted by prior or concurrent association of carbonyl oxygen atom with a lithium cation (House, 1972). The resulting aluminium hydride-lithium alkoxide pair, which exists transiently if at all after transfer of the hydride anion, is converted to the lithium aminoalcohol derivative (D), followed by elimination and subsequent reduction of the resulting iminium ion (or salt) - Scheme 3.9.

The reduction by LAH is advantageous with respect to the time required and freedom from side reactions. The mechanism could be shown according to Scheme 3.9.



Scheme 3.9

Destruction of the excess hydride is accomplished by the cautious addition of wet ether, an ethanol-ether mixture of water (with extra caution).

Isolation of ether soluble product was accomplished by treatment of the mixture after

hydrolysis of excess hydride, with strong sodium hydroxide solution, which dissolved the precipitated alumina giving rise to clean-cut separation of phases which on filteration gave compound (CXIII).

3.8 SYNTHESIS OF 4-BROMO-9b-METHYL-2,4,5,9b-TETRAHYDRO-1H-BENZ(e) INDOLE METHOBROMIDE,(CXIV)

To a stirred solution of bromine in dichloromethane (DCM) below $-10^{o}C$ was added a solution of CXIII in DCM. Removal of the solvent under vacuo gave the methobromide as a crystalline mass (45%, mp 61-62^{o}C). Its i.r. spectrum indicated bands at 1675cm^{-1} (C=N^{+}) and 750cm^{-1} (C-Br).

Halogens, especially bromine and chlorine react smoothly with alkenes to give halogenated addition products. The reaction is usually carried out by mixing the two reactants in an inert solvent (Allinger et al., 1976) such as CCl_4, $CHCl_3$, CH_2Cl_2, CS_2, ether, CH_3COOH, ethyl acetate. (The halogenated solvents are however more commonly used). Avoiding high temperatures and excessive exposure to light, a polar electrophilic addition process occurs (Allinger et al., 1976).

A bromine molecule is non-polar. The two identical atoms share electrons equally. However, when such a molecule is under the influence of a powerful electric field of a nearby carbon-carbon

double bond, the dense electron cloud of the double bond tends to repel the similarly charged electron cloud of bromine molecule, resulting in its polarization. The more positive bromine of this polarized molecule is then abstracted by alkene to form a carbonium ion, leaving a negative bromide ion (Morrison and Boyd, 1977). The reaction is governed by electrophilic addition mechanism.

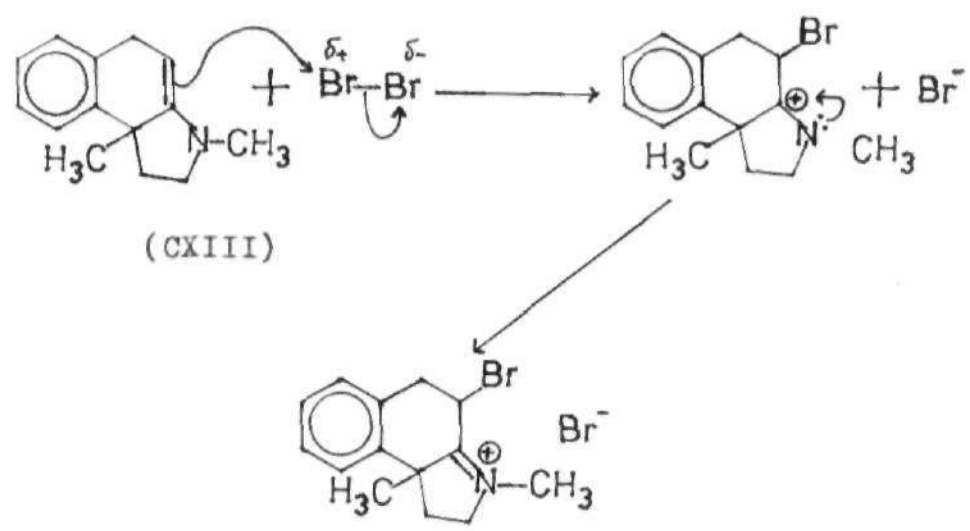


polarization of bromine molecule.

Thus the resulting electrophilic attack of bromine at the double bond causes heterolytic cleavage of the π-bond on the alkene (forming a sigma bond) and of the bromine bond. This generates a carbonium ion and a bromide ion in the first step. For an alkene, this is followed by a second step which involve a nucleophilic attack of the bromide ion on the carbonium ion to give the product.

However, for an enamine, the mechanism of the reaction is thought to be slightly different. The carbonium ion generated by the electrophilic attack of bromine at double bond is believed to undergo an intramolecular nucleophilic reaction by accepting lone electron pair on nitrogen to form the quaternary nitrogen ion (iminium ion) intermediate as a second step of the mechanism. This iminium ion subsequently

reacts very fast with bromide ion to form methobromide salt (CXIV; Scheme 3.10).

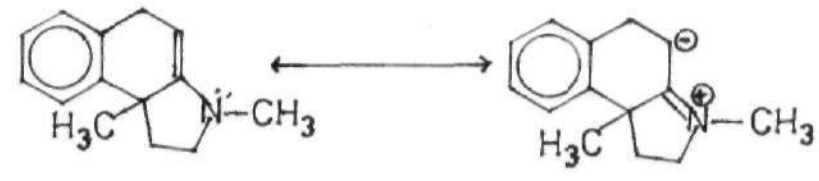


(CXIII)

(CXIV)

Scheme 3.10

The evidence for this mechanism exists. The electron distribution in enamines is shown by the resonance structures:



The beta carbon atom bears an appreciable negative charge and may serve as a nucleophile (House, 1972). Thus subsequent electrophilic attack on such a molecule will occur at the beta

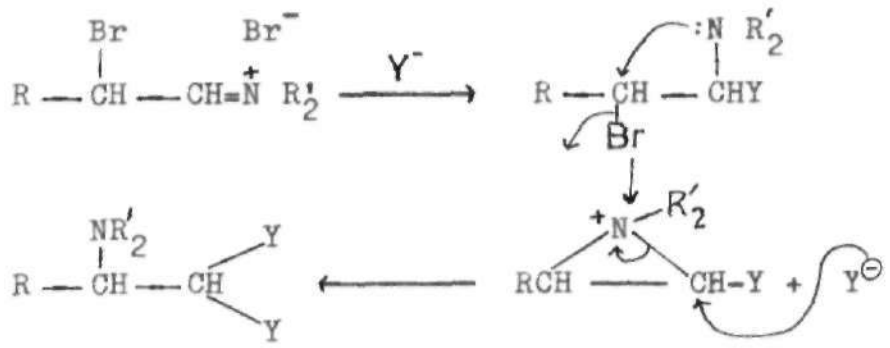
carbon atom, resulting in the formation of desired product.

3.9 SYNTHESIS OF 2,5-DIMETHYL-9-OXO-6,7-BENZOMORPHAN (XLIII)

Aqueous ammonium bicarbonate was added to a stirred solution of the bromoiminium salt (CXIV) in ethanol at -10°C. After stirring for 24 hr , it was extracted with ether, dried and evaporated to give a syrupy residue whose i.r. spectrum gave a carbonyl stretching frequency at 1730cm^{-1}. This was purified by conversion to the oxalate salt (mp 91-93°C) in 50% overall yield. The free base was quantitatively regenerated from its oxalate salt by treatment with ammonium hydroxide followed by extraction with chloroform. The n.m.r. spectrum showed a doublet at δ 2.95 (benzylic protons) and a triplet at δ 3.95 (C_1 proton).

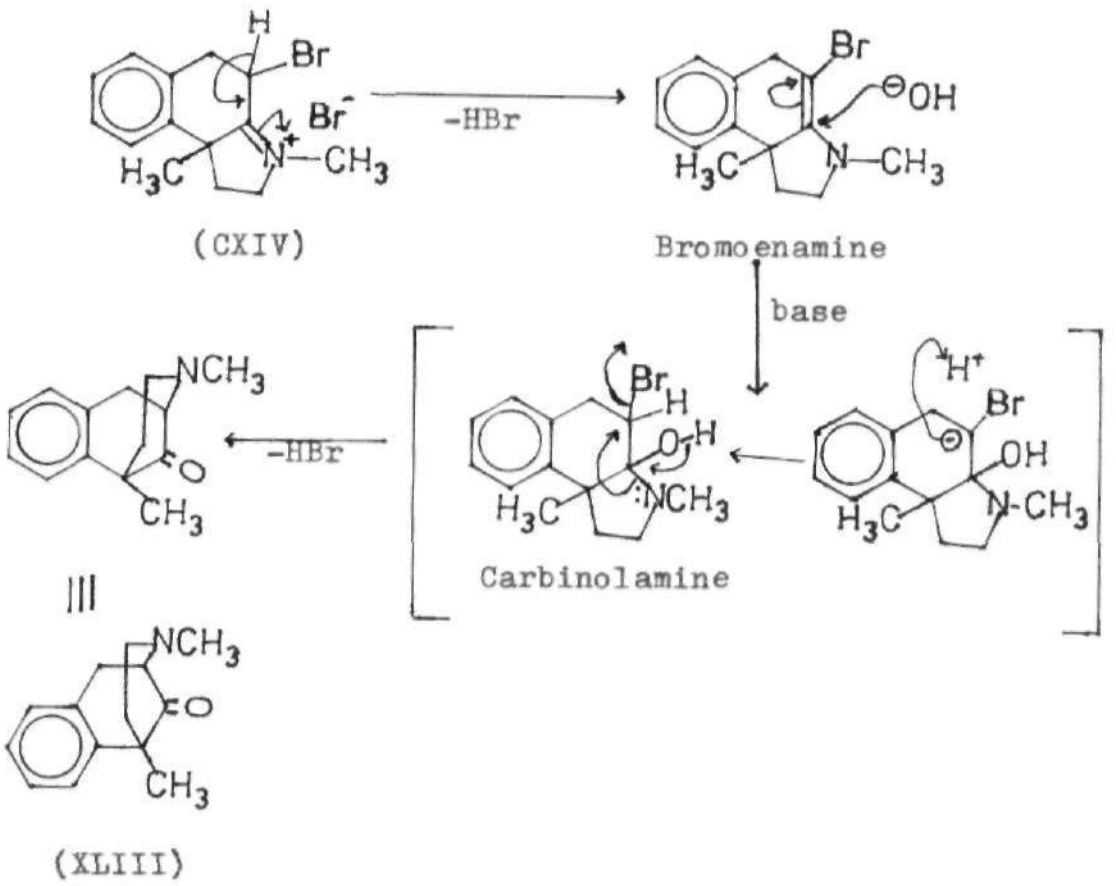
The conversion of bromoiminium salt to 9-oxobenzomorphan (XLIII) by basic hydrolysis of CXIV was anticipated to proceed *via* formation of carbinolamine (Scheme 3.11) as initial product, which could rearrange directly to XLIII or rearrange *via* an intermediate bromoketone (Scheme 3.12) followed by ring closure. The reported (Kavadias *et al.*, 1979) conversion of α-bromoiminium bromides to α-aminoketals and α-aminoaminals by reaction with alkoxides and

secondary amines respectively (equation E) favours the first mechanistic possibility (Scheme 3.11).

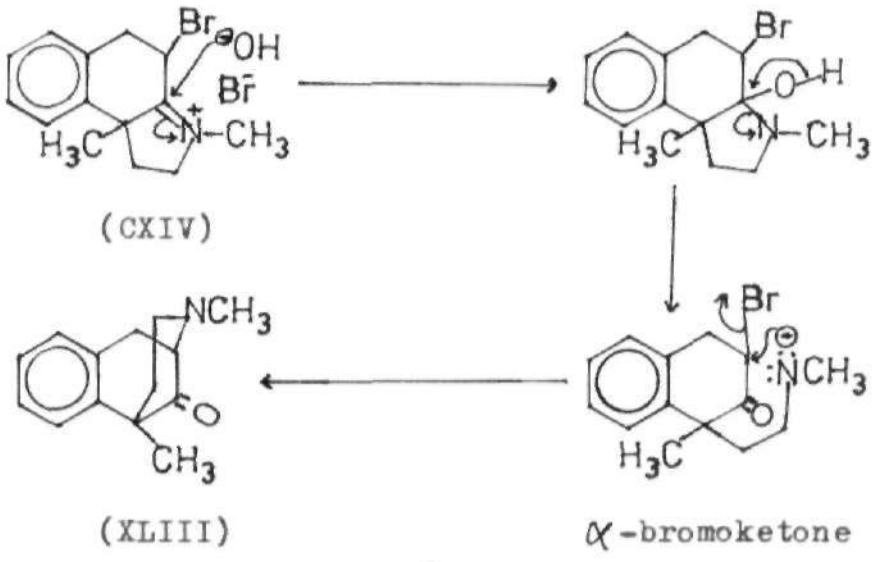


Equation E

The effects of the nature of base (alkali hydroxides, carbonates and bicarbonates), the mode of addition of base, the nature of solvent and the effects of temperature on the yield of this base catalysed hydrolysis reaction has been investigated (Kavadias et al., 1979).

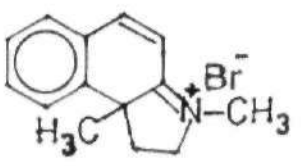


Scheme 3.11



Scheme 3.12

The use of strong bases such as sodium or ammonium hydroxide is reported (Kavadias et al., 1979) to lead to the formation of dehydrohalogenation product (CXVII) as the major product which is not convertible to XLIII, together with α-bromoenamine. However, slow addition of a weak base (ammonium bicarbonate) to a solution of CXIV in 95% ethanol at -10°C followed by stirring at ambient temperature for 24 hr gave good yield of XLIII. This suggests that weak base treatment of CXIV produces bromoenamine (as major product) which could be a precursor of XLIII.

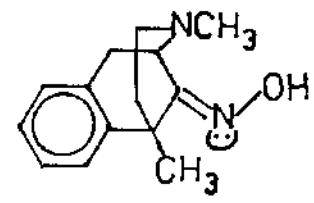


(CXVII)

3.10 SYNTHESIS OF 2,5-DIMETHYL-9-OXO-6,7-BENZOMORPHAN OXIME, (LXIV)

The oxime derivative (LXIV) was prepared by heating 9-oxo-6,7-benzomorphan (XLIII) and hydroxylamine hydrochloride in boiling ethanol for 8 hr . The hydroxylamine salt was neutralized by addition of sodium acetate, which also provided a buffering action near the optimum pH condensation. Although this reaction is reversible, the equilibrium favours condensation under the experimental condition employed.

Since water is one of the reaction products, use of an anhydrous system is advantegeous. Removal of water from the reaction medium to force condensation was unnecessary.



(LXIV)

Carbonyl compounds usually react completely with free hydroxylamine (Equation F) but instability of free hydroxylamine due to air oxidation often discourages its use. On the other hand, although hydroxylamine hydrochloride is relatively stable, an equilibrium is involved in its reaction with carbonyl compounds (Equation G).

The condensation of 9-oxo-6,7-benzomorphan and free hydroxylamine (NH_2OH) was carried out by

$$\rangle C = O \; + \; NH_2 - OH \longrightarrow \rangle C = NOH + H_2O \qquad (F)$$

$$\rangle C = O \; + \; NH_2\text{-}OH.HCl \rightleftharpoons \rangle C = NOH + H_2O + HCl \qquad (G)$$

heating the reactants in ethanol. A solution of free hydroxylamine was prepared from hydroxylamine hydrochloride and sodium acetate in ethanol and after one hour, the mixture was filtered and the filtrate was treated with 9-oxo-6,7-benzomorphan (XLIII)

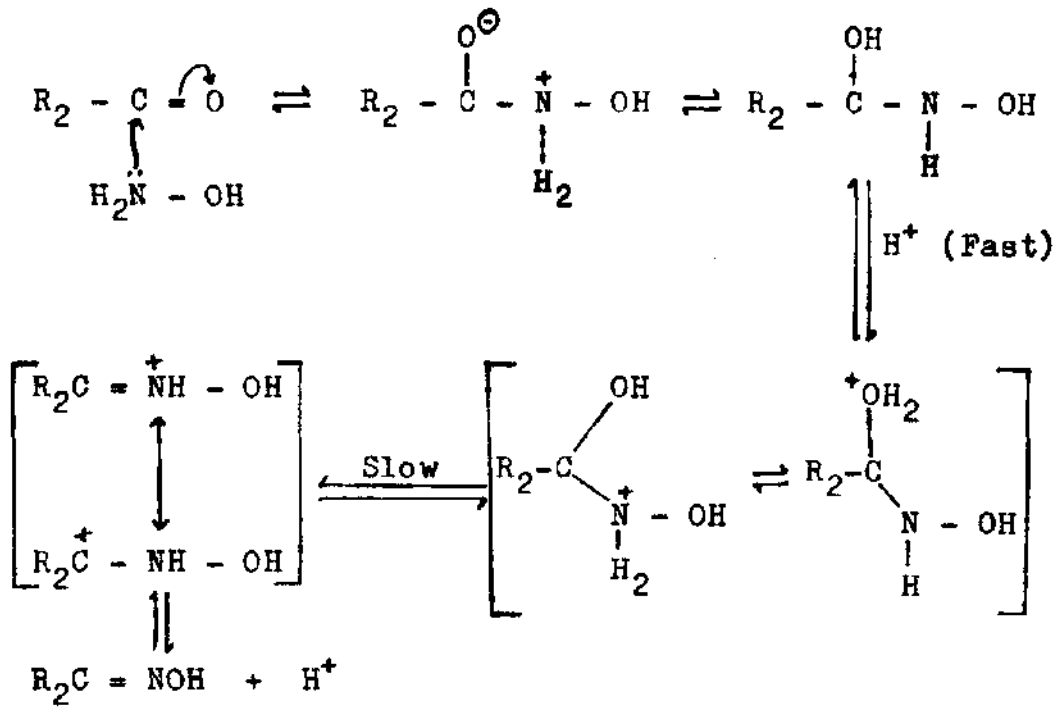
The n.m.r. of oxime (LXIV) shows the alcoholic proton at δ 11.30 as a singlet. A doublet at δ 3.0 is attributed to benzylic protons.

All ketones which have two different groups attached to the carbonyl carbon are capable of affording two isomeric oximes. However, one of the isomers is formed in excess over the other.

The formation and hydrolysis of oximes have been investigated (Anderson and Jencks, 1960; Cordes and Jencks, 1962; Patai, 1966). The reactions are generally acid catalysed and it has been established that in the formation reaction, the addition step is rapid in comparison to the dehydration step. The acid catalysis of hydroxylamine condensation with a ketone in neutral solution involves catalysis of dehydration step and not the facilitation of addition by conversion of carbonyl compound into its conjugate acid.

The observed pH optima of this reaction is mainly due to transitions in the rate determining stages with changing acidity of the reaction medium. At pH 7 the addition step is fast and in this region the overall rate increases with increasing acidity; the acid - catalysed dehydration being now rate-determining step. When acidity is increased, the addition step becomes gradually slower owing to the conversion of nitrogen base into its conjugate acid, and at sufficiently high acidities, this will

determine the overall rate. A possible mechanism for such condensation reaction in acid catalysis is outlined in Scheme 3.13.



Scheme 3.13

However, strong nucleophiles such as hydroxylamine do not require catalysis of their addition to carbonyl group (Sykes, 1975). The dehydration of carbinolamines and addition of water to oximes are subject to general acid catalysis. The addition of hydroxylamine to a carbonyl group also exhibits some acid catalysis (Anderson and Jencks, 1960; Cordes and Jencks, 1962).

3.11 SYNTHESIS OF 9α-AMINO-2,5-DIMETHYL-6,7-BENZOMORPHAN, (CXV)

9α-Amino-2,5-dimethyl-6,7-benzomorphan (CXV), the key compound in this study, was obtained *via* reduction of oxime (XLIV) of 2,5-dimethyl-9-oxo-6,7-benzomorphan. The reduction of oxime (LXIV) by a nickel-aluminium alloy in alkaline solution gave predominantly 9α-amino-6,7-benzomorphan (CXV) (House *et al.*, 1963). Raney alloy was added to a stirred solution of LXIV in ethanol and 2M aqueous sodium hydroxide (1:1). No external cooling was necessary and stirring continued for five hours. The resultant amine was isolated by extraction of the mixture with DCM. Evaporation gave an almost colourless oil (45%) which was purified *via* its dioxalate salt from ethanol.

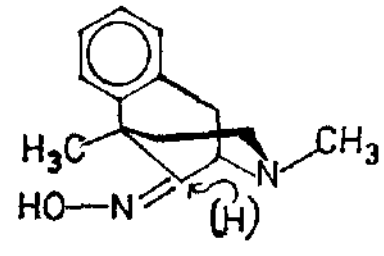
The i.r. spectrum of the oily compound showed bands for $-NH_2$ at 3450 - 3375 cm^{-1} and for C=C at 1600cm^{-1}. The n.m.r. spectrum gave signals at δ 1.55 (singlet amine proton), at δ 3.15 (doublet, benzylic protons) and at δ 3.83 (doublet, C_9-methine proton).

The action of sodium hydroxide on nickel-aluminium provides a source of hydrogen *in situ* permitting direct hydrogenation. This procedure involved, at least in part, a catalytic hydrogenation in which the hydrogen liberated is adsorbed on the surface of newly formed Raney-nickel.

9α-Amino-6,7-benzomorphan (CXV) was purified as the dioxalate salt from ethanol (mp 192 - 194°C).

The usual assumption in predicting the stereochemical outcome of catalytic hydrogenation is that the substrate will adsorb on the catalyst in such a way as to minimize steric interaction between the substrate and catalyst (Burwell, Jr., 1957; 1969; Siegel, 1966). The adsorption is thought to be followed by addition of hydrogen to the side of the molecule adsorbed on the catalyst (Siegel, 1966). Hydrogenation of the oxime gives the product arising from the addition of hydrogen from the less hindered side, and not as weould be expected from the more hindered side.

It is reasonable to assume that the oxime group will be adsorbed preferentially so as to minimize steric interaction between surface and remainder of the molecule. The hydrogen then could be considered to add from the side of molecule opposite to the catalyst, as proposed by Rideal, resulting in the formation of the α-isomer (Laidler, 1966) (Scheme 3.14).



CATALYST

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According to Rideal (Laidler, 1966) only the substrate is chemisorbed on the catalyst and that hydrogen emanates from the reaction medium. Hydrogenation proceeds with addition of hydrogen from the side of the molecule opposite to catalyst. Farina et al.,(1972) have obtained stereochemical evidence which lends support to the Rideal mechanism.

It is noteworthy to add that the stereochemistry of reduction of 9-oxo-6,7-benzomorphan (Scheme 2.9; XLIII) is known to be dependent on whether or not a free pair of electrons is available on nitrogen (May et al., 1961; Kugita and May, 1961; Saito and May, 1962; Carr et al., 1980). Catalytic hydrogenation or hydride reduction of free base (XLIII) affords 9α-ol isomer (LVI), whereas 9β-ol (LVII) is derived from the quaternary salt of (XLIII) under similar conditions. These results may be attributed to prior complexation of amine function with the catalyst surface or to the assistance of hydride transfer by direct participation of amine function. The lone pair is not available in the quaternary salt where nitrogen carries a full positive charge.

This perhaps explains the unsuccessful attempts made for the synthesis of 9β-amino-6,7-benzomorphan by reduction of the oxime (LXIV) with LAH, since free pair of electrons on nitrogen of amine function was present on the molecule.

CHAPTER FOUR

BIOLOGICAL EVALUATION OF 9α-AMINO-6,7-BENZOMORPHAN

PHARMACOLOGY

4.0 INTRODUCTION

Over the centuries that man has been capable or organized thought and action, relief from pain has been one of his most persistent searches. Pain can be defined as a very unpleasant sensation resulting from any intense stimulation of some region of the body (Fennessy and Lee, 1975).

At present the drugs available for relief of pain fall into three broad categories: the narcotic analgesics, the narcotic antagonist analgesics, and the antipyretic analgesics. Each of these drug types has undesirable effects associated with them. The narcotic analgesics have the well-documented capacity to induce tolerance and psychological and physical dependence. Most narcotic antagonist analgesics have some dependence liability and have associated undesirable psychopharmacological effects. The antipyretic analgesic drugs have been shown to be closely associated with renal damage. Consequently the search for ideal analgesic agents is continuing. This search requires the screening of chemical compounds for analgesic activity in animals. At present this search is hindered by the lack of suitable testing procedures.

The search for effective centrally acting analgesic agents devoid of dependence and depressant

properties has led to an usually rich selection of compounds upon which to base proposals for structural requirements for opiate activity. Most structures exhibiting such activity fit a common pattern in possessing a basic nitrogen atom separated by a two carbon unit from an aromatic ring (de Stevens, 1965; Beckett and Casy, 1954a,b; Braenden et al., 1957; Eddy et al., 1969; Casy, 1970; 1978; Schaumann, 1949; Mellet and Woods, 1963; Portoghese, 1965; 1965).

The following criteria have been suggested as being necessary if meaningful information is to be obtained from an analgesic test (Fennessy and Lee, 1975):

(1) A quantitative determination of the threshold value of the noxious stimulus must be possible. In man this usually is the lowest intensity leading to a verbal report by the subjects. In animals this would be the reaction threshold.

(2) Quantitative information upon differences in intensities of stimuli should be yielded. The method must also discriminate between different doses of drugs and drugs of different potencies.

(3) The stimulus applied should not result in tissue damage when applied at the threshold intensity. The application of intensities above the threshold intensity, which is necessary to determine the extent of an increase in reaction threshold

after analgesic administration, should not result in tissue damage or alteration.

(4) Repeated application of the stimulus should not result in tissue damage or an alteration in the reaction threshold.

(5) In addition, for use in screening programs, the technique must be economical and relatively rapid in performance. This tends to exclude any technique that requires surgical preparation of the animal.

Analgesic activity has been demonstrated in simple amines like β-phenylethylamine (Crooks and Rosenberg, 1978). The presence of a β-phenylethylamine moiety is an essential feature of molecules with high analgesic activity. It is noteworthy that structural modification of 6,7-benzomorphans made by changing the position of nitrogen decreases the analgesic activity. (Opheim and Cox, 1977; Schiller et al., 1977; Shiotani, et al., 1978; Kometani and Shiotani, 1978; Shiotani and Kometani, 1978).

The possible role of the 9-methyl group in benzomorphans is the enhancement of analgesic activity. It is a very important pharmacodynamic feature of the molecule (Casy, 1970). It was thus of biological interest in investigating the effect of replacement of this methyl group by an amino group. It was

anticipated this peripheral structural change should give an analgesic with greater affinity for the receptor(s), more potent and longer acting; thus further defining the requirement(s) and mode of interaction of an analgesic with its receptor(s).

An investigation directed toward these derivatives was undertaken, with the 9α-amino analogue of metazocine (without the phenolic hydroxyl group). In this Chapter, therefore, the pharmacology of such an analogue is reported.

4.1 MATERIALS

The experimental animals were white Swiss mice of both sexes weighing between 16 and 32g and were obtained from the Animal House, Department of Pharmacology, Ahmadu Bello University, Zaria. The apparatus includes disposable needles and syringes, stop watch, animal cages, sample bottles, weighing balances, thermometer, spatula, thermostatically controlled water bath, and cylindrical tin can container of suitable height and diameter.

4.2 METHOD OF EVALUATION OF ANALGESIC ACTIVITY

The analgesic activity for the test compound (9-aminobenzomorphan as dioxalate) and morphine (as sulphate) was determined in mice using essentially the hot plate procedure of Portoghese *et al*. (1973).

The hot plate was the top surface of a tin can dipped in a bath containing thermostatically controlled hot water. Under the conditions employed, the temperature of the top of the can was maintained at 55°C. The compounds were administered to the mice subcutaneously (SC) in aqueous solution (using water for injection). For each dose level used, the solutions were prepared so that each mouse received 0.01ml/g of body weight. The doses used were 1mg/kg, 2mg/kg, 4mg/kg and 8mg/kg. Also water for injection was used as the general control.

A group of 10 mice was used for each dose level examined. The mice were placed one at a time, on the hot plate surface and the time taken for the mouse to lick its hind paws (Fennessy, 1968; Glassman, 1971) or attempts to jump out of the cylinder (Fennessy and Lee, 1975) was recorded. Reaction times were recorded at three 15-minute intervals prior to administering the compound to establish a reaction time control value. The mean value of the second and third interval preinjection reaction times for each mouse were taken as the control value, each mouse being used as its own control. Mice having a mean reaction time greater than 30 sec. were excluded as non responders. Reaction times were recorded 15, 30, 60, 90, 120, 180, 240 minutes after SC administration of drug.

The results of the pain threshold response-time were analysed by a plot of response time against post treatment time at each dose. These graphs were compared with statistical results obtained from Student's t-test, using P values. P values ≤ 0.05 were taken as being significant. The null hypothesis (Ho) was that there is no difference between drug and saline (Appendices 4.1 and 4.2) and no difference between benzomorphan and morphine (Appendix 4.3).

4.3 RESULTS AND DISCUSSION

In figures 4.1 - 4.4 are graphical representation of the analgesic activities of 9-aminobenzomorphan (as dioxalate) determined subcutaneously, in comparison to standard (morphine sulphate) and control, as determined in the mouse hot plate method (Portoghese et al., 1973)

The analgesic test indicates that for the test compound, its analgesic activity is dose-dependent. Optimum activity was obtained at dose of 2mg/kg while at a lower dose, it does not exhibit significant analgesic action. At higher dose of 4mg/kg, the test compound (CXV) shows significant analgesia, but the effect is comparatively lower than that shown at 2mg/kg. Further elevation of the dose to 8mg/kg resulted in complete loss of activity.

This effect is in contrast to that of morphine, which showed an increase in analgesia with increasing dose, with increasing tendency of side effects. At a lower dose of 1mg/kg, morphine too did not show significant analgesic effect.

The dose-dependent inhibition analgesia of CXV is not unusual in narcotic analgesic agents. Similar effect has been reported (Parkhouse et al., 1979) for nalorphine when it was tried as an analgesic in man. Nalorphine was found to be relatively potent: 10mg nalorphine had the same analgesic action as 10mg morphine. However, in contrast to morphine, elevation

GRAPH OF PAIN RESPONSE THRESHOLD Vs TIME

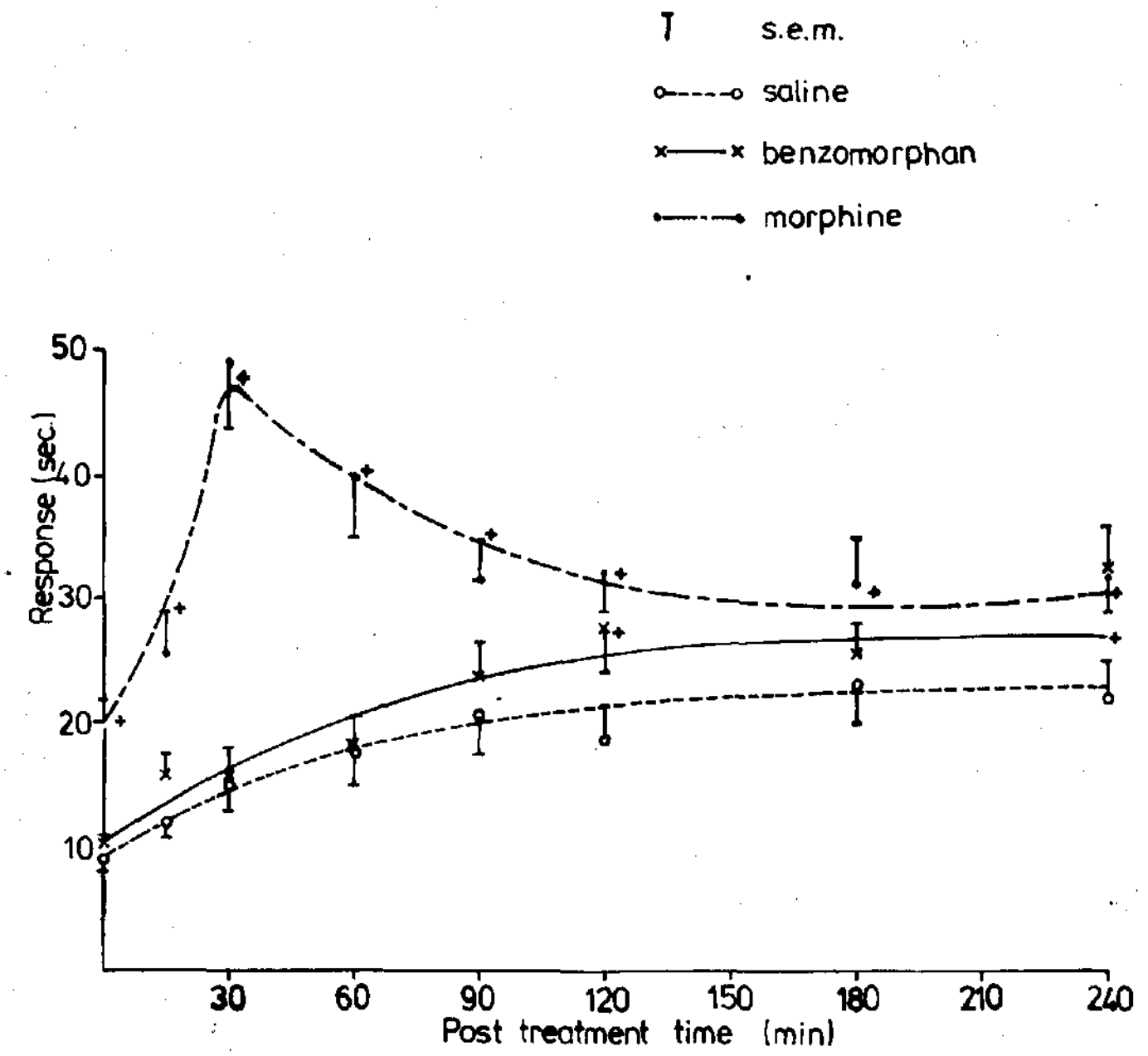


Fig. 4.1 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 1mg/Kg.
(+indicates times at which drugs are significant: $P \leq 0.05$ as compared to saline.) See appendices 4.1 and 4.2

GRAPH OF PAIN RESPONSE THRESHOLD Vs TIME

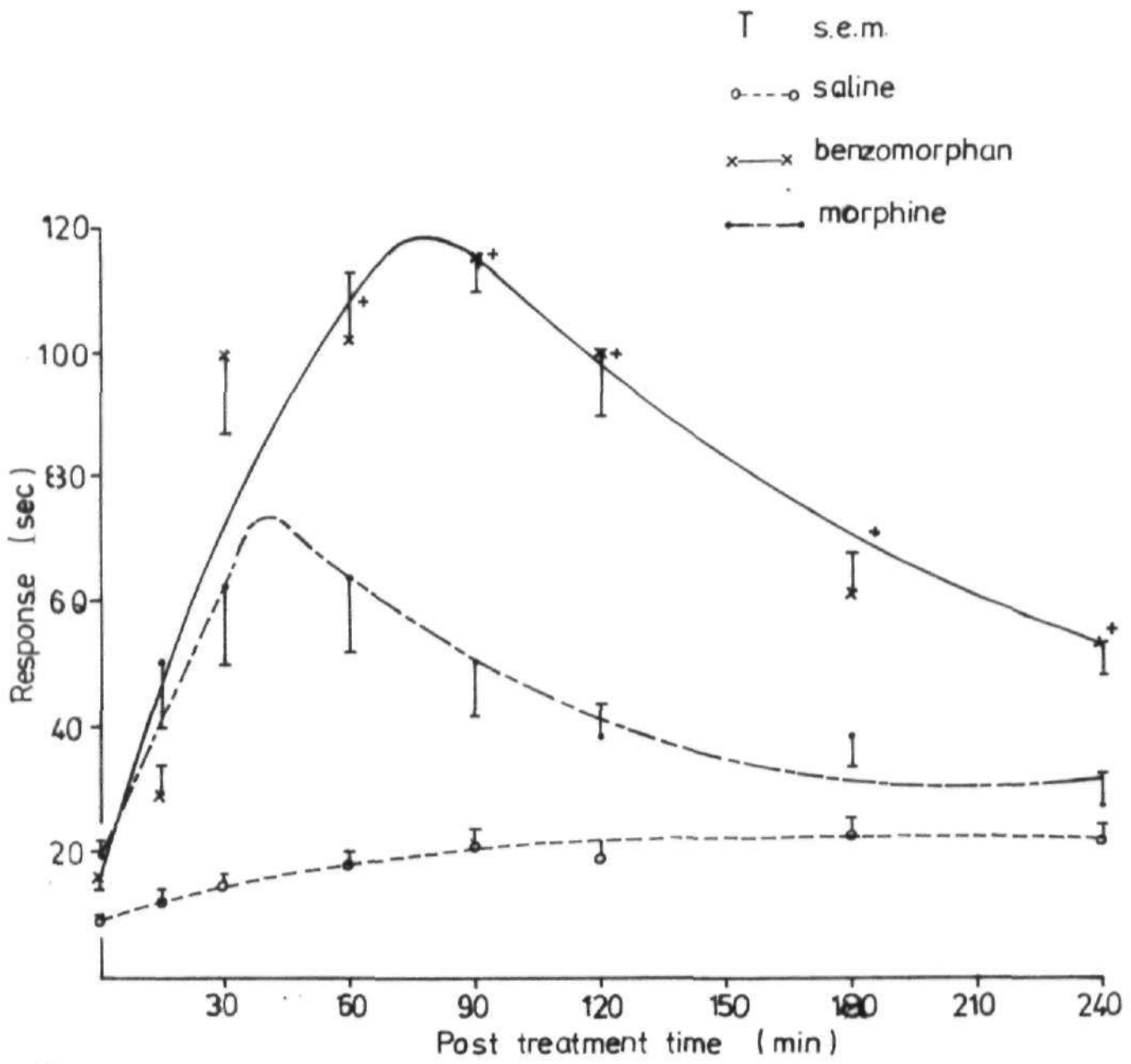


Fig. 4·2 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 2mg/kg. (+ indicates times at which benzomorphan is significant as compared to morphine.) See appendix 4·3a

GRAPH OF PAIN RESPONSE THRESHOLD Vs TIME

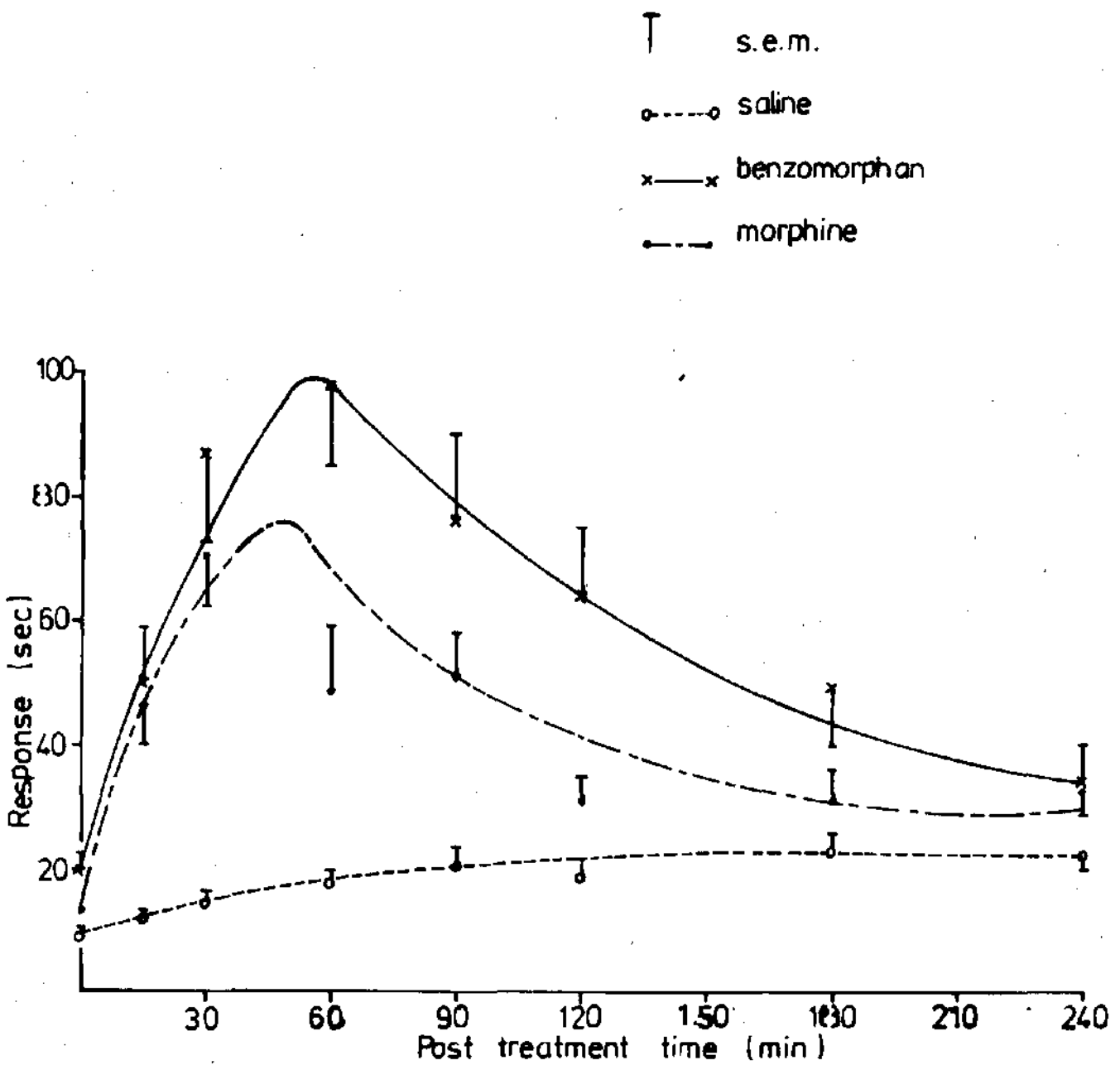


Fig 4·3 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 4 mg/kg.
See appendix 4·3b.

GRAPH OF PAIN RESPONSE THRESHOLD Vs TIME

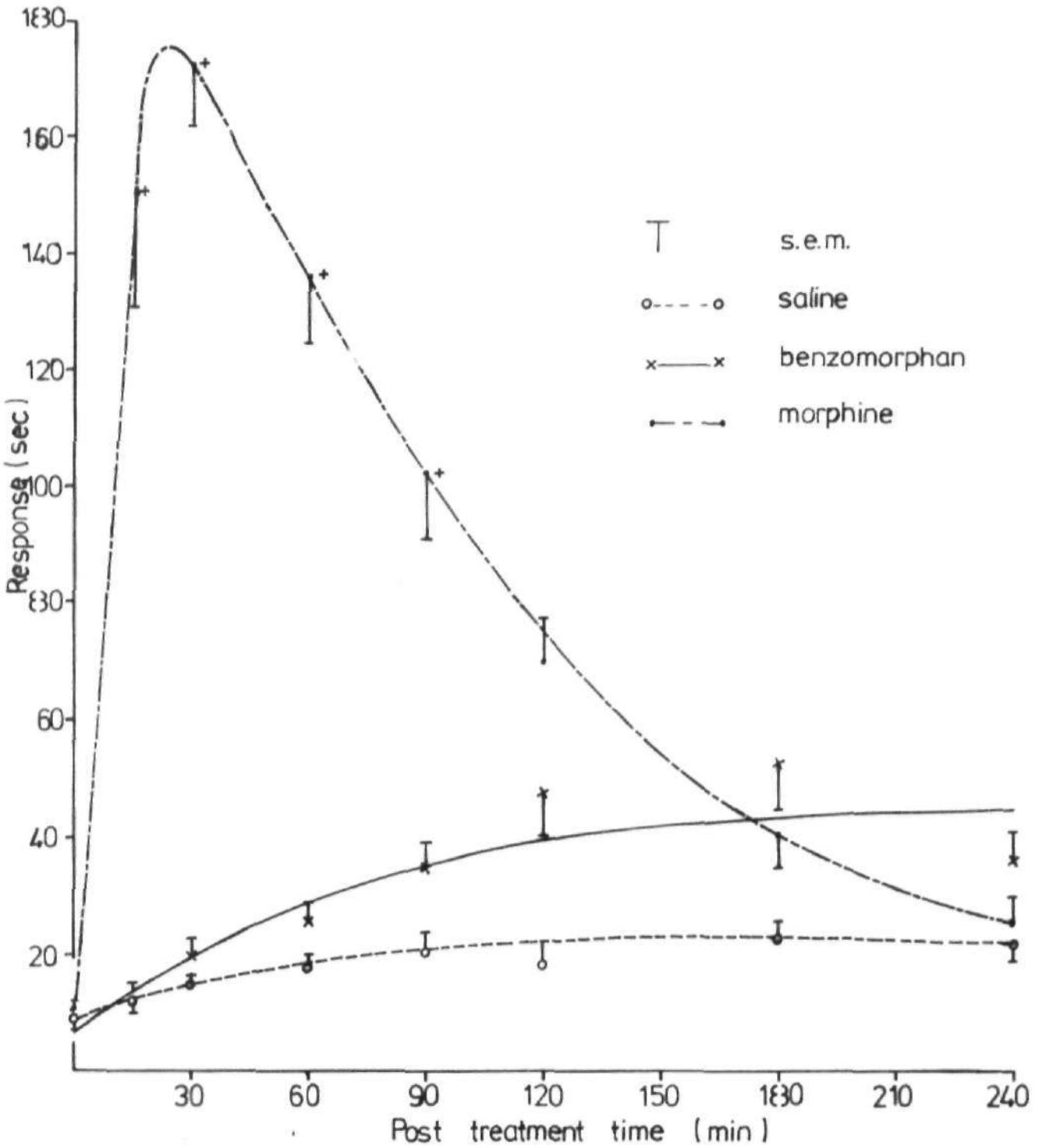


Fig. 4·4 Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 8 3mg/kg. (+ indicates times at which morphine is significant compared to benzomorphan). See appendix 4·3c.

of dose of nalorphine caused no further increase in analgesic effect. Similarly, higher doses than necessary to antagonise a pure agonist through intravenous injection of naloxone has no observable effects in control subjects (Parkhouse et al., 1979).

It is evident from the graphs that in all the doses studied, both morphine and 9-aminobenzomorphan protect better than saline against pain induced by heat on the paws of mice. Saline did not appear at all to have protected mice against heat. At doses of 2mg/kg and 4mg/kg, compound CXV offered better protection than morphine, but at 1mg/kg and 8mg/kg, the standard was superior.

These conclusions are also confirmed by statistical analysis of the data using paired student's t-test. The P values for test compound at 1mg/kg, 2mg/kg, 4mg/kg and 8mg/kg are 0.726, 0.0000, 0.00021 and 0.229 respectively when compared with saline, indicating that the drug is significantly analgesic at 2mg/kg and 4mg/kg only. For morphine the corresponding P values obtained were 0.151, 0.0151, 0.0348 and 0.0000 respectively. This means that morphine exhibited significant analgesia at all doses except at a dose of 1mg/kg (Appendix 4.1).

It was observed that at all the doses used, both morphine and CXV caused either sedation or reduced activity - an indication of depression of the

central nervous system. No death occurred during and seven days after experimentation. This shows that neither of the compounds was toxic at the dose levels studied. At dose level of 4mg/kg, vomiting occurred in 70% of the animals tested with the new compound, while a similar effect was noticed for morphine tested mice at 8mg/kg dose.

4.4 CONCLUSION

It has been demonstrated for the first time that analgesic agonist activity can be found in a class of 6,7-benzomorphan having a 9-amino function. The fact that the 9-amino-6,7-benzomorphan showed dose-dependent inhibition analgesia that has been reported (Parkhouse et al., 1979) for compounds having antagonistic properties might possibly be an indication that it is a partial agonist. This is however, subject to confirmation by animal trial experiments.

The distinction between the effect on pain threshold and the subsequent reaction to pain is difficult. Experimentally-produced pain differs from pathological pain in that a subject exposed to experimental pain knows that at the end of the experiment the pain will cease. His reaction to it will therefore differ from that of a patient suffering from pathological pain who knows that the pain will return, and also that the pain may be

indicative of serious disease.

The usefulness of analgesic testing methods in the experimental animal depend on their ability to predict the analgesic activity of a given compound in man. All the analgesic testing methods can detect the actions of morphine-like drugs and most can predict with fair accuracy relative potency ratios for these drugs in man. Probably one of the most widely used methods has been the application of radiant heat in a controlled manner to a suitably prepared area of skin.

In animals receiving nociceptive stimuli (such as heat, pressure, electrical or chemical stimuli) it is impossible to determine whether these stimuli produce sensations that are similar to those experienced by man. Nevertheless, such stimuli provide typical changes in behaviour by which the animal attempts to escape. It is not known whether these responses in animals are related to human pain, but these responses are used for pharmacological evaluation of analgesics (Fennessy and Lee, 1975).

We must rely on various reflex actions of the test animal - the twitching of muscles, the withdrawal of certain portions of the body from the region of pain stimulus or the outcry of the animal. Obviously, results based on such observations can vary widely.

The crucial point in analgesic testing is of course the determination of efficacy in the relief of clinical pain.

CHAPTER FIVE

E X P E R I M E N T A L

The melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer IR Spectrophotometer 710B. The NMR spectra were recorded on a Varian EM-390 90 MHz NMR Spectrometer using deuteriochloroform as the solvent (except the oxime, which has deuteriomethanol as the solvent). The chemical shifts are expressed in δ values using tetramethylsilane as internal reference.

5.1 SYNTHESIS OF 2-TETRALONE (3,4-DIHYDRO-2(1H)-NAPHTHALENONE), (CVIX)

METHOD A: CORNFORTH et al. (1942) PROCEDURE:

Sodium, (20g, 0.87g-atom) was added during six minutes to a solution of 2-naphthol (14.54g, 0.101 mole) in absolute ethanol (200ml) and heated under reflux bath at 115°. Heating was continued until all metal disappeared; the cooled solution was then diluted with 200ml water and 200ml concentrated HCl added as rapidly as possible. The mixture was heated on steam bath for 15 min. with occasional stirring, then cooled and shaken with diethyl ether, and ether removed by distillation. The ethereal extract was washed with water (100ml), and shaken with a 5M solution of sodium bisulphite (70ml). The crystals that appeared were allowed to stand overnight, then collected and washed well with ether; and decomposed by Na_2CO_3 solution in the cold. The ketone was isolated by means of ether. The ether was removed which gave an almost colourless oily compound.

METHOD B: SOFFER et al. (1963) PROCEDURE:

REDUCTION AND HYDROLYSIS

A solution of 14.417g (0.1 mole) of 2-naphthol in 200ml 95% ethanol was prepared in a 1L round bottomed flask fitted with a three neck tube for a mechanical

stirrer. 30g (1.304 g-atom) of sodium was added in small portions with efficient stirring at a rate sufficient to maintain vigorous boiling. When approximately two-thirds of sodium has been introduced, an additional 50ml of 95% ethanol was added to reduce the viscosity of reaction mixture. At the end of addition, the rate of reaction decreased and heat was supplied by means of an electric heating mantle in order to maintain the reflux temperature. After all the metal had dissolved, heating was discontinued.

The 100ml (H_2O) was cautiously added, with stirring, followed by 200ml concentrated HCl. The acidic mixture containing precipitated NaCl was heated, with stirring, at reflux temperature for 30 min, and then allowed to cool.

The mixture was then extracted with 5 x 25ml portions of benzene. The combined extract was washed with 15ml portions of H_2O until all the washings were neutral to litmus. The organic solvent was removed by distillation on a steam bath. The crude oily residue was converted directly to 2-tetralone bisulphite addition product.

BISULPHITE ADDITION PRODUCT OF 2-TETRALONE

A solution of 43.33g (0.417 mole) of $NaHSO_3$ in 75ml H_2O was added to the crude hot syrup of 2-tetralone, and mixture was shaken vigorously within few minutes,

the addition product separated as a voluminous precipitate. The mixture was kept in cold for several hours, shaken periodically, and then filtered with aid of suction. The precipitate was washed with 4 x 25ml portions of ether. The colourless addition product was air-dried.

REGENERATION OF 2-TETRALONE

10g (0.04 mole) of 2-tetralone bisulphite addition product was suspended in H_2O (50ml) and 15g (0.12 mole) of Na_2CO_3 was added. At this point the pH of solution was approximately 10. The mixture was extracted with 5 x 20ml portions of ether. The combined extract was washed with 20ml of 10% HCl, then with 20ml portions of H_2O until washings were neutral to litmus, and was dried over anhydrous $MgSO_4$. The ether was removed by distillation to give 2.92g (20%) of 2-tetralone.

IR (neat) : 1710 cm^{-1} (C = O)

NMR ($CDCl_3$): δ 2.48 (t, 2H, C_4)methylene protons); 2.98 (t, 4H, C_1 and C_3 methylenic protons); 7.12 (m, 4H, ArH).

5.2 SYNTHESIS OF 3,4-DIHYDRO-1-METHYL-2(1H)-NAPHTHALENONE (XLI)

METHOD A: KAVADIAS et al. (1979) PROCEDURE:

To 2.92g (20 mmol) of 2-tetralone and 25ml of dry benzene was added during 5-10 min. with stirring 2.4ml of pyrrolidine. The mixture was refluxed for 45 min. (0.25ml H_2O distilled azeotropically), cooled, and added to 5-6ml of methyl iodide (stirring) so as to cause gentle refluxing. After an additional reflux period of 4 hrs, 48ml of H_2O was added and refluxing was resumed. After 30 min, benzene layer was shaken with a saturated solution of $NaHSO_3$, then dried (Na_2SO_4) and evaporated through water pump to give 2.2g, (68.8%), of 1-methyl-2-tetralone (XLI).

METHOD B: STORK et al. (1963) PROCEDURE:

PREPARATION OF 2-TETRALONE: PYRROLIDINE ENAMINE

2-Tetralone, 5g (34.25 mmol), with 4g (4.65ml, 55.56 mmol) of pyrrolidine in 100ml of benzene was refluxed for 3 hr . The enamine was obtained crystalline on removing the solvent Recrystallization from petroleum ether (60 - 80°) gave a product whose melting point was 80-82°C.

IR (nujol) : $1620cm^{-1}$, $1570cm^{-1}$ - unresolved benzene and enamine bands.

1-METHYL-2-TETRALONE

The crude pyrrolidine enamine from 8.8g (60.274 mmol) of 2-tetralone and 7.03g (8.3ml, 99.02 mmol) of pyrrolidine was refluxed for 10 hrs with 17.6ml (40.04g, 281.97 mmol) of methyl iodide in 44ml of 1,4-dioxane. Addition of 22ml (H_2O) and 0.9ml (acetic acid) and further heating for 4 hr , followed by removal of most of the solvent under reduced pressure. Extraction with ether, drying (Na_2SO_4) and removal of ether by distillation gave 6.945g (72%) of 1-methyl-2-tetralone (XLI).

IR (neat) : 1710cm^{-1} (C = O)
1380cm^{-1} (C-H for CH_3).

NMR ($CDCl_3$) : δ 1.5 (d, 3H, C_1-CH_3; J = 6.0 Hz); 2.3 (m, 2H, C_4-methylene protons), 2.9 (m, 3H, C_1-methine and C_3 methylene protons); 7.2 (m, 4H, ArH).

5.3 SYNTHESIS OF ETHYL-1-METHYL-2-OXO-1,2,3,4-TETRHYDRO-1-NAPHTHALENE ACETATE, (CX).

NaH, 1.203g (50% dispersion in oil, 50.125 mmol) was placed in 250ml round bottom flask. The mineral oil was washed out with benzene (3 x 15ml), then 10ml of dry dimethylformamide (DMF) was added, and the suspension stirred while cooling in an ice-bath. A solution of 8.02g (50.125 mmol) of XLI in 4ml of DMF was

added dropwise (5 min.). The cooling bath was removed and stirring continued at room temperature until evolution of gas ceased (2 hrs). The brown-coloured reaction mixture was cooled (ice-bath) and a solution of 8.38g (5.6ml. 50.125 mmol) of ethyl bromoacetate in 10ml DMF was added dropwise while keeping the reaction temperature below 25°C. After the addition was complete (10 - 15 mins), stirring in the cold was continued for 1 hr, and then overnight at room temperature. Water (102 ml) was added and the mixture extracted with ether (3 x 35ml), the combined ether extracts were washed with H_2O (2 x 35ml), dried ($MgSO_4$), and the solvent removed by evaporation to give 6.905g (56%) of ethyl-1-methyl-2-oxo-1,2,3,4-tetrahydro-1-naphthalene acetate (CX) as an oily material.

IR (neat) : $1740cm^{-1}$ - unresolved ketone and ester bands.

NMR ($CDCl_3$) : δ 1.2 (t, 3H, terminal CH_3); 1.5 (s, 3H, C_1-CH_3); 2.4 (m, 4H methylenic protons), 4.1 (m, 2H, OCH_2); 7.18 (m, 4H, ArH).

5.4 SYNTHESIS OF 3,9b-DIMETHYL-3a-HYDROXY-2-OXO-2,3,3a,4,5,9b-HEXAHYDRO-1H-BENZ(e)INDOLE, (CXI)

A solution of 15.8g (64.23 mmol) of CX and 6g (193.4 mmol) of methylamine in 20ml of ethanol was left at room temperature for 24 hr . The crystalline precipitate which formed was collected. After evaporation ($30^{o}C$) of the filtrate and treatment of the residue with ether, another quantity of CXI was obtained to give a total of 8g (54g, mp 72-$74^{o}C$).

IR (nujol) : 3300cm^{-1} (OH-stretch)
1670cm^{-1} (Lactam)

NMR ($CDCl_3$) : δ 1.30 (s, 3H, CH_3); 2.5 (s, 2H, CH_2CO); 2.9 (s, 3H, NCH_3); 3.35 (m, 2H, benzylic protons); 4.61 (s, 1H, OH, exchangeable); 6.8-7.2 (m, 4H, ArH).

5.5 SYNTHESIS OF 3,9b-DIMETHYL-2-OXO-2,3,5,9b-TETRAHYDRO-1H-BENZ(e)INDOLE, (CXII).

A solution of 9.46g (40.95 mmol) of CXI and 23.7mg of PTSA in 95ml of benzene was heated under reflux for 2 hr with azeotropic removal of water. After cooling to room temperature, the solution was washed with water and dried (Na_2SO_4). Removal of the solvent in vacuo and treatment of the residue with

ether (19ml) gave 4.36g (50%) of the indole (CXIV) as a crystalline product (mp 83-85°C.

IR ($CHCl_3$) : 1725cm^{-1}, 1675cm^{-1}, 1600cm^{-1}.

NMR ($CDCl_3$) : δ 1.35 (s, 3H, CH_3); 2.9 (s, 2H, CH_2CO); 3.0 (s, 3H, NCH_3); 3.35 (d, 2H, benzylic protons; j = 5.5 Hz); 5.0 (t, 1H, NC=CH); 6.8 - 7.3 (m, 4H, ArH).

5.6 SYNTHESIS OF 3,9b-DIMETHYL-5,9b-DIHYDROBENZ (e) INDOLE, (CXIII)

To a stirred suspension of 1.36g (35.9 mmol) of LAH in 44ml of dry ether was added dropwise a solution of 5.10g (23.94 mmol) of crude CXII in 200ml of dry ether and at such a rate as to maintain gentle refluxing. After the addition was complete (25min) stirring was continued at room temperature for 1½ hr . The reaction mixture was cooled in an ice-bath and treated successfully with 2.3ml H_2O, 1.8ml 20% aqueous NaOH and 8.2ml H_2O to provide a granular precipitate which was filtered and rinsed with ether. The combined filtrate and washings were evaporated to dryness under reduced pressure to give 2.5g (53%) of the indoline (CXIII) as a syrup.

IR (neat) : 1670 cm^{-1} (NC=CH).

NMR ($CDCl_3$) : δ 1.25 (s, 3H, CH_3); 1.75 (m, 4H, methylenic protons); 2.53 (s, 3H, NCH_3); 2.8 (d, 2H, benzylic protons, j = 5.8 Hz); 4.15 (t, 1H, NC=CH); 6.9 - 7.3 (m, 4H, ArH).

5.7 SYNTHESIS OF 4-BROMO-9b-METHYL-2,4,5,9b-TETRAHYDRO-1H-BENZ(e)INDOLE METHOBROMIDE, (CXIV)

To a stirred solution of 3.05g (19.1 mmol) of bromine in 195ml of DCM cooled in an ice-salt bath at -10°C with stirring was added all at once a solution of 3.8g (19.1 mmol) of enamine (CXIII) in 20ml DCM. After stirring at -10° for 10 min, cooling bath was removed and stirring continued at room temperature for another 20 min. Removal of the solvent under reduced pressure and trituration of the syrupy residue with ether gave a crystalline mass (3.07g, 45%).

The analytical sample was recrystallized from ethanol (mp 61-62°C).

IR (nujol) : 1675cm^{-1} ($C=N^+$)
750 cm^{-1} (C-Br).

5.8 SYNTHESIS OF 2,5-DIMETHYL-9-OXO-6,7-BENZOMORPHAN, (XLIII)

A solution of 4.74g (13.62 mmol) of CXIV in 120ml of 95% ethanol was placed in a 250ml round bottom flask and cooled to -10°C. To this stirred solution was added dropwise over a period of 1 hr (61 min) a solution of 1.12g (14.14 mmol) of NH_4HCO_3 in 28.6ml H_2O. The mixture was stirred in the cold for 2 hrs and, after stirring at room temperature for 24 hrs, the mixture was concentrated in vacuo to a small volume (≈ 30ml), treated with 10% aqueous $NaHCO_3$ (34ml) and extracted with ether (3 x 34ml). The combined ether extracts were washed with water (2 x 34ml), dried (Na_2SO_4) and evaporated to give a syrupy residue, which was dissolved in 6.8ml dry acetone and the solution added to a solution of 1.36g anhydrous oxalic acid in 6.8ml acetone. Crystals separated first at room temperature and then at 0°C overnight. The product was collected, washed with acetone and dried to give the oxalate salt (1.30g, 50%) of 9-oxobenzomorphan (mp 91-93°C).

The free base was quantitatively regenerated from its oxalate salt by treatment with NH_4OH followed by extraction with chloroform. The chloroform extracts was washed with water, dried (Na_2SO_4) and evaporated to give the base as a syrup.

IR (neat) : 1730 cm^{-1}

NMR ($CDCl_3$) : δ 1.35 (s, 3H, C_5-CH_3); 2.28 (s, 3H, NCH_3); 2.95 (d, 2H, benzylic protons; J = 6.1 Hz); 3.4 (m, 4H, methylenic protons); 3.95 (t, 1H, C_1-H); 6.7 - 7.2 (m, 4H, ArH).

5.9 SYNTHESIS OF 2,5-DIMETHYL-9-OXO-6,7-BENZOMORPHAN OXIME, (LXIV)

A solution of hydroxylamine was prepared by mixing hydroxylamine hydrochloride (1.4g, 20 mmol) and sodium acetate (1.7g, 20 mmol) in 70ml ethanol. After 1 hr, the mixture was filtered and the filtrate was treated with 2.8g (14.7 mmol) of 9-oxobenzomorphan. After 8 hr of reflux, the solution was concentrated to 20ml and upon cooling and filtering, 1.21g (40%) of oxime was obtained (mp 54-55°C).

NMR (CD_3OD) : δ 1.33 (s, 3H, C_5-CH_3); 2.3 (s, 3H, NCH_3); 3.0 (d, 2H, benzylic protons; J = 6.0 Hz); 3.65 (m, 4H, methylenic protons); 7.3 (m, 4H, ArH); 11.30 (s, 1H, OH, exchangeable).

5.10 SYNTHESIS OF 9α-AMINO-2,5-DIMETHYL-6,7-BENZOMORPHAN, (CXV)

Raney alloy (1.5g, 13 mmol) was added in small portions to a magnetically stirred solution of oxime (1.0g, 4.85 mmol) in ethanol (20ml) and 2M NaOH (20ml). The mixture was stirred at ambient temperature for 5 hr and then filtered. The filtrate was extracted with DCM (3 x 75ml), washed with water (50ml), dried ($MgSO_4$) and evaporated to give 9-aminobenzomorphan as an almost colourless oil (0.42g, 45%).

The dioxalate was crystallized from ethanol (mp 192 - 194°C).

IR (neat) : 3450 - 3375 cm^{-1} (NH_2)
1600 cm^{-1} (C=C).

NMR ($CDCl_3$) : δ 1.4 (s, 3H, C_5-CH_3); 1.55 (s, 2H, NH_2, exchangeable); 1.8 (m, 4H, methylenic protons); 2.4 (s, 3H, NCH_3); 2.85 (t, 1H, C_1-methine proton); 3.15 (d, 2H, benzylic protons; J = 6.0Hz); 3.83 (d, 1H, C_9-methine proton); 7.0 - 7.4 (m, 4H, ArH).

REFERENCES

Adkins, H., Rossow, A.G., Carnaham, J.E. (1948). 3,4-Dihydro-2(1H)-naphthalenone. J. Am. Chem. Soc., 70, 4247.

Ager, J.H., Fullerton, S.E., Fry, E.M. and May, E.L., (1963). Structures related to morphine.XXVI. Cyclization experiments with 2-benzyl-1,3,4-trialkyl-1,2,5,6-tetrahydropyridines. Improved yields of β-5,9-dialkyl-6,7-benzomorphans. J. Org. Chem., 28, 2470.

Ager, J.H., Fullerton, S.E. and May, E.L. (1963). Structures related to morphine. XXV. 5-Propyl- and 5,9-dipropyl-6,7-benzomorphans and a pharmacologic summary. J. Med. Chem., 6, 322.

Ager, J.H., Jacobson, A.E. and May, E.L. (1969). Separation of morphine-like effects by optical resolution. Levo isomers as strong analgetics and narcotic antagonists. ibid ., 12, 288.

Albertson, N.F. (1975). Effect of 9-hydroxylation on benzomorphan antagonist activity. ibid., 18, 619.

Albertson, N.F. and Walterau, W.F. (1970). Synthesis of pentazocine. ibid., 13, 302.

Allinger, N.L., Cava, M.P. De Jough, D.C., Johnson, C.R., Lebel, N.A. and Stevens, C.L. (1976). Preparation and reactions of alkenes. In: "Organic Chemistry", 2nd ed. Worth Publishers, Inc. New York, pp. 296.

Anderson, B.M. and Jencks, W.P. (1960). Effect of structure on reactivity in semicarbazone formation. J. Am. Chem. Soc., 82, 1773.

Archer, S., Albertson, N.F., Harris, L.S., Pierson, A.K. and Bird, J.G. (1964). Pentazocine. Strong analgesics and analgesic antagonists in the benzomorphan series. J. Med. Chem., 7, 123.

Audigier, Y., Malfroy-Camine, B. and Schwartz, J.S. (1977). Binding of ^{3}H-leu-enkephalin in rat stritium: partial inhibition by morphine or naloxone. Eur. J. Pharmacol., 41, 247.

Barltrop, J.A. (1947). Synthesis in the morphine series (I). Derivatives of bicyclo[3.3.1]-2-azanonane. J. Chem. Soc., 399.

Barltrop, J.A. and Saxton, J.E. (1952). Synthesis in the morphine series (III). β-Tetralone. ibid., 1038.

Beckett, A.H. and Casy, A.F. (1954a). Synthetic analgesics - stereochemical considerations. Prog. Med. Chem., 1, 43.

Beckett, A.H. and Case, A.F. (1954b). Stereoisomerism and biological action. J. Pharm. Pharmacol., 6, 986.

Belleau, B., Conway, T., Ahmed, F.R. and Hardy, A.D. (1974). Importance of the nitrogen lone electron pair orientation in stereospecific opiates. J. Med. Chem., 17, 908.

Bentley, K.W. and Hardy, D.G. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. I. Ketones derived from 6,14-endo-ethenotetrahydrothebaine. J. Am. Chem. Soc., 89, 3281.

Birch, A.J. (1944). Reduction by dissolving metals. I. J. Chem. Soc., 430.

Birch, A.J. (1950). The reduction of organic compounds by metal-ammonia solutions. Quart. Rev., 4, 69.

Birch, A.J. and Smith, H. (1958). Reduction by metal-amine solutions; applications in synthesis and determination of structure. ibid., 12, 17.

Block, F.B. and Clarke, F.N. (1969). 1,2,3,4,5,6-Hexahydro-6-phenyl-2,6-methano-3-benzazocines. 1. 3-carbamoyl-8-hydroxy derivative as an orally effective analgetic. J. Med. Chem., 12, 845.

Braenden, O.J., Eddy, N.B. and Halbach, H. (1955). Synthetic substances with morphine-like effect-relation between structure and analgesic action. Bull. WHO., 13, 937.

Braenden, O.J., Eddy, N.B. and Halbach, N. (1957). Synthetic substances with morphine effect - clinical experience, potency, side effects, and addiction liability. ibid., 17, 569.

Brown, W.C. (1951). Reductions by lithium aluminium hydride. Org. React., 6, 469.

Buchanan, J.G.St.C. and Woodgate, P.D. (1969). Clemmensen reduction of difunctional ketones. Quart. Rev., 23, 522.

Burckhalter, J.H. and Campbell, J.R. (1961). C_2H_4 and phenylacetyl chloride in the Friedel-Crafts re action - Synthesis of 2-tetralones and benzofuranones. J. Org. Chem., 26, 4232.

Burgstahler, A.W. and Worden, L.R. (1964). Synthesis of abietadienoic acids from dehydroabietic acid. J. Am. Chem. Soc., 86, 96.

Burwell, R.L. Jr. (1957). Stereochemistry and heterogeneous catalysis. Chem. Rev., 57, 895.

Burwell, R.L. Jr. (1969). Deuterium as a tracer in reactions of hydrocarbons on metallic catalysis. Acc. Chem. Res., 2, 289.

Carr, D., Iddon, B., Suschitzky, H. and Parfitt, R.T. (1980). Synthesis and some reactions of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1 (2H)-one (2,5-dimethyl-8-oxo-6,7-benzomorphan). J. Chem. Soc., Perkin Trans., 1, 2374.

Casy, A.F. (1970). Analgesics and their antagonists: recent developments. Prog. Med. Chem., 7, 229.

Casy, A.F. (1978). Agonist-Antagonist ligand structure as a guide to receptor characteristics and topography. Prog. Drug Res., 22, 150.

Casy, A.F. and Parulkar, A.P. (1969). Conformational studies of some 5,9-dimethyl-6,7-benzomorphan diastereoisomers and related compounds. Can. J. Chem., 47, 3624.

Cherest, M. and Felkin, H. (1968). Torsional strain involving partial bonds. The steric course of the reaction between allylmagnesium bromide and 4-tert-butyl-cyclohexanone. Tetrahedron Lett., 18, 2205.

Chignelli, C.F. and May, E.L. (1965). Structures related to morphine XXIX. Stereo-controlled reduction of 9-methylene-6,7-benzomorphans. J. Med. Chem., 8, 385.

Childers, S.R., Creese, I., Snowman, A.M. and Snyder, S.H. (1979). Opiate receptor binding effected differentially by opiates and opioid peptides. Eur. J. Pharmacol., 55, 11.

Cordes, E.H. and Jencks, W.P. (1962). General acid catalysis of semicarbazone formation. J. Am. Chem. Soc., 84, 4319.

Cornforth, J.W., Cornforth, R.H. and Robinson, R.H. (1942). Preparation of 2-tetralone from 2-naphthol and some analogous transformations. J. Chem. Soc., 689.

Cowan, A. Lewis, J.W. and Macfarlane, J.R. (1977). Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br. J. Pharmacol., 60, 537.

Crooks, P.A. and Rosenberg, H.E. (1978). Synthesis of spiro(tetralin-2,2'-pyrrolidine) and spiro(indan-2,2'-pyrrolidine) derivatives as potential analgesics. J. Med. Chem., 21, 585.

Davis, B.R. and Woodgate, P.D. (1965). The Clemmensen reduction II. Cyclohexenones. J. Chem. Soc., 5943.

De Stevens, G. (1965). Benzomorphans. In: "Analgesics", Academic Press, New York, pp. 189.

Dwyer, J.D. and Bloomfield, V.A. (1981). Influence of bivalent ligands on opiate receptors. Biopolymers, 20, 2323.

Eastham, J.F. and Larkin, D.R. (1959). Effect of variables on reductions by alcohol and potassium in ammonia. J. Am. Chem. Soc., 81, 3652.

Eddy, N.B. (1959). Chemical structure and action of morphine-like analgesics and related substances. Sixth Lister memorial Lecture. Chem. and Ind.(London), 1462.

Eddy, N.B. and May, E.L. (1966). Stereochemistry of benzomorphans. In: "Synthetic Analgesics, Part IIB, 6,7-Benzomorphans", Pergamon Press, Oxford, P113ff.

Eddy, N.B. and May, E.L. (1973). Search for a better analgesic. Science, 181 (4098), 407.

Erez, M., Takemori, A.E. and Portoghese, P.S. (1982). Vicinal opioid receptors: stereoselective potency enhancement by bivalent ligands. J. Med. Chem., 25, 847.

Farina, M., Morandi, C. and Mantica, E. (1972). High symmetry chiral molecules, J. Chem. Soc., Chem. Commun., 816.

Fauley, J. and Lapidus, L. (1973). Synthesis and analgetic activity of the diastereomeric 8-hydroxy-6,7-benzomorphans. J. Med. Chem., 16, 181.

Feinberg, A.P., Creese, I. and Snyder, S.H. (1976). Butyrophenone influences of the opiate receptor. Proc. Natl. Acad. Sci., (U.S.A.), 73, 4215.

Fennessy, F.R. (1968). Analgesic action of morphine N-oxide. Br. J. Pharmac., 34, 337.

Fennessy, M.R. and Lee, J.R. (1975). The assessment of and the problems involved in the experimental evaluation of narcotic analgesics. In: "Methods in Narcotic Research", Eds. Ehrenpreis, S. and Neidle, A., Marcel Dekker, Inc. New York, pp. 73-77.

Fried, J., Abraham, N.A. and Santanakrishnan, T.S. (1967). Birch reduction of phenols. J. Am. Chem. Soc., 89, 1044.

Fry, E.M. (1963). Stereospecific tautomerism in a 1,2-dihydropyridine. A β-benzomorphan synthesis. J. Org. Chem., 28, 1869.

Fry, E.M. and May, E.L. (1961). Mannich derivatives of analgesic agents. ibid., 26, 2592.

Fullerton, S.E., May, E.L. and Becker, E.D. (1962). Structures related to morphine XXIII. Stereochemistry of 5,9-dialkyl-6,7-benzomorphans. ibid., 27, 2144.

Gacel, G., Fournie-Zaluski, M.C., Fellion, E. and Roques, B.B. (1981). Evidence of the preferential involvement of μ-receptors in analgesia using eukephalins highly selective for peripheral μ or δ receptors. J. Med. Chem., 24, 1119.

Galt, R.H.B. (1977). The opiate anomalies - another possible explanation? J. Pharm. Pharmacol., 29, 711.

Gates, M. and Tschudi, G. (1952). The synthesis of morphine. J. Am. Chem. Soc., 74, 1109.

Gates, M. and Tschudi, G. (1956). Synthesis of morphine, ibid., 78, 1380.

Gaylord, N.G. (1956). Reduction of carbonyl derivatives. In: "Reduction with complex metal hydrides." Interscience New York, p. 124ff.

Gilbert, P.E. and Martin, W.R. (1976). The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther., 198, 66.

Glassman, J.M. (1971). Agents with analgesic activity and dependence liability. In: "Screening methods in Pharmacology", Vol.II, Eds. Turner, R.A. and Nebborn, P., Academic Press, New York, pp. 231.

Goodman, L.S. and Gilman, A. (1965). Narcotic Analgesics: Pentazocine. "The Pharmacological basis of Therapeutics", Macmillan, New York, pp. 269-271.

Grewe, R. (1946). Synthesis in the Phenanthrene Series V. Ber., 33, 313.

Grewe, R. and Mondon, A. (1948). Synthesis in the phenanthrene series VI. Synthesis of morphinane. Chem. Ber., 81, 279.

Grewe, R., Mondon, A. and Nolte, E. (1949). Synthesis of tetrahydrodeoxycodeine. Ann. Chem., 564, 161.

Halsall, T.G., Theobald, D.W. and Walsaw, K.B. (1964). Synthesis of terpenes VIII. Absolute configuration of elemol. J. Chem. Soc., 1029.

Hellerbach, J., Schnider, O., Besendorf, H. and Pellmont, B. (1966). Pharmacology. In: "Synthetic Analgesics, Part IIA, Morphinans", Pergamon Press, Oxford, p. 39.

House, H.O. (1972). The alkylation of active methylene compounds. In: "Modern Synthetic Reactions", W.A. Benjamin, Inc. London, p. 573.

House, H.O., Giese, R.W., Kronberger, K., Kaplan, J.K. and Simeone, J.F. (1970). Reactions involving electron transfer. II. Reductions of enones with alkali metal solutions. J. Am. Chem. Soc., 92, 2800.

House, H.O., Muller, H.C. and Pitt, C.G. (1963). Reduction of azabicyclic ketones. J. Org. Chem., 28, 2407.

Inoue, H. and May, E.L. (1976). Synthesis and Pharmacology of 2,9α-dimethyl-2'-hydroxy-6,7-benzomorphan. J. Med. Chem., 19, 259.

Inoue, H. Oishi, T. and May, E.L. (1975). Synthesis and Pharmacology of 5-noralkyl-9β-methyl-6,7-benzomorphans and stereochemistry of some intermediates. ibid., 18, 787.

Jacobson, A.E. and May, E.L. (1965). Structures related to morphine XXXI. 2-Substituted **benzomorphans**. ibid., 8, 563.

Janssen, P.A.J. (1973). Antagonists: Overview. In: "Narcotic Antagonists", Eds. Braude, M.C., Harris, L.H. May, E.L., Smith, J.P. and Villareal, J.E., Raven Press, New York, p.109.

Joshi, B.C. and May, E.L. (1965). 6,7-Benzomorphan from 3-methyl-4-propyl-pyridine. J. Med. Chem., 8, 696.

Kametani, T., Kigasawa, K., Hiiragi, M., Wagatsuma, N., Saito, H. and Sugi, H. (1973). Syntheses of heterocyclic compounds. DXXI. Syntheses of analgesics. XXXVII. Alternative synthesis of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocine. J. Heterocyl. Chem., 10, 313.

Kanematsu, K., Parfitt, R.T., Jacobson, A.E., Ager, J.H. and May, E.L. (1968). Synthesis of 6,7-benzomorphan from 4-phenylpyridine. J. Am. Chem.Soc., 90, 1064.

Kanematsu, K., Takeda, M., Jacobson, A.E. and May, E.L. (1969). Synthesis of 6,7-benzomorphan and related nonquaternary carbon structures with marked analgesic activity. J. Med. Chem., 12, 405.

Kavadias, G., Velkof, S. and Belleau, B. (1979). 9-Oxobenzomorphans I. General syntheses of dihydrobenz-(e)indolines as key intermediates. Can. J. Chem., 57, 1852-1865.

Kolb, V. (1978). New opiate-receptor model. J. Pharm. Sci., 67, 999.

Kometani, T. and Shiotani, S. (1978). Synthesis and analgesic activity of some benzomorphan analogs. J. Med. Chem., 21, 1105.

Kosterlitz, H.W., Lord, J.A.H., Paterson, S.J. and Waterfield, A.A. (1980). Effect of changes in the structure of enkephalins and of narcotic analgesic drugs on their interactions with μ- and δ -receptors. Br. J. Pharmacol., 68, 333.

Krapcho, A.P. and Bothner-By, A.A. (1959). Kinetics of the metal-ammonia-alcohol reductions of benzene and substituted benzenes. J. Am. Chem. Soc., 81, 3658.

Krapcho, A.P. and Bothner-By, A.A. (1960). Kinetics of the metal-ammonia-alcohol reduction of benzene. ibid., 82, 751.

Krapcho, A.P. and Nadel, M.E. (1964). Structure-reactivity relation of olefin reductions with lithium in ethylamine. Comparison of the ethylamine and ammonia systems. ibid., 86, 1096.

Kugita, H. and May, E.L. (1961). Structures related to morphine. XVI. Stereochemical control of addition of hydrogen to 9-oxobenzomorphans. J. Org. Chem., 26, 1954.

Kugita, H., Saito, S. and May, E.L. (1962). Structures related to morphine. XXII. A benzomorphan congener of meperdine. J. Med. Pharm. Chem., 5, 357.

Kugita, H. and Takeda, M. (1963). Syntheses of morphine-like structures, I. 9-Hydroxymethyl-2,5-dimethyl-6,7-benzomorphan. Chem. Pharm. Bull., 11, 986.

Lambert, Y., Daris, J.P. and Monkovic, I. (1978). 5-Allyl-9-oxobenzomorphans. Part 4. Syntheses of 3-hydroxy-8-oxyisomorphinans, 5-allyl-9α-hydroxy-6,7-benzomorphans, and related tetrahydrofuranobenzomorphans. J. Med. Chem., 21, 423.

Lednicer, D. and Mitscher, L.A. (1977). Derivatives of morphine, morphinan, and benzomorphan; 4-phenyl-piperidines. In: Organic Chemistry of Drug Synthesis", John Wiley and Sons, New York, pp. 286.

Leslie, F.M., Charkin, C. and Cox, B.M. (1980). Opioid binding properties of brain and peripheral tissues: evidence for heterogeneity in opioid ligand binding sites. J. Pharmacol. Exp. Ther., 214, 395.

Lewis, J.W., Bentley, K.W. and Cowan, A. (1971). Analgesic, sedative and antitussive derivatives of morphinan and benzomorphan, and their salts. Ann. Rev. Pharmacol., 11, 241.

Lever (Jr.), O.W., Bhatia, A.V. and Chang, K.J. (1985). Opioid receptor interactions and conformations of the 6α and 6β epimers of oxymorphamine. Solid state conformation of 6α-oxymorphamine. J. Med. Chem., 28, 1652.

Loew, G.H. and Berkowitz, D.S. (1975). Quantum chemical studies of morphine-like opiate narcotics. Effect of N-substituent variation. ibid., 18, 656.

Loew, G.H. and Berkowitz, D.S. (1976). Quantum chemical studies of methadone. In: "Opiates and endogeneous opioids." Elsevier, N. Holland, Biomedical Press, Amsterdam, pp. 387.

Lord, J.A.H., Waterfield, A.A., Hughes, J. and Kosterlitz, H.W. (1977). Endogeneous opioid peptides: Multiple agonists and receptors. Nature (London)., 267, 495.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E. and Gilbert, P.E. (1976). Effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther., 197, 517.

Martindale (1982). Narcotic analgesics: Pentazocine. In: "The Extra Pharmacopoeia", 28th ed., The Pharmaceutical Press, London, pp. 1024.

Marvel, C.S. and Lazier, W.A. (1944). Benzoyl piperidine. Org. Syn., Coll. Vol. 1., 99.

May, E.L. and Fry, E.M. (1957). Structures related to morphine. VIII. Further syntheses in the benzomorphan series. J. Org. Chem., 22, 1366.

May, E.L. Kugita, H. and Ager, J.H. (1961). Structures related to morphine. XVII. Further stereochemical studies with 9-oxobenzomorphans. ibid., 26, 1621.

May, E.L. and Murphy, J. (1955). Structures related to morphine. III. Synthesis of an analog of N-methylmorphinan ibid., 20, 257.

May, E.L. and Takeda, M. (1970). Optical isomers of miscellaneous strong analgesics. J. Med. Chem., 13, 805.

McKenna, J., Norymberski, J.K. and Stubbs, R.D. (1959). Partial reduction of steroid hormones and related substances. III. Reaction of α,β -unsaturated ketones and zinc in acetic acid. J. Chem. Soc., 2502.

Mellet, L.B. and Woods, L.B. (1963). Analgesia and addiction. Prog. Drug Res., 5, 155.

Merz, H., Langbein, A., Stockhaus, K., Walther, G. and Wick, H. (1974). Structure-activity relations in narcotic antagonists with N-furylmethyl substituents. In: "Narcotic Antagonists", Eds. Braude, M.C., Harris, L.S., May, E.L., Smith, J.P. and Villareal, J.E. Raven Press, New York, pp. 91.

Merz, H. and Stockhaus, K. (1979). N-[(Tetrahydrofuryl) alkyl] and N- (alkoxyalkyl) derivatives of (-) normetazocine, compounds with differentiated opioid action profiles. J. Med. Chem., 22, 1475.

Merz, H., Stockhaus, K. and Wick, H. (1975). Stereoisomeric 5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans, strong analgesics with nonmorphine-like action profile. ibid., 18, 996.

Michne, W.F. (1978). 2,6-Methano-3-benzazocine-11-propanols. Lack of antagonism between optical antipodes and observation of potent narcotic antagonism by two N-methyl derivatives. ibid., 21, 1322.

Michne, W.F. and Albertson, N.F. (1972). Analgetic 1-oxidized-2,6-methano-3-benzazocines. ibid., 15, 1278.

Michne, W.F., Lewis, T.R., Michalec, S.J., Pierson, A.K. and Rosenberg, F.J. (1979). (2,6-Methano-3-benzazocin-11β-yl)alkanones. 1. Alkylalkanones: a series of N-methyl derivatives with novel opiate activity profiles. ibid., 22, 1158.

Michne, W.F. Salsbury, R.L. and Michalec, S.J. (1977). Synthesis and narcotic agonist-antagonist evaluation of some 2,6-methano-3-benzazocine-11-propanols. Analogs of the ring C bridged oripavine-7-methanols. ibid., 20, 682.

Mitsuhasi, K., Shiotani, S., Oh-Uchi, R. and Shiraki, K. (1969). Structure-activity relation of analgetics. IX. Syntheses of azabenzobicycloalkanes. Chem. Pharm. Bull., 17, 434.

Monkovic, I., Conway, T.T., Wong, H., Perron, Y.G., Pachter, J.J. and Belleau, B. (1973). Total synthesis and pharmacological activities of N-substituted. 3,14-dihydroxymorphinans. 1. J. Am. Chem. Soc., 95, 7910.

Morrison, R.T. and Boyd, R.N. (1977). Alkenes II. Reactions of carbon-carbon double bond and carbanions I. Aldol and Claisen condensations. In: "Organic Chemistry", 3rd ed., Allyn and Bacon, Inc. London, p. 198, 701.

Murphy, J.G., Ager, J.H. and May, E.L. (1960). Structures related to morphine. XIV. 2'-Hydroxy-5-methyl-2-phenethyl-6,7-benzomorphan, the 9-demethyl analog of NIH 7519 (Phenazocine) from 3,4-dihydro-7-methoxy-2(1H)-naphthalenone. J. Org. Chem., 25, 1386.

Ogundaini, A.O. and Parfitt, R.T. (1985). Synthesis, stereochemistry, and analgesic activity of 4-mono- and 4,4-disubstituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine. J. Med. Chem., 28, 177.

O-ishi, T., Jacobson, A.E., Wilson, R.S., Yeh, H.H. and May, E.L. (1974). Synthesis of 2,9β-dimethyl-6,7-benzomorphan. J. Org. Chem., 39, 1347.

Opheim, K.E. and Cox, B.M. (1976). Stereospecific interaction of the quaternized opiate, N-methyllevorphanol, with opiate receptors. J. Med. Chem., 19, 859.

Palmer, D.C. and Strauss, M.J. (1977). Benzomorphans: Synthesis, stereochemistry reactions ans spectroscopic characterizations. Chem. Rev., 77, 1.

Parfitt, R.T., Redfern, P., Carr, D., Iddon, B. and Suschitzky, H. (1981). Synthesis and some reactions of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2H)-one (2,5-dimethyl-8-oxo-6,7-benzomorphan). Eur. J. Med. Chem., 16, 421.

Pasternak, G.W., Snowman, A.M. and Snyder, S.H. (1975). Selective enhancement of tritium-labelled opiate agonist binding by divalent cations. Mol. Pharmacol., 11, 735.

Patai, S. (1966). Reduction of carbonyl groups. In: "The chemistry of the carbonyl group". Interscience Publishers, London, Chap. 11.

Portoghese, P.S. (1965). A new concept on the mode of interaction of narcotic analgesics with receptors. J. Med. Chem., 8, 609.

Portoghese, P.S. (1966). Stereochemical factors and receptor interactions associated with narcotic analgesics. J. Pharm. Sci., 55, 865.

Portoghese, P.S., Alreja, B. and Carson, D. (1981). Allylprodine analogs as receptor probes. Evidence that phenolic and nonphenolic ligands interact with different subsites on identical opioid receptors. J. Med. Chem., 24, 782.

Portoghese, P.S., Gomaa, Z.S.D., Larson, D.L. and Shefter, E. (1973). Stereochemical studies on medicinal agents. 13. Correlation of the solid-state conformations of 1,3,5-trimethyl- and 1,3-dimethyl-4-phenyl-4-propionoxypiperidine enantiomers with their absolute stereoselectivity at analgesic receptors. Ibid., 16, 199.

Portoghese, P.S., Larson, D.L., Yim, C.B., Sayre, L.M., Ronsisvalle, G., Lipkowski, A.W., Takemori, A.E., Rice, K.C. and Tam, S.W. (1985). Stereostructure-activity relationship of opioid agonist and antagonist bivalent ligands. Evidence for bridging between vicinal opioid receptors. ibid., 28, 1140.

Portoghese, P.S. and Takemori, A.E. (1983). Different receptor sites mediate opioid agonism and antagonism. ibid., 26, 1341.

Reusch, W. (1968). Deoxygenation of carbonyl compounds. In: "Reduction techniques and applications in organic synthesis", Ed. Augustine, R.L., Marcel Dekker, New York, p. 171-211.

Richards, M.L. and Sadee, W. (1985). in vivo Binding of benzomorphans to mu, delta and kappa opioid receptors: comparison with urine output in the rat. J. Pharmacol. Exp. Ther., 233, 425.

Saito, S. and May, E.L. (1961). Structures related to morphine. XVIII. Stereochemical control of addition of hydrogen and methylmetallo reagents to 5-ethyl-2-methyl-9-oxo-6,7-benzomorphan. J. Org. Chem., 26, 4536.

Saito, S. and May, E.L. (1962). Structures related to morphine. XX. Stevens reaction in the synthesis of 5-ethyl-2'-hydroxy-2-methyl-(Or phenethyl)6,7-benzomorphan. ibid., 27, 948.

Saucier, M., Daris, J.P., Lambert, Y., Monkovic, I. and Pircio, A.W. (1977). 5-Allyl-9-oxobenzomorphans. 3. Potent narcotic antagonists and analgesics-antagonists in the series of substituted 2',9β-dihydroxy-6,7-benzomorphans. J. Med. Chem., 20, 676.

Scheiner, S. and Kolb, V. (1980). Influence of intramolecular hydrogen bonding on the electronic structure of oxymorphone. Proc. Natl. Acad. Sci., (U.S.A), 77, 5602.

Schiller, P.W., Yam, C.F. and Lis, M. (1977). Evidence for topographical analogy between methionine-enkephalin and morphine derivatives. Biochemistry, 16, 1831.

Schnider, O. and Grussner, A. (1949). Synthesis of hydroxy morphinans. Helv. Chim. acta., 32, 821.

Shiotani, S. and Kometani, T. (1980). Synthesis of 1,3-bridged 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine derivatives. Chem. Pharm. Bull., 28, 1928.

Shiotani, S., Kometani, T., Iitaka, Y. and Itai, A. (1978). X-ray analytical re-examination of correlation of nitrogen lone-pair orientation with analgesic activity. J. Med. Chem., 21, 153.

Shiotani, S. and Mitsuhasi, K. (1972). Structure-activity relation of analgetics. XII. Syntheses of acetamidoazabenzobicyclo [3.3.1] nonanes. Yakugaku Zashi, 92, 97.

Siegel, S. (1966). Stereochemistry and the mechanism of hydrogenation of unsaturated hydrocarbons. Advan. Catal., 16, 123.

Simonds, W.F., Koski, G., Streaty, R.A., Hjelmeland, L.M. and Klee, W.A. (1980). Solubilization of active opiate receptors. Proc. Natl. Acad. Sci., (U.S.A), 77, 4623.

Soffer, M.D., Bellis, M.P., Gellerson, H.E. and Stewart, R.H. (1963). β-Tetralone. Org. Syn., Coll. Vol. IV, 903.

Soffer, M.D., Steward, R.N., Cavagnol, Gellerson, H.E. and Bowler, E.A. (1950). Synthesis in the direction of morphine. II. Some intermediates and model compounds. J. Am. Chem. Soc., 72, 3704.

Stork, G., Brizzolara, A., Laudesman, H., Szmuszkovicz, J. and Terell, R. (1963). Enamine alkaylation and acylation of carbonyl compounds. ibid., 85, 207.

Stork, G. and Foreman (1946). Preparation of β-tetralone by the catalytic reduction of β-naphthol. ibid., 68, 2172.

Smith, M. (1968). Dissolving metal reductions. In: "Reduction techniques and applications in Organic Synthesis", Ed. Augustine, R.L., Marcel Dekker, New York, pp. 95-170.

Sykes, P. (1975). Nucleophilic addition to C=O. "A guide book to mechanism in organic chemistry", 4th ed. Longman, London, pp. 216.

Takeda, M., Inoue, H., Konda, M., Saito, S. and Kugita, H. (1972). Improved synthesis of a 9-oxo-6,7-benzomorphan and its homolog. Novel rearrangement of heterocyclic enamines via bromination. J. Org. Chem., 37, 2677.

Terrenius, L. (1977). Opioid peptides and opiates differ in receptor selectivity. Psychoneuroendocrinology, 2, 53.

Thyagarajan, G. and May, E.L. (1971). Improved synthesis of 2-benzyl-1,2,5,6-tetrahydropyridines, precursors of analgetic 6,7-benzomorphans. J. Heterocyl. Chem., 8, 465.

Trevoy, L.W. and Brown, W.G. (1949). Lithium aluminium hydride reactions. J. Am. Chem. Soc., 71, 1675.

Tullar, B.F., Harris, L.S., Perry, R.L., Pierson, A.K., Soria, A.E., Wetterau, W.F. and Albertson, N.F. (1967). Benzomorphans. Optically active and trans isomers. J. Med. Chem., 10, 383.

Walker, G.N. and Alkalay, D. (1966). New benzomorphan ring closure in the synthesis of 5-phenylbenzomorphans. J. Org. Chem., 31, 1905.

Watt, G.W. (1950). Reactions of inorganic substances with solutions of metals in liquid ammonia. Chem. Rev., 46, 289.

Wentland, M.P., Albertson, N.F. and Pierson, A.K. (1980). Synthesis and pharmacology of 8-amino-3-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-cis-6,11-dimethyl-2,6-methano-3-benzozocine and related compounds. J. Med. Chem., 23, 71.

Weyenberg, D.R. (1965). Monomolecular and bimolecular reduction of aryl olefins. J. Org. Chem., 30, 3236.

Yokoyama, N., Almaula, P.I., Block, F.B., Granat, F.R., Gottfried, N., Hill, R.T., McMahon, E.H., Munch, W.F., Rachlin, H., Saelens, J.K., Siegel, M.R., Tomaselli, H.C. and Clarke, F.H. (1979). Synthesis, analgetic activity and physical dependence capacity of 5-phenyl-6,7-benzomorphan derivatives. J. Med. Chem., 22, 537.

Yokoyama, N., Block, F.B. and Clarke, F.H. (1970). 1,2,3,4,5,6-Hexahydro-6-phenyl-2,6-methano-3-benzazocines. II. ibid., 13, 488.

Ziering, A., Malatestinic, N., Williams, T. and Brossi, A. (1970). 3'-Methyl, 8-methyl, and 8-phenyl derivatives of 5,9-dimethyl-6,7-benzomorphans. ibid., 13, 9.

APPENDIX 4.1

P values obtained by comparing benzomorphan vs saline and morphine vs saline using whole data at the stated dose.

Dose	P value for morphine	P value for benzomorphan
1mg/kg	0.151	0.726
2mg/kg	0.0151	0.00000
4mg/kg	0.0348	0.00021
8mg/kg	0.000000	0.229

- Ho = no difference between drug and saline That is, saline and drug are same.

- Values for which P is significant are those in which $P \leq 0.05$.

- P being sifnificant means Ho is not true - saline and drug are not the same. There is difference between them.

APPENDIX 4.2

P values obtained by comparing morphine vs saline and benzomorphan vs saline at various time intervals at a dose of 1mg/kg (Values of $P \leq 0.05$ are significant).

Time (min.)	P value for morphine	P value for benzomorphan
0	0.0000	0.17
15	0.0000	0.029
30	0.0000	0.849
60	0.0000	0.898
90	0.0000	0.411
120	0.0000	0.00001
180	0.00028	0.492
240	0.00013	0.00004

APPENDIX 4.3

P values obtained by comparing benzomorphan vs morphine at various time intervals. (Values of $P \leq 0.05$ are significant; Ho = no difference between benzomorphan and morphine).

(a) 2mg/kg Dose

Time	P value
0	0.217
15	0.121
30	0.08
60	0.0372
90	0.00001
120	0.00000
180	0.0214

For drug with high analgesic activity, refer to Figure 4.2.

(b) 4mg/kg Dose

Time	P value
0	0.07
15	0.724
30	0.429
60	0.118
90	0.331
120	0.119
180	0.289
240	0.98

NB: From the P values, there is no difference between benzomorphan and morphine. However, Figure 4.3 shows benzomorphan to be a better analgesia at this dosage.

(c) 8mg/kg Dose

Time	P value
0	0.453
15	0.0000
30	0.0000
60	0.0000
90	0.0000
120	0.113
180	0.284
240	0.218

For a drug with higher analgesic activity, refer to Figure 4.4.