# THE TOTAL SYNTHESIS OF 3-HYDROXY-17-DEAZA-17-THIAMORPHINAN, 3-HYDROXY-17-DEAZA-17-THIAISOMORPHINAN, AND 3-METHOXY-17-DEAZA-17-THIA-$\Delta^{9,10}$-HASUBANAN

J. RICHARD M. CAMICIOLI

DEPARTMENT OF CHEMISTRY

MCGILL UNIVERSITY, MONTREAL

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# The Total Synthesis of 3-Hydroxy-17-deaza-17-thiamorphinan, 3-Hydroxy-17-deaza-17-thiaisomorphinan, and 3-Methoxy-17-deaza-17-thia-$\Delta^{9,10}$-hasubanan

J. Richard M. Camicioli MSc Chemistry

## ABSTRACT

The synthesis of the analogue of 3-hydroxy-morphinan in which nitrogen has been replaced by sulfur is described. In developing the synthesis, unsaturated analogues of 3-methoxy-hasubanan in which nitrogen was replaced with oxygen and sulfur were produced. The starting compound for each of these syntheses was 6-methoxy-4α-(aminoethyl)-1,2,3,4,4α,9-hexahydrophenanthrene. The intermediates and final products were characterized by NMR, IR and mass spectroscopy.

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J. Richard M. Camicioli MSc Chimie

## R E S U M E

La synthèse des analogues de 3-hydroxy-morphinan et son isomère dans lesquels l'azote a été remplacé par le soufre est décrite. En plus, on a réussi la synthèse des analogues de methoxyhasubanan dans lesquels l'azote a été remplacé par l'oxygène et par le soufre. Le produit de départ pour toutes les synthèses est le 6-methoxy-4α- (aminoethyl)-1,2,3,4,4α,9-hexahydrophenanthrène. Les produits intermédiaires et les produits finals ont été caractérisés par spectroscopie infrarouge, résonance magnétique nucléaire et la spectrométrie de masse.

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## ABBREVIATIONS AND FORMULAE

| | | |
|---|---|---|
| DMSO | – | dimethylsulfoxide |
| TMS | – | tetramethylsilane |
| THF | – | tetrahydrofuran |
| IR | – | infrared spectroscopy |
| PMR | – | proton magnetic resonance spectroscopy |
| MS | – | mass spectroscopy |

PMR

| | |
|---|---|
| m. | multiplet |
| br | broad |
| d | doublet |
| dd | doublet of doublets |
| s | singlet |
| t | triplet |
| q | quartet |

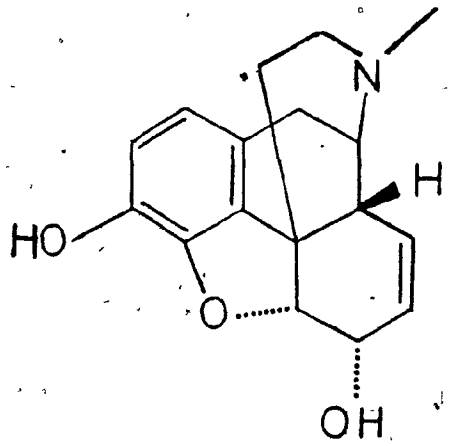
IR

| | |
|---|---|
| br. | broad |
| s. | strong intensity |
| sh. | sharp |
| m. | medium intensity |
| w. | weak intensity |
| sh.-mw | sharp to medium width |
| w.-s | weak to strong |
| d. | doublet |
| vb | very broad |

# CHAPTER I

## INTRODUCTION

Morphine (1) is an alkaloid endowed with a variety of physiological and psychological properties. It is known to induce analgesia, drowsiness, euphoria, respiratory depression, constipation, nausea, and emesis. In addition, it is highly addictive. In spite of its many undesirable properties, it has been, and is still used in medicine because of its analgesic activity.[1]



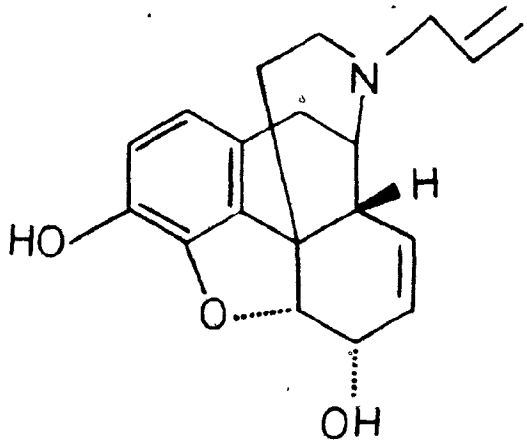

MORPHINE (1)

Hundreds of more or less related analogues have been synthesized with the hope of achieving dissociation of the desirable from the undesirable properties.[2] Research continues undauntedly in this area with the aim of synthesizing selective antitussives, antidiarreals, diuretics as well as analgesics and other drugs.

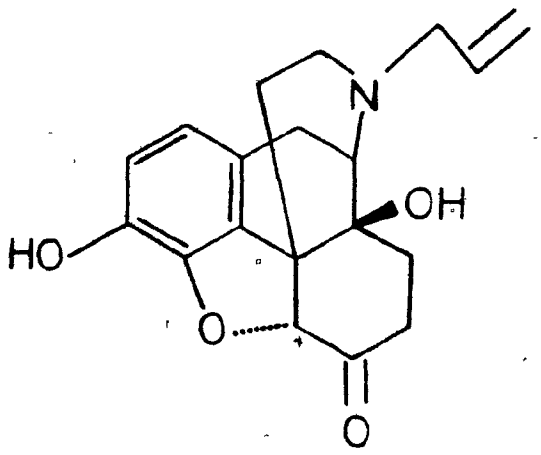
The term opiod is used to designate, in a generic sense, all drugs - natural and synthetic - with morphine-like properties. Pharmacologically speaking, any molecule displaying strong analgesic properties is often referred to as an opiate receptor agonist. Conversely, if a compound blocks the morphine-like effects of another drug, it is referred to as an antagonist. However, classes of compounds are known which behave as both agonists and antagonists as judged from the pharmacological criteria in use.

Nalorphine (2) was used for the first time in 1951 as an antidote for morphine poisoning in man because of its ability to antagonize the latter's effects on respiration. In 1953 it was found that nalorphine precipitated the withdrawal symptoms normally associated with drug deprivation in addicts. According to these criteria, nalorphine behaved as a genuine morphine antagonist. However, it was also found to induce strong analgesia in man, a criterion by which agonists are grouped into a separate class. Nalorphine was the first example of a drug displaying both agonistic and antagonistic properties. The expression matagonist has been proposed on the basis of mechanistic considerations to describe such compounds.[3] The drug appeared to have lower potential for abuse which raised the possibility that a pharmacologically clean non-addictive analgesic may be capable of existence. A serious drawback of nalorphine is the acute dysphoria that it induces in man, a property which disqualifies it for use as an analgesic.

Pure antagonists (that is, compounds inducing no obvious pharmacological response) have been discovered. The first member of this remarkable class is naloxone (3), whose activity could be detected only after challenging a pre-treated animal with morphine because all effects of the latter are blocked by this "pure" antagonist.

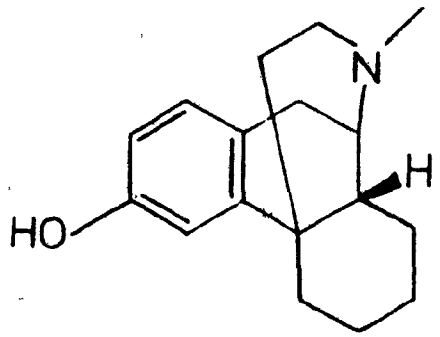



**NALORPHINE (2)**




**NALOXONE (3)**

An opiate agonist which is structurally much simpler than morphine, but much more effective as an analgesic is levorphanol (4)[4].



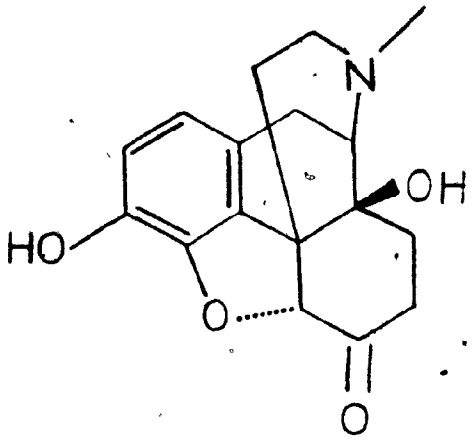

LEVORPHANOL (4)

Levorphanol incorporates only the morphine skeleton which is known as morphinan. It is totally synthetic but displays all the undesirable properties of morphine including increased addictive properties. Since it is structurally much simpler than morphine and readily available by synthesis, the generation of analogues became attractive from the standpoint of economics. Several syntheses of morphinans have been achieved.[4,5,6]

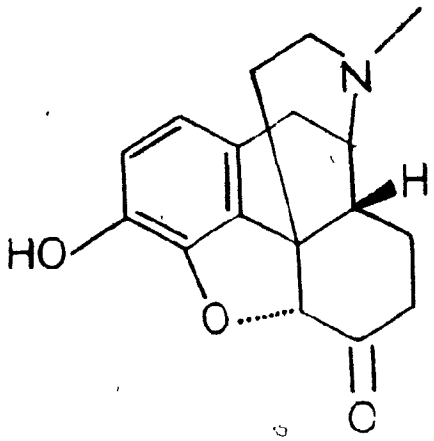
Replacement of the methyl group of levorphanol by an allyl group, as in the case of morphine produces a potent opiate antagonist, known as levalorphan, but again displaying analgesic activity in man. Unfortunately, it also exhibits all of the side effects of nalorphine. Other substituents on the nitrogen, such as cycloprophylmethyl, also generate agonist-antagonist activity of variable potencies.[7]

When the hydrogen at position 14 of the ring system is replaced by a hydroxyl group in the presence of a N-cyclobutylmethyl substituent, a potent analgesic-antagonist devoid of addiction potential is obtained.[8] This drug, known as butorphanol, constitutes a clear example of the subtle effects of substituents at strategic positions on the pharmacological profile of morphinans in man.

Attempts have been made using theoretical calculations to explain the role of the 14-hydroxyl group of butorphanol and oxymorphone (5) on the stereoelectronic properties of the nitrogen atom and all that could be said was that the vicinal OH group causes a distortion about the nitrogen lone pair of electrons apart from lowering the pKa of the molecule, as would be expected. However, it is not clear how these effects can serve to explain the pharmacological profile of butorphanol. Hydromorphone (6) and oxymorphone (5) were compared in this study,[9] but the conclusions do not provide an explanation as to why the 14-OH. enhances analgesic activity in the case of oxymorphone but antagonist activity in the case of butorphanol.

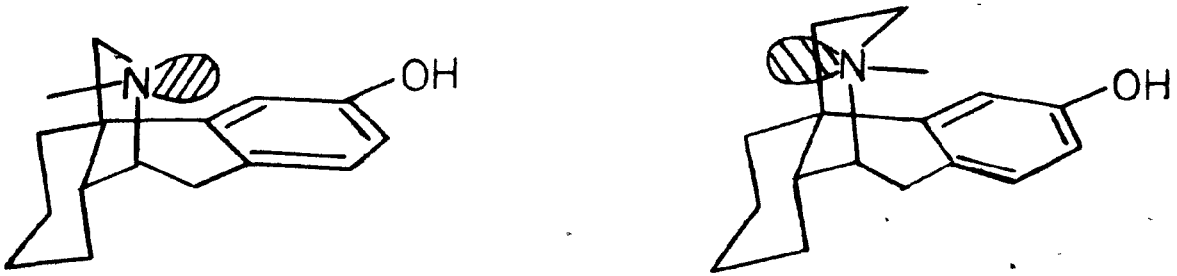



OXYMORPHONE (5)




HYDROMORPHONE (6)

Fundamental structure-activity studies led to the significant discovery that the directionality of the N-17 lone pair of morphinans has a controlling effect on productive binding on the opiate receptor.[10] This was dramatically illustrated by the complete lack of opiate-like activity of N-methyl-D-normorphinan (shown in Figure 1), a synthetic analogue of levorphanol in which the piperidine ring is contracted to a five-membered ring - an operation which forces the N-lone pair to project in a direction opposite to that of levorphanol. This conformation for the ring D nor analogue was deduecd by X-ray analysis[10] and molecular mechanics calculations (private communication from Roussel Uclaf).

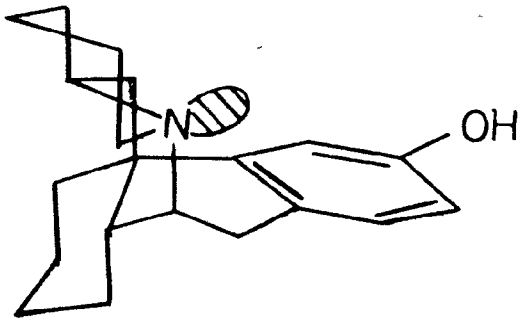



A B

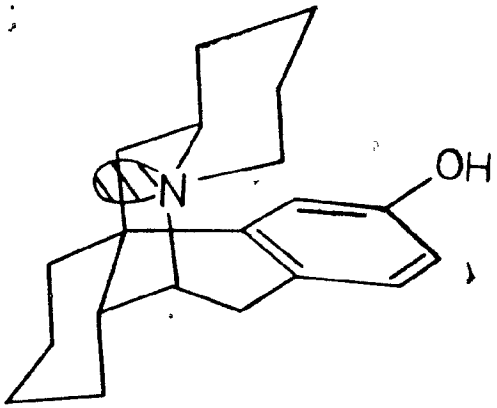
Figure 1: Nitrogen lone electron-pair orientations in N-methyl-D-normorphinan (A) and in levorphanol (B).

On that basis it is inferred that an analgesic response is initiated by a stereoelectronically controlled proton transfer at the receptor level. If only a charge-charge interaction were necessary, the D-ring nor analogue would be active because the simple electrostatic interactions are insensitive to geometrical effects. The D-ring nor analogue cannot, in its protonated form, participate in a stereo-controlled proton transfer in a direction predetermined by the nirogen geometry of levorphanol. However, the electrostatic part of the attraction of levorphanol to its receptor may contribute a pharmacological effect which is impossible to predict. All that one can say is that this attraction is not evident with the D-ring nor analogue since no morphinan-like activity was measurable. Quinolizidine analogues of levorphanol (Figure II) have served to confirm the key role of the N-lone pair directionality. The isomer with the N-lone pair pointing towards the phenyl group (A) had no analgesic activity while the one with the lone pair pointing away from the phenyl group (B) displayed significant activity.[7,11]

These conclusions have been questioned[12,13,14] on the grounds that quaternary nitrogen analogues of opiates display very weak, but measurable agonist activity in various test systems.[12] Also, the necessity of an equatorially oriented N-methyl group in morphine for activity has been questioned on the basis of 600 MHz solution NMR spectroscopy which showed that a significant portion of the N-axially oriented conformer is present.[13] The properties of quaternary morphine with an axially oriented N-allyl group may also appear to contradict the N-lone pair orientation theory.[12b]




A

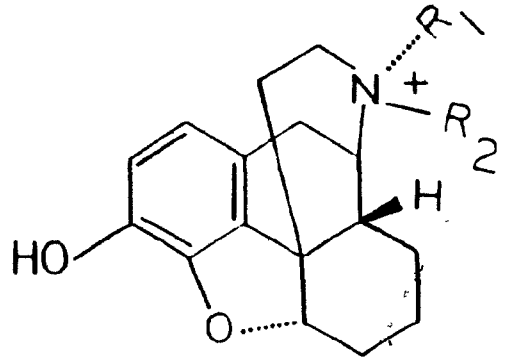



B

Figure II: Nitrogen lone electron-pair orientation in quinolozidine analogues of morphinans: 16 α, 17-butanorphinan (A) and 16 β, 17-butanormorphinan (B).

Similar contradictions were emphasized using benzomorphans as substrates.[14] However, it should be noted that all quaternary analogues thus far reported display greatly reduced activities and that this is especially true of the N-allyl antagonist analogues (Figure III).[12c]

For instance, the axial N-allyl isomer A, shown in Figure III, has very low agonist activity on the guinea pig ileum preparation assay and is not antagonized by naloxone. Reversal of agonist activity by a specific antagonist such as naloxone in the case of opiates is a requirement for receptor mediated activity. The absence of such a response in the case of the axial N-allyl isomer suggests that its weak activity is not a true morphine-like activity at the morphine receptor. Thus, one cannot draw conclusions about the morphine receptor from these results. The equatorial isomer B (Figure III) is, however, an effective antagonist in the mouse vas deferens preparation (one third the activity of nalorphine). These presumed evidences against the N-lone pair directionality theory are not as convincing as they appear. Firstly, stereospecificity of interaction with the receptor was not demonstrated in all cases.[12a,b] A direct interaction with the receptor, as opposed to a less specific indirect membrane effect, is expected to be stereospecific. More important, however, is the fact that no attention was paid to the pharmacokinetics of the quaternary compounds.[12b,c] In some cases, it was not measured;in the others, the time of onset and offset of the biological effects, although at marked variance with the behavior of standard opiates, was not commented upon.[12] All quaternary analogues thus far studied are characterized by rapid onsets and offsets of activity in marked contrast with classic opiates which also display much greater potency.



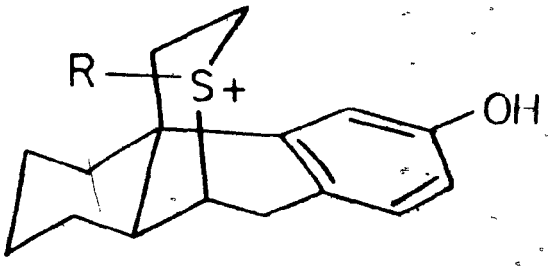

A: $R_1 = CH_3$; $R_2 = CHCH = CH_2$

B: $R_1 = CHCH = CH_2$; $R_2 = CH_3$

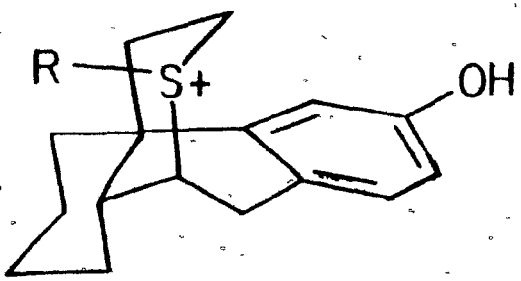
**Figure III**: Allyl substituted quaternized morphine derivatives.

There is no doubt that these remarkable differences have mechanistic significance, but not necessarily in relation to the directional proton transfer theory. Rather, the quaternary compounds may reveal only a possible, but weak effect of the charge-charge interaction per se or may be acting indirectly. With quaternary analogues, the axially oriented proton of the piperidine part is replaced by a bulky, hydrophobic allkyl group which prevents optimal charge-charge interactions with the receptor. Closeness of approach to a counter anionic site of the receptor is hindered, and distortions about the receptor conformations may well be induced.

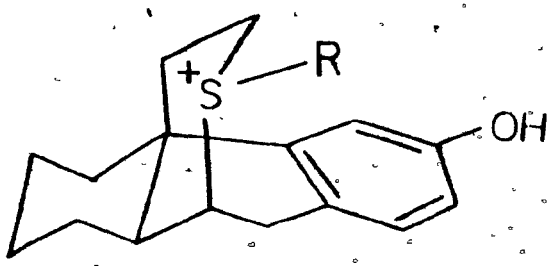
The present research was undertaken with a view of specifying, with greater precision, the respective roles of the charge-charge interaction and the protophilic nitrogen lone pair in the receptor response. An attractive approach consists in substituting the nitrogen atom of agonists and antagonists by a sulfur. Sulfonium salts are tetrahedral like tertiary amines, are permanently charged, but unable to carry a proton. The structures of some relevant analogues are shown in Figure IV. Isomorphinan analogues are equally desirable targets because isolevorphanol is known to be more active than levorphanol.[15] Clearly, the equatorially oriented sulfonium species should allow optimal approach to the counter anionic site of the receptor; this would not be possible with the axial configuration. The first goal was to synthesize the parent cyclic sulfides which could then be submitted to alkylation reactions using appropriate reagents. Accordingly, we set about to synthesizing 3-hydroxy-17-deaza-17-thiamorphinan and its isomorphinan stereoisomer.



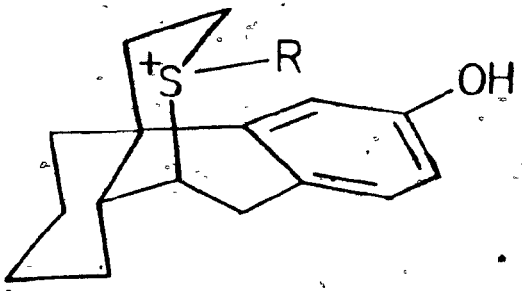

A - axial alkyl




B - axial alkyl




A - equatorial alkyl




B - equatorial alkyl

Figure IV: Target S-alkyl-thiaisomorphinan (A) and thiamorphinan (B) analogues.

Retrosynthetic analysis (Figure V) suggested that approaches previously used successfully in the nitrogen series might be applicable. Some key disconnections of the ring system are shown in Figure V which have successfully led to syntheses of morphinans and closely related compounds. Disconnection a. formed the basis of Evan's approach to the morphinan skeleton.[5] Earlier, Grewe pioneered approach b. to morphinan itself involving a Friedel-Crafts ring closure reaction where the aromatic group is effectively nucleophilic and an olefin elctrophilic.[4] It has been adapted successfully to the synthesis of the thiaisomorphinan skeleton in our laboratories.[16] Surprisingly, this route led to the isomorphinan stereochemistry in contrast to the morphinan stereochemistry which is generated in the nitrogen series. Route c. formed the basis of the synthesis of 14-hydroxy substituted morphinans as conceived by Belleau and industrially exploited by the Bristol-Myers Company.[17,18] It offers the potential for defining the stereochemistry at position 14 prior to cyclization to the fundamental skeleton.

A generous gift of the Bristol-Myers Company of the key intermediate 1 shown in Scheme I, Chapter 2, used in this route was of great help in initiation of this work. Our first goal was to develop methods for the replacememt of the amine group by other functionalities.

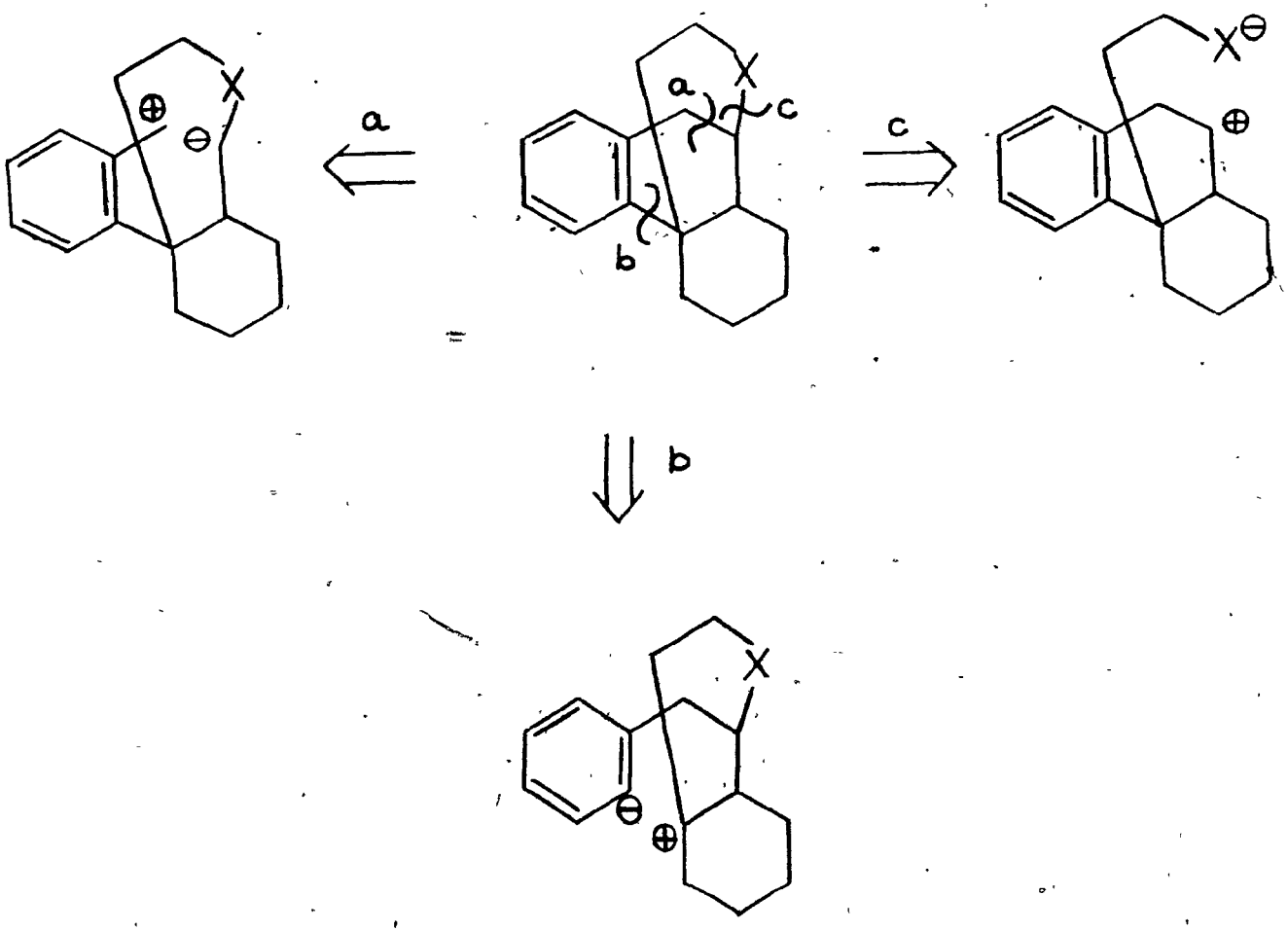
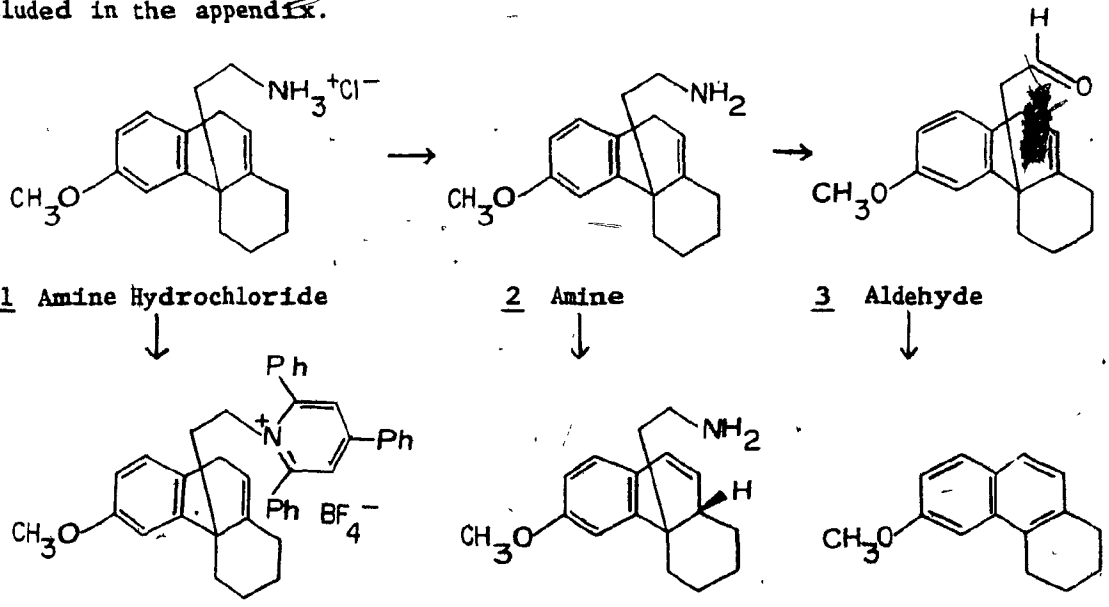



Figure V: Retrosynthetic analyses of the morphinan skeleton.

# CHAPTER 2

## DISCUSSIONS AND RESULTS

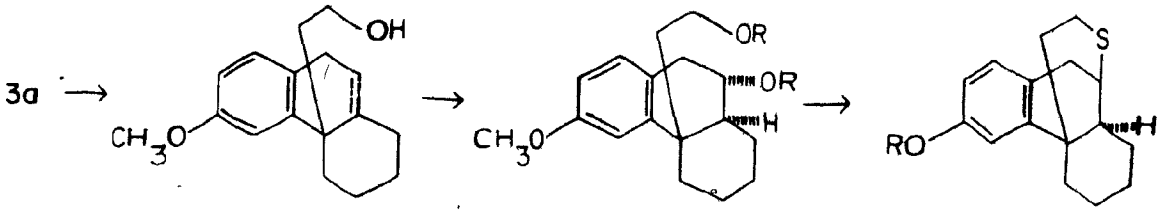
The following discussion centers on transformations of the substituted phenanthrene system used as a starting material (Scheme I) and on the synthesis of 3-hydroxy-17-deaza-17-thiaisomorphinan, (Scheme II), 3-methoxy-17-deaza-17-thia-$\Delta^{9,10}$-hasubanan (Sceme III), and 3-hydroxy-17-deaza-17-thiamorphinan (Scheme IV). Numbering of the compounds is as shown in the three following schemes unless otherwise stated (consult Figure VI especially). The transformations outlined in Schemes I - IV are described in the experimental section. Detailed spectral analyses are contained in the text. Only the highlights of the work are included in the text; details are to be found in the experimental part. Some relevant spectra are included in the appendix.




1 Amine Hydrochloride 2 Amine 3 Aldehyde

1b Pyridinium Tetrafluoroborate 2b Isomerized Amine 3b Aromatic

**Scheme I:** Amine Hydrochloride, Amine, and Aldehyde Transformations.




4 - Alcohol

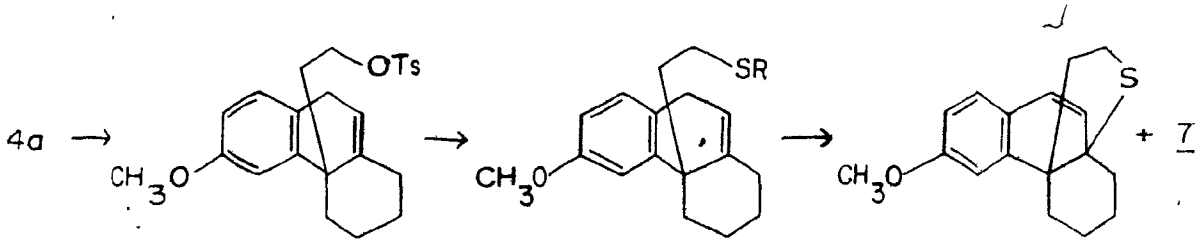
5 - Diol

6 - Dimesylate R=$SO_2CH_3$

7 - Methoxy-thiaisomorphinan $RCH_3$

8 - Hydroxy-thiaisomorphinan R = H

Scheme II: 3-Hydroxy-17-deaza-17-thiaisomorphinan synthesis



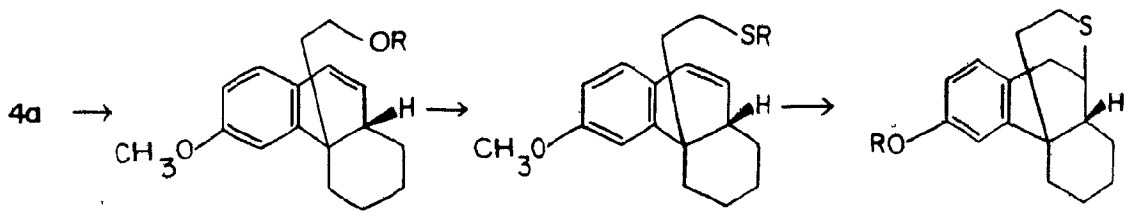

9 - Tosylate

10 - Thioxanthate: R = $C(S)OCH_2CH_3$

11 - Thiol: R = H

12 - Methoxy-dehydro-thiahasubanan

Scheme III: 3-methoxy-17-deaza-17-thiahasubanan synthesis




13 - Isomerized Alcohol R = H

14 - Isomerized Tosylate: R = $SO_2C_6H_5CH_3$

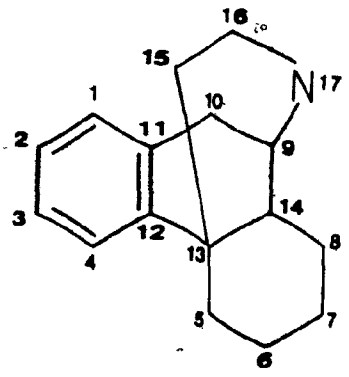
15 - Thiolacetate: R = $C(O)CH_3$

16 - Isomerized Thiol: R = H

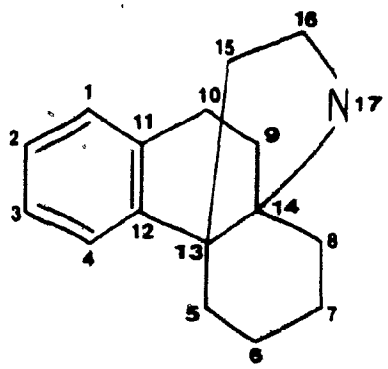
17 - Methoxy-thiamorphinan R = $CH_3$

18 - Hydroxy-thiamorphinan R = H

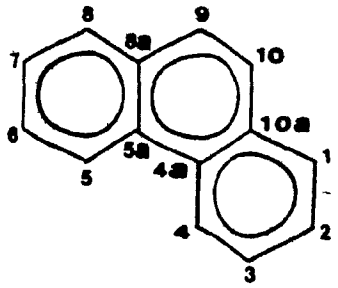
Scheme IV: 3-hydroxy-17-deaza-17-thiamorphinan synthesis.




Morphinan and Isomorphinan




Hasubanan



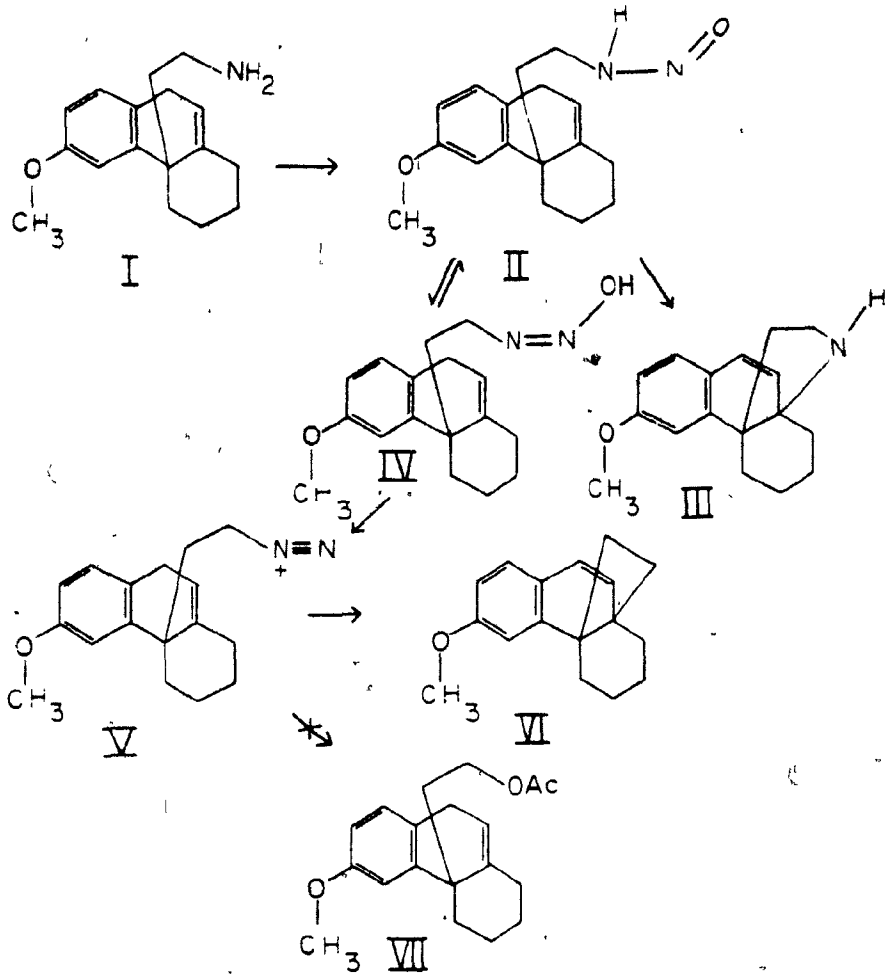

Phenanthrene

Figure VI: Numbering scheme for morphinan and isomorphinan, hasubanan and phenanthrene.

## 2.1 Removal of a Primary Amino Group

Several methods are available for the conversion of primary amines to other functional groups.[19] One approach is to transform the amine into a good leaving group so as to allow for subsequent nucleophilic substitution. Diazotization of an amino group would accomplish this; however, with primary amines, elimination to form an olefin competes effectively with nucleophilic substitution.[20] Despite the potential drawbacks of this approach, an attempt was made to diazotize the amine 2 in the presence of the acetate ion as the external nucleophile. When the reaction was attempted according to the conditions of Streitweiser[21] using sodium nitrite in acetic acid at 0°C, a complex mixture of products was obtained. Some of the desired acetate ester may have been produced because there was a band in the IR spectrum of the mixture which is characteristic of the acetate carbonyl absorption at 1730 $cm^{-1}$. The major product, as judged from the NMR spectrum of the mixture appeared to be an olefin whose alpha carbons carried no hydrogens, indicated that the double bond of the starting material had isomerized. The chemical shifts of these protons in the olefinic product suggests that they are attached to a styrene function. Given the acidic conditions prevailing during the nitrosation reaction, double bond isomerization may not be surprising. Since the reaction products were not characterized further, the mechanisms underlying these observations cannot be clearly identified, although one may speculate that generation of a reactive electrophile in the presence of an equally reactive olefin may well favour side reactions such as shown in Scheme V.

**Scheme V: Diazotization and plausible reaction pathways.**




These results suggest that the amine should be transformed into a leaving group less reactive than the diazonium species, but allowing for nucleophilic displacement by an external nucleophile (such as the acetate anion). Katrizky[22] had successfully displaced primary amines with other functional groups by way of nucleophilic substitution of the corresponding

2,4,6-triphenylpyridinium derivatives. Accordingly, the pyridinium derivative was generated in 70% yield reacting the amine with 2,4,6-triphenylpyrylium tetrafluoroborate[23] in ethanol.[24] The product was recrystallized from ethanol and characterized by NMR. The spectrum was entirely consistent with the expected structure. Attempts were therefore made to react it (1b) under a wide variety of conditions with many different nucleophiles. In no case was any product isolated which corresponded to the expected substitution products in spite of the numerous precedents for such displacement processes.*[25]

It is revealing that with sodium acetate or potassium ethyl thioxanthate as the nucleophiles, the same product was formed. On the basis of the NMR and Mass Spectrum of this product the structure was deduced to correspond to the aromatized compound 3b.**

A plausible mechanism for its formation would involve a bimolecular elimination reaction, where 2,4,6-triphenylpyridine, and ethylene appear as products in addition to 3b. A two step mechanism where an allylic-benzylic anion would be formed is also possible.

* Nucleophiles tried were: 1. thiourea (in chlorobenzene at reflux and neat); 2. potassium iodide (in ethanol at reflux); 3. potassium thiolacetate (in benzene at reflux); 4. potassium ethyl thioxanthate (in benzene at reflux); 5. sodium acetate (neat at 185°C).

** Discussed later.

It is clear that the nucleophiles used behaved as protophiles in this reaction. It is possible that Katrizky's modification of the approach and which involves dihydro-benzoquinolinium salts that are more susceptible to

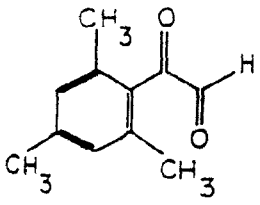
nucleophilic attack than the corresponding 2,4,6-triphenylpyridinium salts, might offer a solution to the problems. However, we elected to use another approach involving the iodide ion as the nucleophile. Instead of the tetrafluoroborate, the iodide salts were prepared according to Chadwick's[26a] and Balaban's[26b] method from the red pyrylium iodide salt itself obtained from the yellow tetrafluoroborate. Thermolysis of the pyridinium iodide at 150°C gave a mixture of products containing none of the desired iodide.

Another useful method for the replacement of primary amines by another functionality involves the thermal rearrangements of N-nitroso amides.[27] This approach is shown in Scheme VI. N-acetyl and 3,5-dinitrobenzoyl amides of amine 2, were prepared by conventional methods from the corresponding acid chlorides. When these amides were subjected to nitrosating and rearrangement conditions,[28,29]* none of the desired O-acetate could be detected spectroscopically.

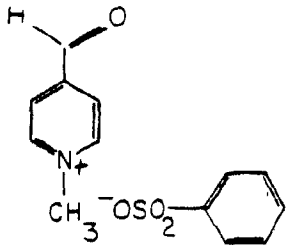
* Nitrosating conditions: (a) Sodium nitrite in acetic acid and acetic anhydride. (b) Nitrogen dioxide in dichloromethane.

Rearrangement conditions: Heating in dioxane.

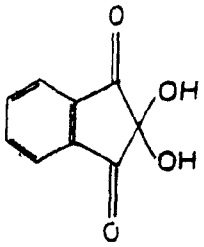
These attempted transformations as outlined above leave unchanged the oxidation state of the carbon atom bearing the amine function. However, methods are known which involve oxidative elimination of nitrogen from primary carbons. For example, the Schiff base of the isomerized amine 2b, is obtainable according to the method of St. C. Black.[30] Oxidation of this intermediate gave a compound whose NMR spectrum was in agreement with the expected oxaziridine.* Base-induced decomposition of this material under known conditions[30] gave none of the desired aldehyde. The three mildest methods of transamination available in the literature utilize mesitylglyoxal,[31] 4-formyl-methylpyridinium benzenesulfonate,[32] or ninhydrin[33] as reagents. They all function by mechanisms similar to that of pyridoxal phosphate-dependent enzymes.[34]



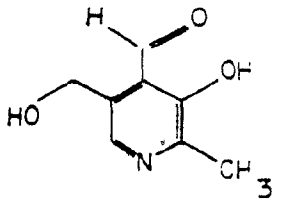
mesitylglyoxal



4-formyl-1-methylpyridinium benzenesulfonate



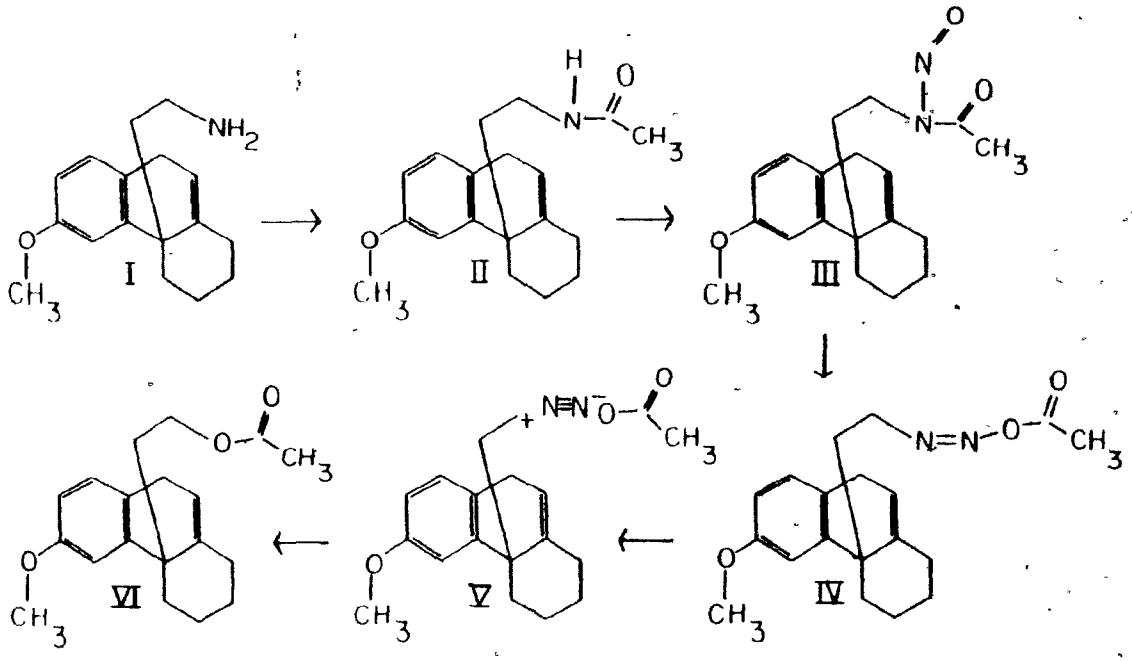
ninhydrin



pyridoxal

Figure VII: Reagents for oxidative amine transformation.

*The Schiff base showed two methyl group peaks in addition to the methyl aryl peak at 1.3 and 1.0 ppm. Two singlets appeared at 1.30 and 1.45 ppm in the oxidized compound.




**Scheme VI: N-nitroso-amide transformations.**

When an excess of ninhydrin was combined with the amine 2 under nitrogen in 1/1 ethanol-water in the presence of sodium bicarbonate, a 50% yield of the desired aldehyde 3 was obtained after chromatography. This yield compares favorably with literature examples of transamination but does not match the results of Rapoport's method as will be discussed later. Our observations extend the scope of Gibson's method.

The infrared spectrum of the aldehyde showed a carbonyl absorption at 1712 $cm^{-1}$ as well as C(O)-H vibrations at 2718 and 2815 $cm^{-1}$ which are also characteristic of aldehydes.[35,36] The 200 MHz NMR spectrum of the aldehyde displayed interesting features. The doublet of doublets expected for an aldehyde proton coupled to two different protons, is centered 9.26 ppm (Figure VIIIa). The diastereotopic protons alpha to the carbonyl are coupled to each other giving rise to a coupling constant of about 15.3 Hz as would be expected for geminal protons (Figure VIIIb). The two protons alpha to the carbonyl are diastereotopic, hence are expected to be magnetically non-equivalent and accordingly they appear at 2.54 and 3.13 (Figure VIIIb). The relevant coupling constants are 2.54 Hz and 3.87 Hz, as anticipated. The other pertinent peaks in the NMR spectrum include the aromatic, benzylic, olefinic and methoxy protons, the chemical shift being similar to those of the starting amine 2. The mass spectrum showed no parent ion; a peak at m/z 212 had an abundance of 100%, which can be accounted for by the loss upon impact of the side chain plus a hydrogen atom by a mechanism which has precedent.[37]

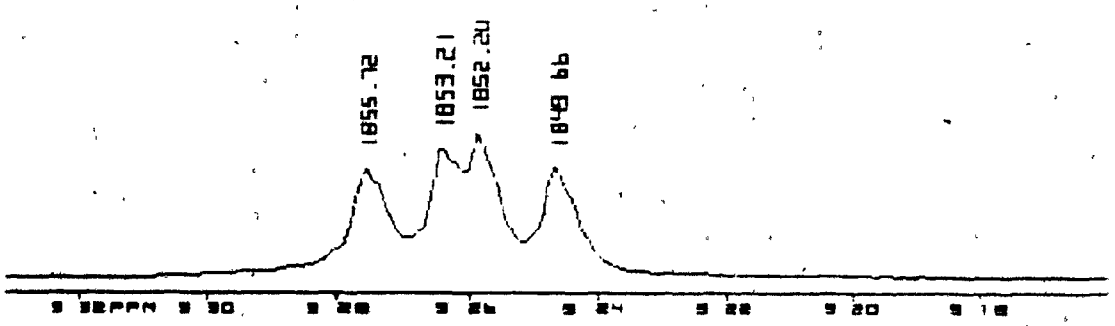



Figure VIII a): Aldehyde proton by 200 MHz NMR spectroscopy.

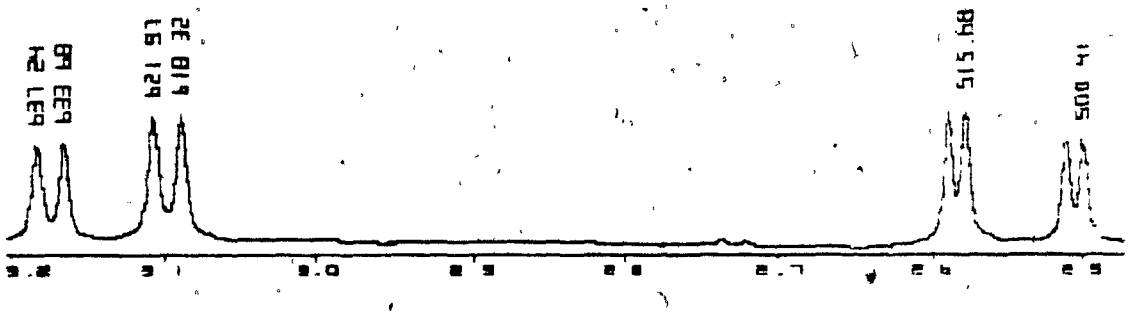
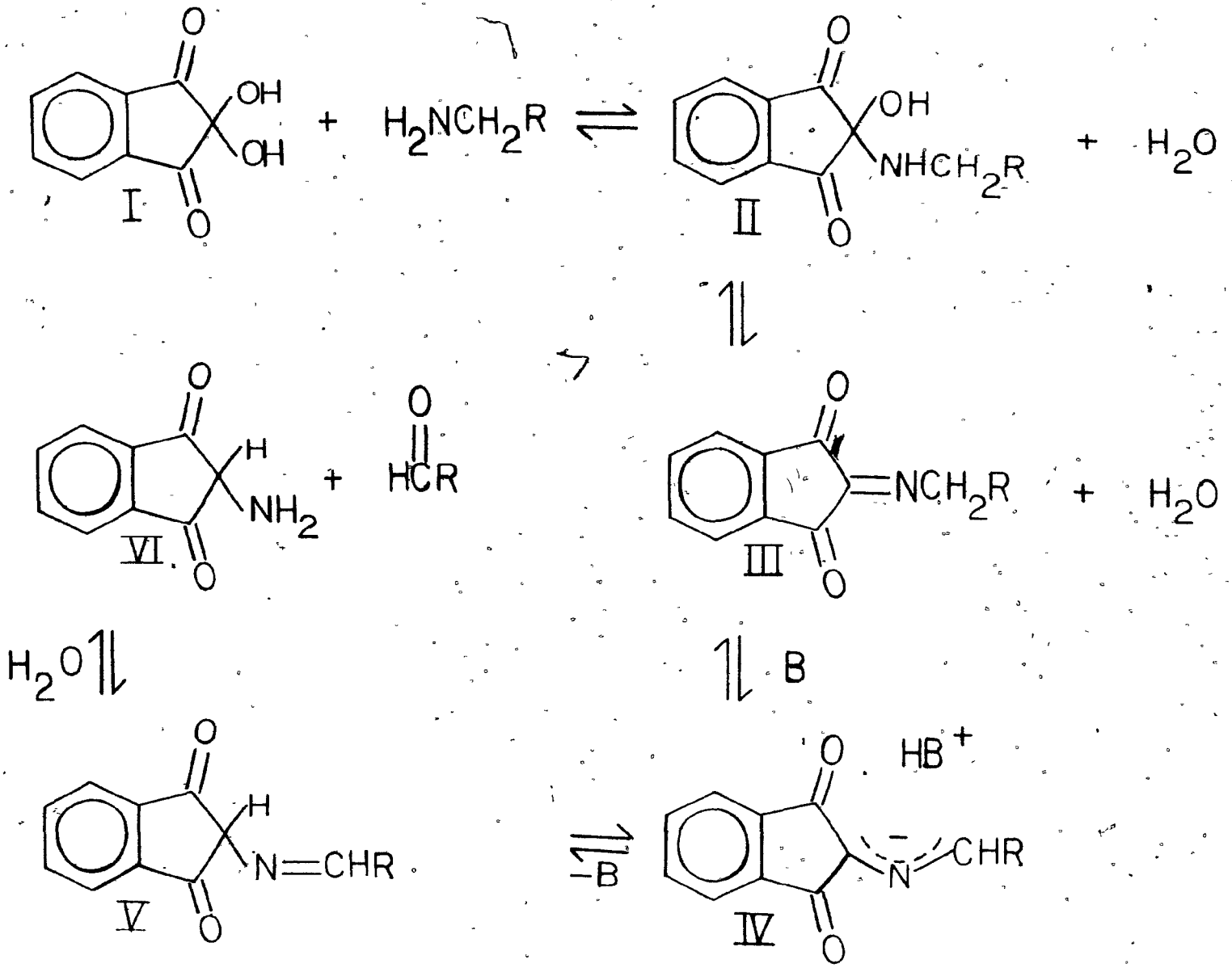



Figure VIII b): Protons alpha to carbonyl of aldehyde by 200 MHz NMR spectroscopy.

A plausible mechanism for the ninhydrin mediated transformation is presented below (Scheme VII). The first step undoubtedly involves the formation of a Schiff base (III) which tautomerizes by way of an azaallylic anion (IV). Schiff base (V) can then suffer hydrolysis to the desired aldehyde with concomitant formation of the deep blue animated ninhydrin complex (Ruehman's purple).[38,39]



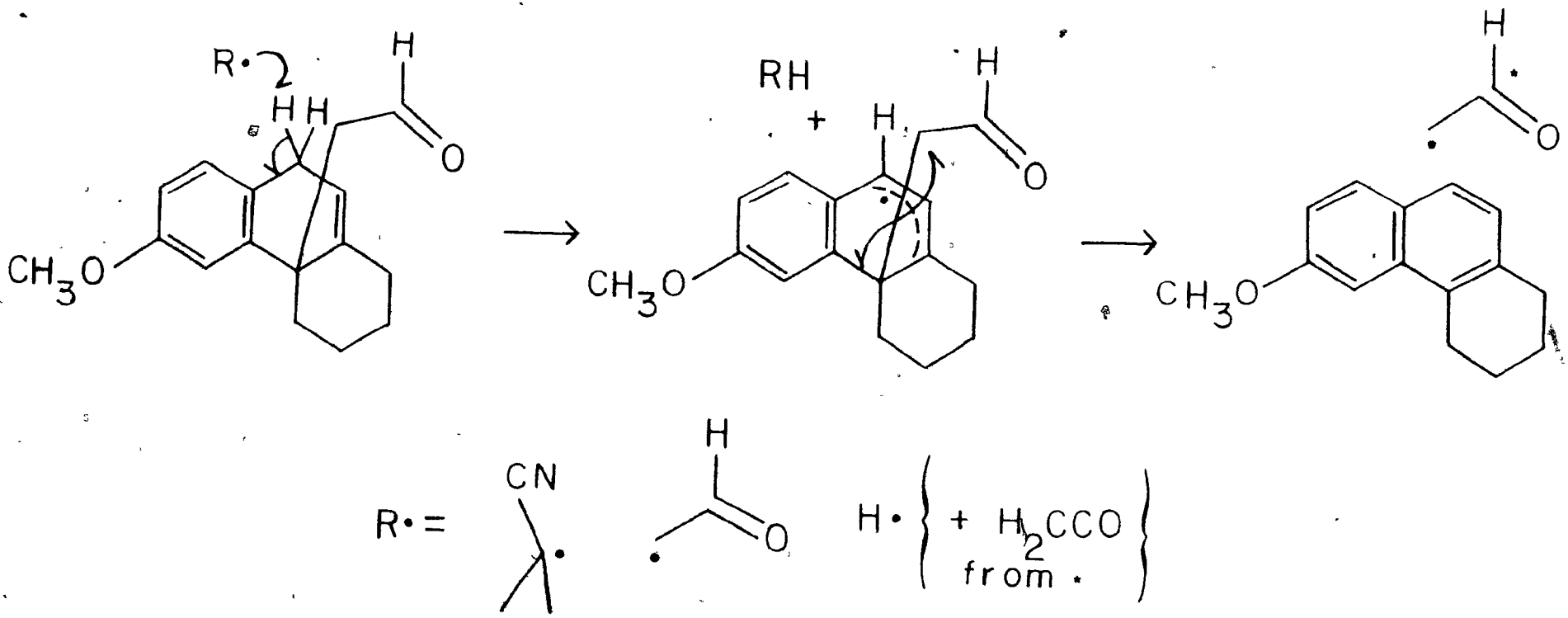

Scheme VII: Mechanisms of ninhydrin mediated transformations.

Color development occurred very soon after mixing the reactants. Surprisingly, when the isomerized amine 2b was subjected to the same reaction conditions, none of the corresponding aldehyde was produced! This observation remains unexplained. Only one other transamination process for the purpose of generating the aldehyde was attempted. The amine 2 was subjected to rappoport's conditions[32] using 4-formyl-1-methylpyridinium p-toluenesulfonate (prepared analogously to the benzenesulfonate), but against expectations, a very low yield of aldehyde was obtained even though longer reaction times were used. Also, attempts were made to accelerate Schiff base formation by heating in the presence of molecular sieves or anhydrous sodium sulfate. It is possible that impurities, either in the starting amine, or the solvent and catalyst inhibited the reaction. It seems unlikely that the change to a toluenesulfonic acid salt can explain the observed inhibition. Further investigation of Rapoport's method may be rewarding in the view of the high yields of transamination products from other types of substrates that were reported.

One interesting reaction of the aldehyde concerns its decomposition by a free radical process. Upon heating in carbon tetrachloride in the presence of azobisisobutyronitrile (AIBN), the aldehyde gave the same aromatic compound already obtained from the reaction of 2,4,6-triphenylpyridinium salts with acetate, or thioxanthate. A plausible mechanism for this aromatization is shown in Scheme VIII.

In the presence of free radical initiators, abstraction of the hydrogen atoms in the allylic-benzylic position should be very facile due to the extensive delocalization pathways available to the resulting free electron. Moreover, the alpha face of the molecule is sterically unhindered, thus permitting easy approach of the attacking radical.

The 60 MHz spectrum of this decomposition product agrees well with the suggested aromatic structure. The ratio of aromatic protons (between 6.8 - 7.67 ppm), to those of the methoxy group (at 3.87 ppm), is about 5 to 3. The other protons form two groups adding up to more than three protons each between 1.7 and 2.1 ppm and 2.7 and 3.15 ppm. The latter group corresponds to the protons alpha to the aromatic ring, whereas the former, to those that are in the beta position. No other structure can be conceived that accounts so well for the NMR spectrum.[40]



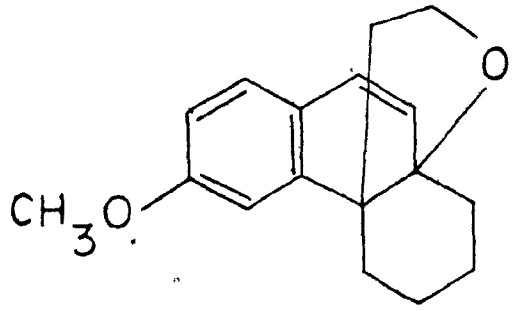

**Scheme VIII: Free radical aromatization.**

## 2.2 Conversion of 4a-(Acetaldehyde) - 1,2,3,4,4a,9-hexahydrophenanthrene (3) to 3-Hydroxy-17-deaza-thiaisomorphinan (8).

The aldehyde 3 was reduced to the corresponding alcohol 4, with sodium borohydride in 1/1 ethanol-chloroform in 70% yield (after purification).[41] The reaction was followed by TLC and conversion to the more polar alcohol was complete in about 30 minutes. As expected, the alcohol showed a broad, intense, infrared band centered at 3380 $cm^{-1}$ and no absorption in the carbonyl region. The position of the hydroxyl stretching mode indicates the presence of intermolecular hydrogen bonding.[42] The correctness of the structure is supported by the mass spectrum which showed the parent ion at m/z 258. Important peaks also appeared at m/z 256 and 257, as expected for an alcohol losing H and $H_2$ upon electron impact, a well precedented behavior of alcohols in a mass spectrometer.[37] The 60 MHz NMR spectrum was also consistent with the loss of the aldehyde proton and the shifting of those alpha to the carbonyl group which appeared buried in the alkyl region of the spectrum. The two protons alpha to the hydroxyl gave a peak between 3.1 and 3.5 ppm where the benzylic protons resonate. The 200 MHz spectrum was no more revealing than the 60 MHz spectrum. All of the other spectral features of the reduced compound remained unaltered relative to those of the aldehyde precursor.

An interesting side product was formed in trace amounts. This product was less polar than the alcohol, and contained no hydroxyl group as judged from the IR spectrum. It had a double bond belonging to a styrene system attached to a carbon bearing no hydrogen atom, and a molecular

weight of 256 as determined by mass spectometry. Consistent with these data is the structure shown below which corresponds to oxadehydrohasubanan(7).




3-Methoxy-17-deaza-17-oxadehydrohasubanan (7)

In agreement with this structure, the two protons alpha to the oxygen appear distinctly as a multiplet between 3.53 and 4.25 ppm in the NMR spectrum along with the methoxy protons at 3.83 ppm. This region of absorption integrates for five protons relative to the three aromatic protons. A free-radical mechanism of cyclization may account for the formation of this product. Radical oxygen species are known and radicals derived from boron intermediates are possible; in fact, they may be involved in the reductive demercuration of alkylmercury compounds.[43,44]

Attack by oxygen to form a tetrahydrofuran ring would appear favorable on the basis of known stereoelectronic principles.[45] Abstraction of an allylic-benzylic proton would again be expected to be facile for reasons already mentioned. These features would account for the generation of the oxadehydro-hasubanan by-product.[43]

When the alcohol was hydroborated, and treated with borane-dimethyl-sulfide and basic hydrogen peroxide, a single diol was produced,[46] in 40% yield. This compound was more polar than the starting alcohol and its infrared spectrum was similar to that of the starting material. The mass spectrum was also very similar. However, the NMR spectra of these compounds are different. The spectrum of the diol is very complicated between 2.6 and 4.2 ppm where the protons alpha to the hydroxyl group would be expected to absorb together with the benzylic protons and the methoxy group. This broad band integrates for eight protons relative to the aromatic region. The 200 MHz spectrum was much more useful in establishing the structure. The proton decoupled spectra in the region of greatest interest are shown in Figure IX. Since there is a proton alpha to the newly introduced ring hydroxyl group at 3.95 ppm, it can be concluded that the regiochemistry of the hydroboration is anti-Markownikov as expected.[47] The hydroxyl can only be at position 10 as the proton alpha to it is coupled to two protons appearing as doublets of doublets at 2.68 and 3.33 ppm; coupling of this proton to the benzylic protons is characterized by constants of 7.9 and 6.6 Hz. They are reduced to two doublets resulting from coupling of the two protons to each other with a constant of 17Hz after decoupling of the proton

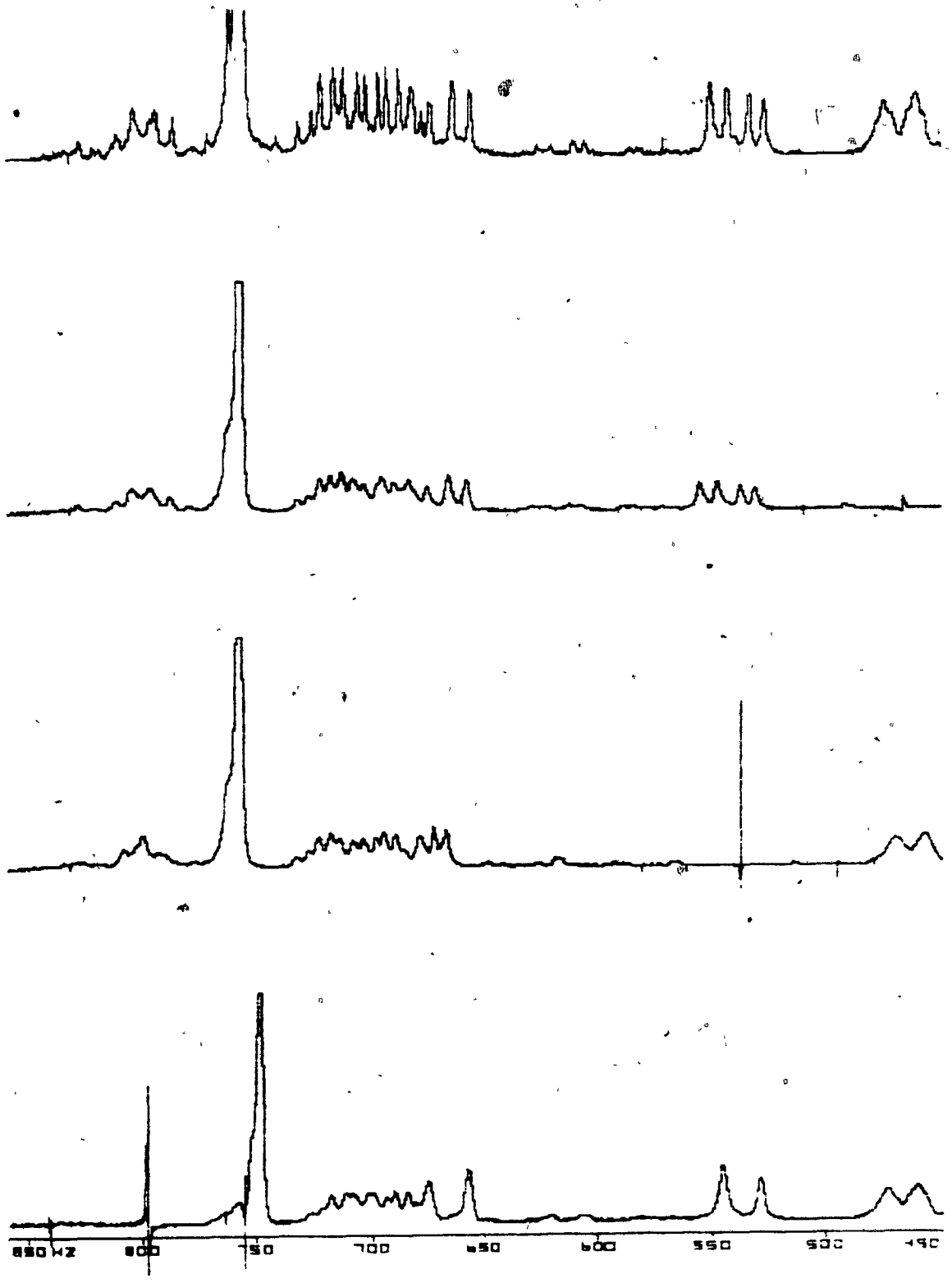



Figure IX: 200 MHz decoupled spectrum of 450-800 Hz region of Diol 5.

at position 10. The stereochemistry at position 10 cannot be established from the NMR spectrum alone; however, given the known marked sensitivity of hydroboration to steric effects and the fact that only one product was detected chromatographically, the alpha configuration for the new hydroxyl group is inferred. Indeed, approach of boron from the beta face of the molecule should be strongly disfavoured by steric hindrance from the side chain at position 4a.[48]

Reaction of the diol with methanesulfonylchloride in pyridine gave the more polar mesylate 6 in 78% yield (crude product). The absence of absorptions for the hydroxyl groups in the infrared spectrum and absorbance at 1170 and 1340 $cm^{-1}$ confirm structure 6 for the product. The 60 MHz NMR spectrum showed the general features characteristic of the starting diol except that the methyls of the sulfonate groups appeared as singlets at 2.83 and 3.00 ppm and the protons alpha to these groups were shifted significantly downfield. The protons attached to the side chain sulfonate group appear between 3.8 and4.4 ppm while the ring proton alpha to the sulfonate group appears between 4.63 and 5.17 ppm. The reason for this shift lies in the electron withdrawing properties of the sulfonate group.

The sulfonate was reacted with sodium sulfide nonahydrate in ethanol to give a good yield (56%) of the cyclic sulfide 7, a relatively less polar compound as judged from its behavior in the TLC systems used (hexanes-ethyl acetate). This method for cyclic sulfide formation bears analogy to the synthesis of sulfur analogues in the steroid series.[49] Identification of the compound was based mainly on 200 MHz NMR spectroscopy.

In the mass spectrum, the expected parent ion at m/z 274, was observed.

Pertinent features of the 200 MHz NMR spectrum of the cyclic sulfide include a doublet of doublets centered at 4.56 ppm with coupling constants of 16.5 Hz and 3.5 Hz and a doublet at 3.23 ppm with a coupling constant of 16.5 Hz, (Figure XI). Each of these bands, integrating for one proton, probably originates from a benzylic proton; the larger coupling constant would arise from the geminal coupling of these two protons. The fact that one of the two protons appears as a doublet of doublets and the other only as a doublet can be explained by considering the angles between the C9-H and the C10-H bonds. A Dreiding model of the thiaisomorphinan (or thiamorphinan)revealed that the dihedral angle between C9-H bond and the C10-Hα bond is about 30° while that between CA9-H and C10-Hβ is approximately 90° (Figure X). Consideration of the Karplus relationship allows the conclusion that the coupling between C9 and the C10β proton should be minimal while that with the C10α proton should be significant; approximately, the coupling constant should be about 0 Hz for dihedral angle of about 90° and about 4 Hz for an angle of 30° as observed.[50] The proton appearing at 2.78 ppm is probably that at C9. Decoupling of this proton eliminates coupling to the proton centered at 4.56 leaving a doublet whereas only a sharpening of the peaks of the other C10 proton is observed (Figure XI A, B). As expected, decoupling of each of the benzylic protons affects the other one (Figure XII A, B) while only decoupling of the downfield benzylic proton affects the C9 proton significantly (Figure XII B) causing sharpening to a broad singlet in contrast to the broad doublet in the absence of

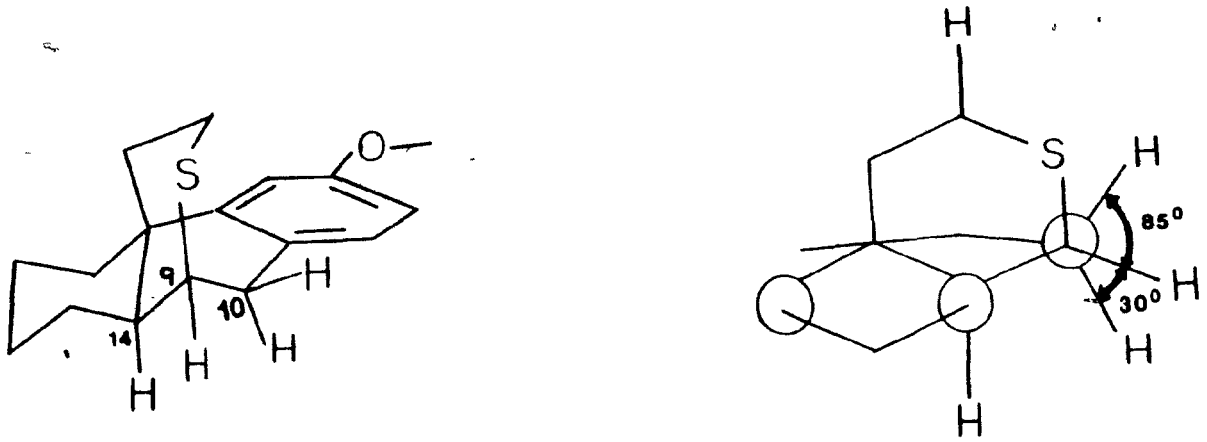



Figure X: The structure of thiaisomorphinan and a projection indicating selected dihedral angles.

decoupling (Figure XI B). The C9 proton would be expected to be coupled to that at C14 and might also be coupled to one of the two protons at C16 (to the sulfur atom) as the dihedral angle between the C9 - C14 bond and one of the C16-H bonds is 0°, a value which is optimal for the coupling of four bonds.[36] This coupling behavior accounts for the broadness of the C9 proton resonance as well as the fact that decoupling of this proton affects peaks in the upfield region of the spectrum where alkyl protons would be expected to absorb; a sharpening of resonances is observed between 1.76 and 1.96 ppm - a region that integrates for two protons (Figure XII C). The rest of the NMR spectrum is similar to that of the precursors of this molecule as regards the aromatic protons, the methoxy group and the other alkyl groups, all absorbing in the expected regions.

The $^{13}C$ spectrum of the compound was uniquely characteristic of structure 7 (Figure X, see Table I). However, one resonance is missing in the aromatic region and although it is possible that the relevant carbon resonance may be of very low intensity, it is more likely to coincide with another resonance.[52] With the ATP method (Attached Proton Test) it is possible to distinguish between carbons bearing odd or even numbers of protons.* The missing carbon carries no proton. By analogy with the spectrum of 3-methoxy-morphinan [53] the peak at 158 ppm can be safely assigned to carbon 3, that is the aromatic carbon bearing the oxygen. Similarly, we can identify the aromatic carbon resonances including the carbon carrying the methoxy function which absorbs at 55.24 ppm. On the basis of the ATP experiment one can conclude that there are only two other carbons carrying

* These experiments were performed by Mr. F. Lepine.

Figure XI: Decoupling experiments on 3-methoxy-thiaisomorphinan

A. Undecoupled spectrum

B. Decoupling of putative C9 H and effect on benzylic Hs and upfield Hs.

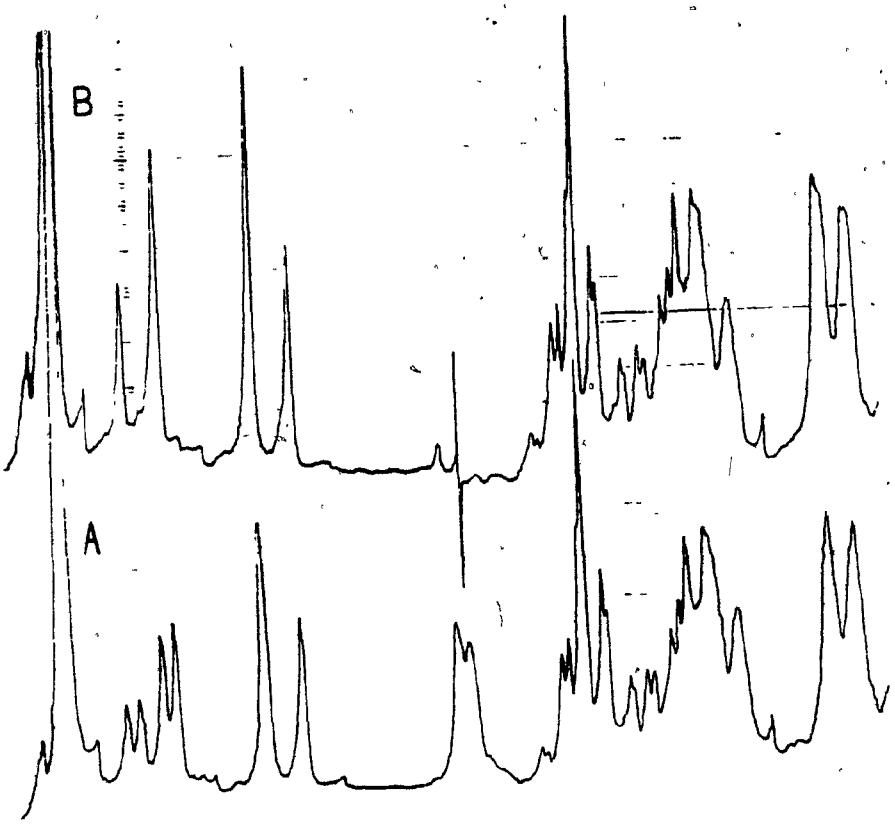


Figure XII. Decoupling experiments on 3-methoxy-thiaisomorphinan

A. Decoupling of benzylic H.

B. Decoupling of benzylic H.

C. Decoupling of upfield group of protons.

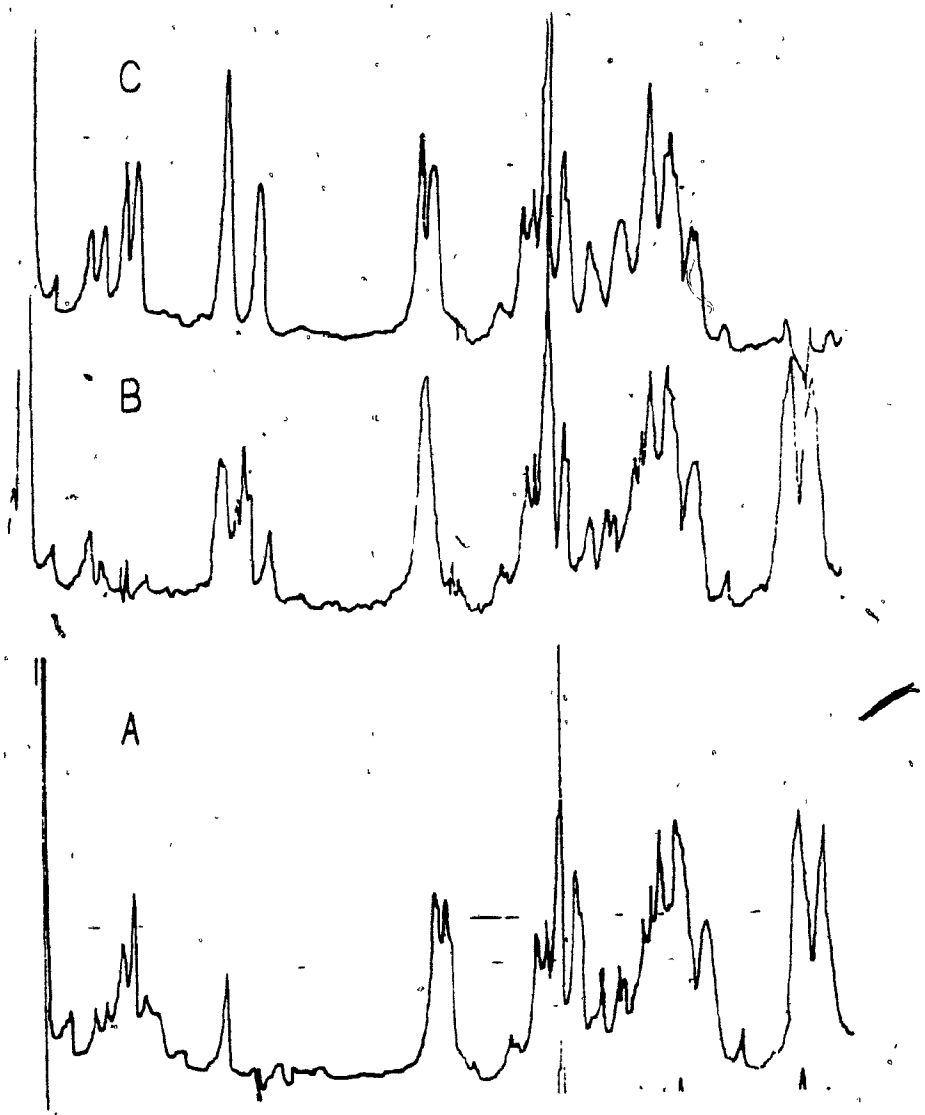


TABLE I

Thiaisomorphinan C-13 Spectrum

| Chemical Shift | Assignment |
|---|---|
| 158.17 ppm (-35) | aromatic |
| 145.71 (5.06) | aromatic |
| 129.20 (-0.1) | aromatic |
| 111.24 (0.04) | aromatic |
| 110.32 (-0.64) | aromatic |
| 55.24 (0.00) | $CH_3O-\phi$ |
| 41.27 (-4.95) | CH |
| 40.89 (-3.52) | $CH_2$ |
| 39.76 (1.35) | CH |
| 38.14 (0.08) | $CH_2$ |
| 35.82 (-1.38) | C |
| 31.61 (-4.04) | $CH_2$ |
| 27.62 (-1.99) | $CH_2$ |
| 26.00 (-0.93) | $CH_2$ |
| 23.14 (0.48) | $CH_2$ |
| 22.28 (0.03) | $CH_2$ |
| (Shifts relative to thiamorphinan) | |

an odd number of protons: those at 41.27 and at 39.76 ppm. It can be deduced that one of these belongs to C14 and the other to C9 (alpha to sulfur). In going from a nitrogen to a saturated sulfur heterocycle, an upfield shift is expected for the carbons alpha to the heteratom. Ignoring the change in overall ring size, and its configuration, the change in chemical shift for the C9 carbon should amount to about 10 ppm as judged from the chemical shift of 51.3 ppm of the analogous carbon at C9 in 3-methoxy-morphinan. This is a reasonable estimate because the range of upfield chemical shift changes for carbons alpha to nitrogen and sulfur atoms are in the range of 10 and 20 ppm.[54] The balance of the carbon atoms originate from methylene carbons which cannot be specifically identified without additional work.

The melting point of this material was identical with that of synthetic material prepared by a completely different route. The latter was converted to a crystalline derivative whose structure was determined by X-ray analysis. The results corroborated fully our structural assignment. In conclusion an alternative practical synthesis of 3-methoxy-17-deaza-17-thiamorphinan 7 was accomplished.

O-demethylation of the thiaisomorphinan 7 could be achieved with boron tribomide in dichloromethane in 60% yield. The product 8 was recrystallized from dichloromethane to produce crystals with a melting point of 182.5 - 184°C, a value identical to that of material prepared by the alternate route. However, upon mixing, the melting point showed depression and and a broadening of the melting range to 169 - 178°C. Since these different

batches of crystals were produced from different solvents, it is likely that polymorphism may explain the melting point depressions. The 200 MHz NMR spectrum of the product was similar to that of the 3-methoxy-thiamorphinan starting material. Differences include the absence of the methoxy peak at 3.77 ppm and the appearance of a broad peak integrating for one proton and appearing at 4.76 ppm. This band probably originates from the phenolic hydroxyl group. The aromatic region was also somewhat changed in that an increase in peak multiplicity was observed. Finally, the infrared spectrum showed the expected hydroxyl stretching mode as a broad, strong band at 3300 $cm^{-1}$.

In summary, 3-hydroxy-17-deaza-17-thiaisomorphinan was successfully synthesized in an overall yield of 4%, starting from 4a-amine-ethyl-1,2,3,4,4a,9 - hexahydrophenanthrene.

## 2.3 The Synthesis of 3-Methoxy-$\Delta^{9,10}$-17-deaza-17-thiahasubanan; Unsuccessful Approaches to the Thiamorphinan Skeleton.

Conceptually, another approach to the synthesis of cyclic sulfides would involve the free radical cyclization of a thiyl radical to an appropriate olefin,[55] a process which finds precedent in the field of steroid analogues.[56] To this end the oxygen of the intermediate alcohol 4 had to be transformed into a thiol function which should serve as a source of thiyl radicals. Accordingly, alcohol 4 was treated with p-toluenesulfonyl chloride in pyridine, and the corresponding tosylate 9 isolated. The reaction was followed by TLC. The NMR spectrum of the crude product showed that most of the basic characteristics of the starting alcohol were retained except, of course, for additional resonances contributed by the tosyl group. The expected proton ratios were observed.

The tosylate 9 was then treated in boiling THF under nitrogen with potassium ethyl thioxanthate for 22 hours to give the corresponding ethyl thioxanthate 10. This reaction was also followed by TLC and the product behaved as a less polar (see Scheme III) entity than the tosylate. It was purified by flash chromatography and obtained pure in an overall yield of 50% (based on the starting alcohol 4). The xanthate methylene protons appeared as a quartet at 4.57 ppm with a coupling constant of 7 Hz in the NMR spectrum. The methyl group gave a triplet centered at 1.35 ppm as expected. Several new peaks appeared between 2.4 and 3.1 ppm and the peaks for the protons alpha-to the side chain oxygen were shifted to give new proton peaks originating from the hydrogens alpha to the sulfur atom.

The rest of the spectrum was essentially similar to that of the starting alcohol.

In the mass spectrum the parent ion at m/z 316 was not observed, however, a peak appeared at 212 corresponding to partially aromatized material resulting from the loss of the side chain. Thioxanthates can be readily converted to thiols, [57] which in turn are an excellent source of thiyl radicals,[58] when submitted to a variety of conditions. Treatment of the xanthate with lithium aluminumhydride in THF at reflux for half an hour gave a new product as ascertained by TLC. The crude oily product (presumably the thiol 11) was used as such without further purification. A 60 MHz NMR spectrum of the product showed that the xanthate ethyl group had disappeared. The peaks for the protons alpha to the sulfur atom were shifted upfield relative to the thioxanthate, but the rest of the spectrum remained essentially unchanged in agreement with the expected structure. It was dissolved in de-aerated carbon tetrachloride ($CCl_4$) and azobisisobutyronitrile (AIBN) added under nitrogen. Irradiation of the product with a sunlamp while heating at reflux for six hours (adding some AIBN every two hours) caused the disappearance of the thiol function. The NMR spectrum of the resulting crude mixture after removal of the solvent indicated the presence of several compounds. For instance, more than one kind of methoxy protons were present, but the olefinic protons of the starting materials were absent, and instead two-doublets centered at 5.7 (J = 9Hz) and 6.3 ppm (J = 9Hz) were observed. The pattern for the aromatic protons was also altered. Two chromatographic purifications of the crude mixture allowed the isolation of

two pure products: 3-methoxy-$\Delta^{9,10}$-17-deaza-17-thiahasubanan, 12, and 3-methoxy-17-deaza-17-thiaisomorphinan, 7 (Scheme II). The latter was identified by its TLC behavior and by 200 MHz NMR spectroscopy using the previously prepared material as a basis for comparison. The former structure was assigned on the basis of 60 MHz NMR spectroscopy (Figure XIII).

The four resonance peaks (two doublets) in the olefinic region are clearly reminiscent of those previously observed for the oxygen analogue (7). One significant difference with the latter, however, is the apparent absence of absorption in the methoxy region. This may not be too surprising because of the difference in electronegativity between sulfur and oxygen. In fact, oxygen is more electronegative than sulfur so that the protons attached to carbons attached to oxygen should be shifted downfield. A multiplet integrating for 3 protons appeared between 2.6 and 3.1 ppm in the sulfur compound. It is reasonable to assign these resonances to the protons alpha to the sulfur atom. The coupling constant of 9 Hz for the olefinic protons is also consistent with their cis-stereochemistry. Moreover, their chemical shifts of 5.7 and 6.3 ppm indicate that they are part of a styrene system. From a consideration of relative intensity of the olefinic and aromatic (or methoxy) peaks in the crude product mixture it can be deduced that the thia-dehydrohasubanan was produced in 30% yield. Only a trace of thiaisomorphinan was produced. These results are rationalized in Scheme IX.

The generated thiyl radical I can react in several ways. They are known to add reversibly to double bonds so that radicals III and V would be in equilibrium.[59] The benzylic and allylic protons at C-10 would be

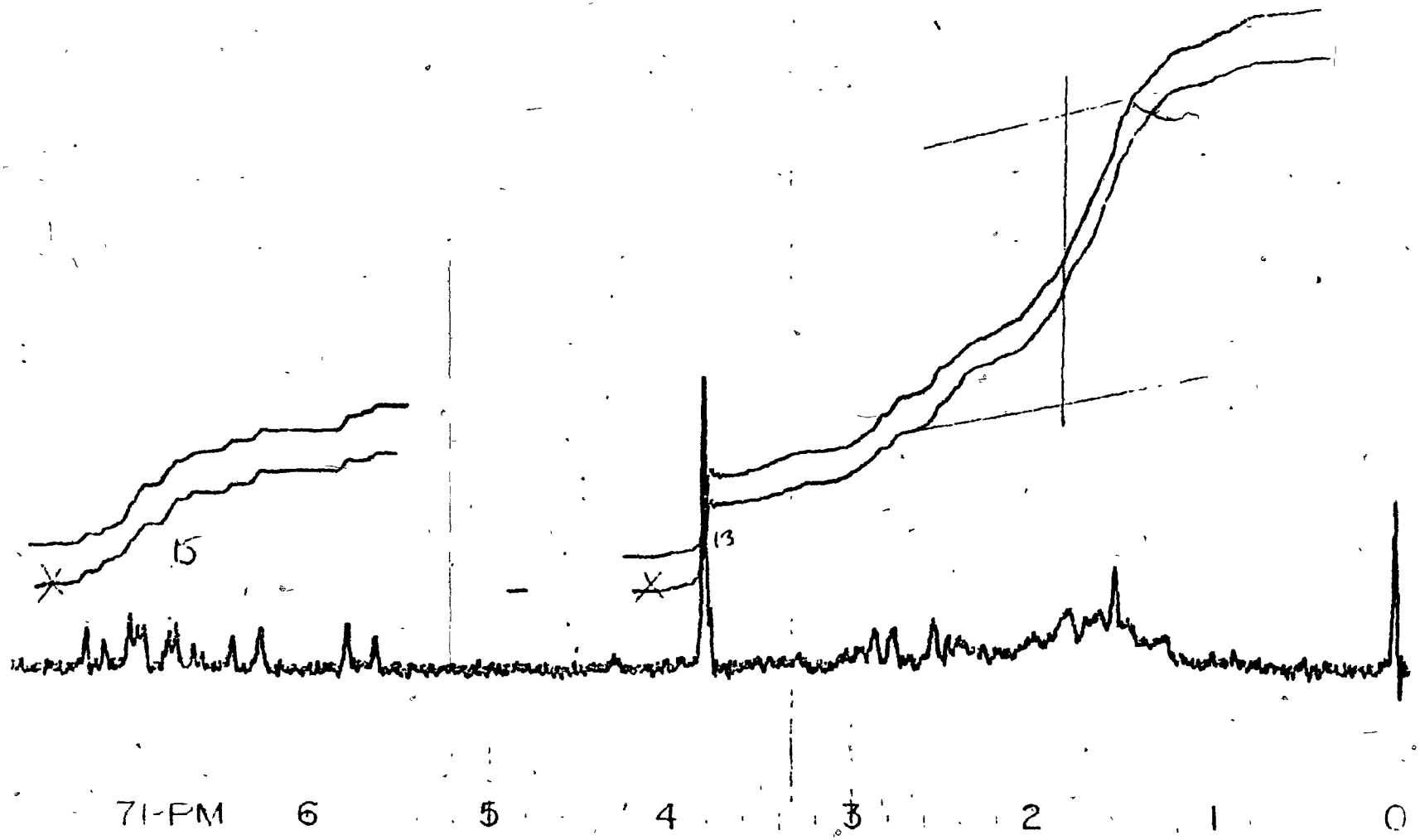



Figure XIII: 60 MHz NMR spectrum of thiadehydrohasubanan 12.

expected to be highly susceptible to hydrogen abstration giving rise to the highly stabilized allylic radical IV.* Either IV or V could lead, after loss of a hydrogen atom, directly to the observed major product. Intermediate IV is favored because of its stability.[60] In principle, radical III could lead to either a morphinan or an isomorpinan skeleton. That thiaisomorphinan is formed exclusively suggests that steric hindrance about the beta face of this radical favors attack of hydrogen abstrators from the opposite side (Figure XIV).

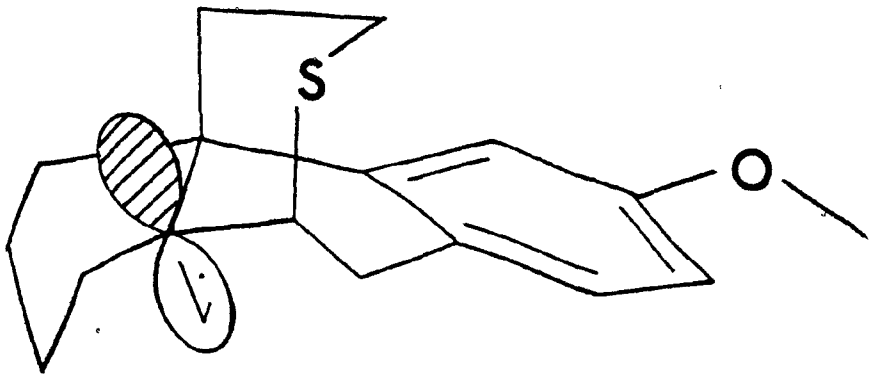
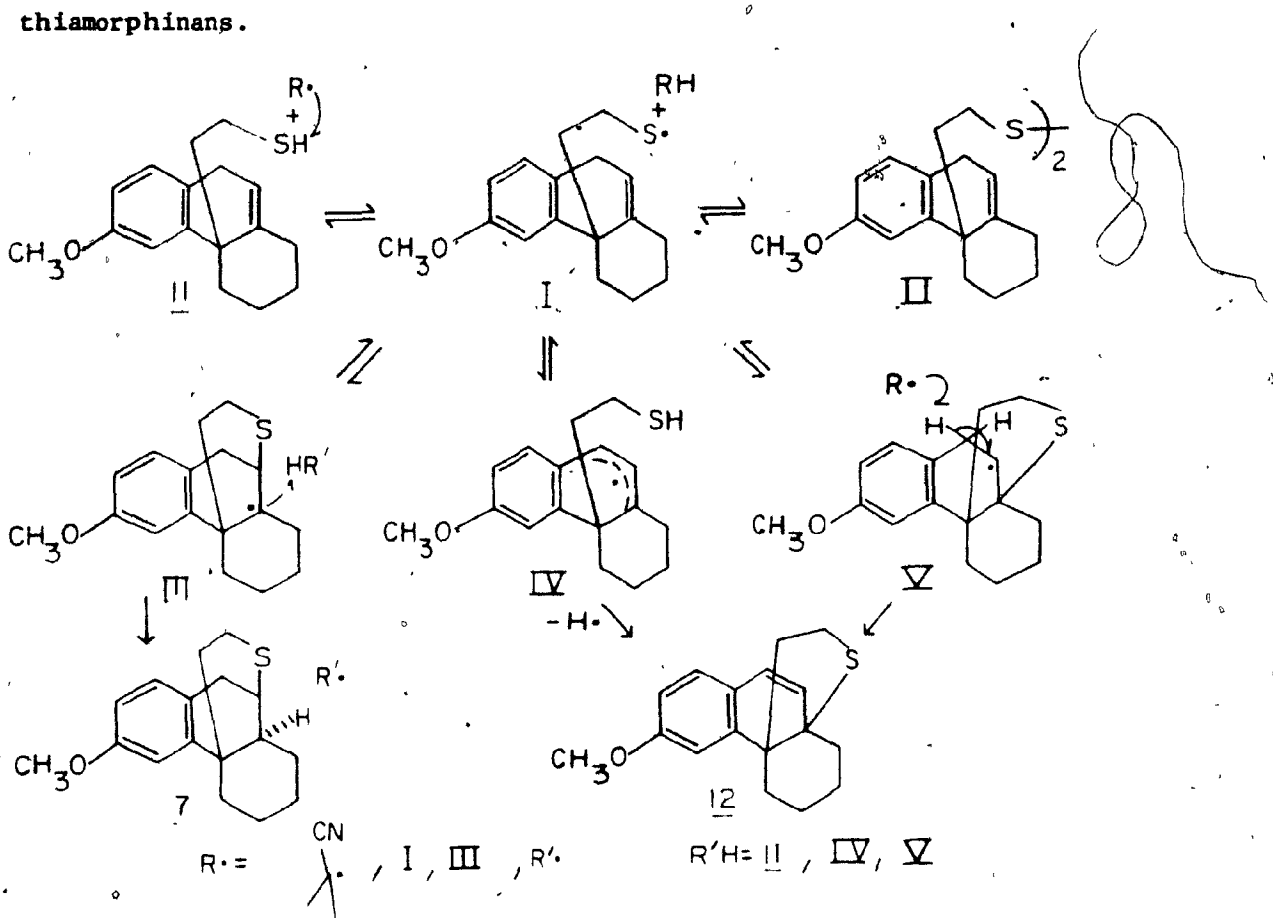



Figure XIV: The Structure of the free-radical Intermediate.

Given the above result it was obvious that the isomeric olefinic thiiyl radical already possessing a preformed morphinan-like stereochemistry (cis) would be required in order to generate the desired thiamorphinan analogue. This problem will now be discussed in relation to the accessibility

of 4a,10a-cis-1,2,3,4,10a-hexahydrophenanthrenes, their elaboration into sulfur containing intermediates and their transformation into thiamorphinans.




**Scheme IX:** The formation of thiadehydrohasubanan and thiaisomorphinan via a free-radical pathway.

## 2.4 Approaches to the Synthesis of Thia-morphinans

4a-Aminoethyl-1,2,3,4,4a,9,10-hexahydrophenanthrenes have been isomerized previously to 4a; 10a-cis-4a-aminoethyl-1,2,3,4,5a,10a-hexahydrophenanthrenes.[61] When the aminoethyl analogue 2 was treated with an excess of potassium tert-butoxide in dimethylsulfoxide for 96 hours the isomerized amine 2b was obtained in 90% yield (Figure XV, X=$NH_2$).


A B

**Figure XV:** The Structure of two possible cisoid 4a-substituted hexa-hydrophenanthrene and conformations.

The identity of 2b was established by 60 MHz NMR spectroscopy. Notable features of the NMR spectrum include the absence of the allylic-benzylic protons of 2, which regularly appear between 3.2 and 3.4 ppm. Also, the olefinic proton at 5.6 ppm was absent. The olefinic region

of 2b displayed two sets of resonances: a doublet at 6.3 ppm (J = 10Hz) and a doublet of doublets at 5.8 ppm (J = 10 Hz, 6 Hz); a pattern which is characteristic of the styrene system as in 2b. The aromatic protons formed a multiplet between 6.5 and 7.1 ppm, whereas the methoxy group appeared at 3.8 ppm as a singlet. The alkyl protons gave a broad band below 2.6 ppm. The expected structure is thus well supported.

Examination of the olefinic resonances confirmed the cis-fusion for rings B and C. Tha Ha-Hb coupling constant amounts to 10 Hz in agreement with their cisoid arrangement. In fact, Ha is not coupled to any other protons and gives a single resonance at 6.3 ppm. It is also more downfield than Hb because of the anisotropic effect of the aromatic moiety. The coupling constant for Hb and Hc is 6 Hz which is consistent only with a cis fusion of the two rings. Examination of Dreiding models, in fact, revealed that with a cis ring fusion, the dihedral angle between Hb and Hc is about 10°. On that basis, the Karplus equation predicts a coupling constant of 4Hz, as was observed.[62] Should the ring juncture be trans, the dihedral angle between Hb and Hc would be about 100° and the Karplus equation would predict a coupling constant near zero.[63] Accordingly, the desired cis-fusion was the exclusive consequence of the isomerization reaction. With a simpler trans-fused hexahydrophenanthrene model, the relevant coupling constant ranged from 0 to 1 Hz, thus corroborating the above conclusion.[64]

Subjecting 2b to the conditions used previously to transform 2 into the corresponding aldehyde (using ninhydrin) gave none of the desired product.

It is possible that the reactive double bond of the para-methoxysterene system participates somehow in the reaction with ninhydrin. In view of this negative result we turned our attention to the isomerization of the alcohol corresponding to the amine. This isomerization of the alcohol also occured and the corresponding pure alcohol 13 was obtained in 42% yield. It exhibited all the NMR spectral characteristics expected for the cis-fused structure 13. In addition to the olefinic peaks at 6.25 ppm ($J_{ab}$ = 9 Hz) and 5.75 ppm ($J_{ab}$ = 9 Hz, $J_{bc}$ = 6 Hz) the methylene group alpha to the hydroxyl group appeared as a multiplet between 3.17 and 3.67 ppm. Its IR spectrum showed a broad, strong O-H stretching mode between 3100 and 3600 $cm^{-1}$. The mass spectrum of the compound exhibited the parent ion at m/z 258 (15%). A peak of equal intensity appears at 256 and can be accounted for by loss of hydrogen. Peaks of high intensity appeared at 214 (28%), 213 (34%), 212 (44%), and can be accounted for by loss from the parent ion of the 4a side chain as well as loss of the latter plus one or two hydrogen atoms. These data agree with the expected structure. The fragmentation pattern of the unisomerized alcohol was different, however, with the 258 peak being strong (73%). The peak at 213 is the base peak, and one peak at 212 is major (75%). These differences in the respective fragmentation patterns for the two alcohols is not surprising. Loss of the side chain in the case of the unisomerized alcohol would be expected to be easy because of its allylic positioning. This is inconsistent with the relatively small amount of parent ion in that case. Again, the fragmentation data are consistent with structure 13 for the isomerized alcohol.

Two possible conformations of this system are shown in Figure XV.[61] Ring C could be either in a chair (A) or a boat form (B). The chair should be the favored form because, although there are 1,3 diaxially disposed groups, the carbons involved are $sp^2$ hybridized so that the interaction should be smaller than the usual 1,3 diaxial interaction between $sp^3$ hybridized carbons and hydrogens. Also in the cis conformer (A), a Hc-Hb gauche interaction is present. The boat conformer(B)is subject to more unfavorable non-bonded interactions. It is concluded, in contrast to the conclusions of Conway, et al, that conformer (A) would predominate.[61]

The trans isomer incorporates two obvious 1,3 diaxial interactions and one gauche interaction between the C10a - C1 bond and Hb, (Figure XVII). Thus, even though there is one more 1,3 diaxial interaction in the cis isomer (Figure XVI) these are of a different nature than would be found in the trans isomer where the relevant interactions would have a greater destabilizing effect. The same argument applies to the gauche interaction as well as the interaction of a C-C bond which is expected to be more destabilizing than its interaction with a C-H bond. In conclusion, the B/C-cis geometry may be more stable thermodynamically, but it is not known at this stage whether we are dealing with equilibrating conditions.

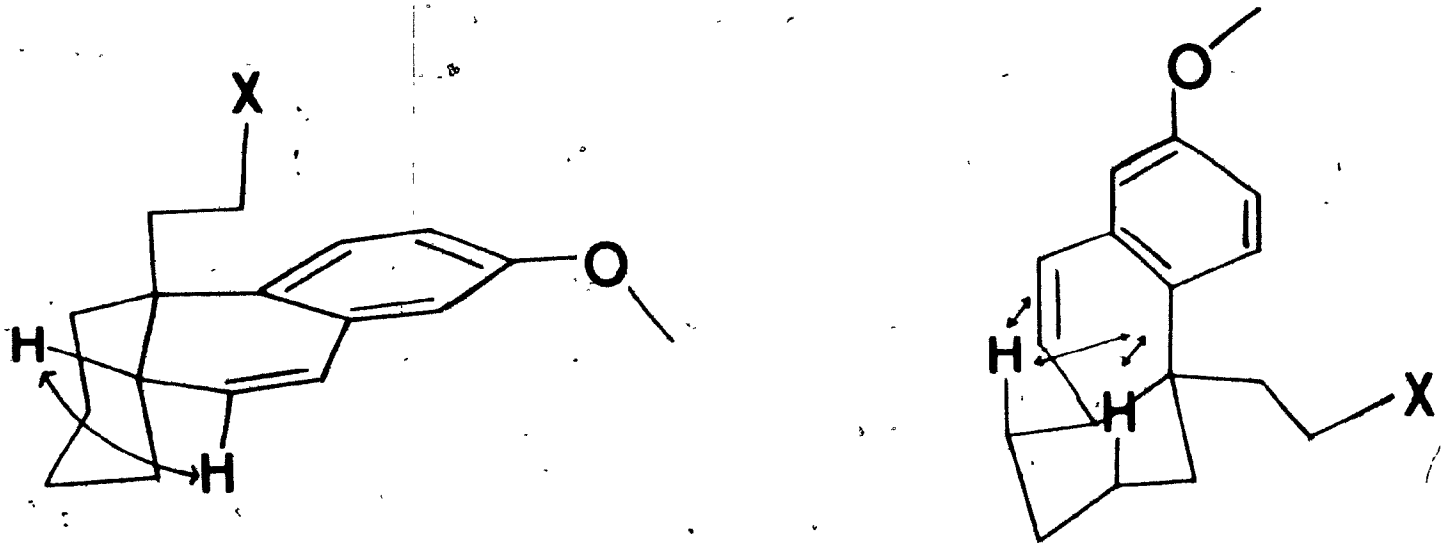



Figure XVI: Steric interactions in cis-hexahydrophenanthrene.

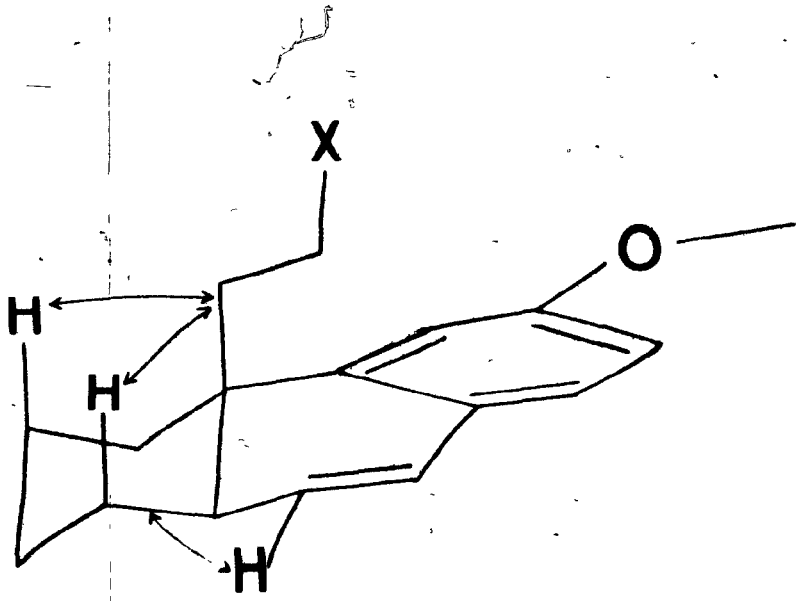


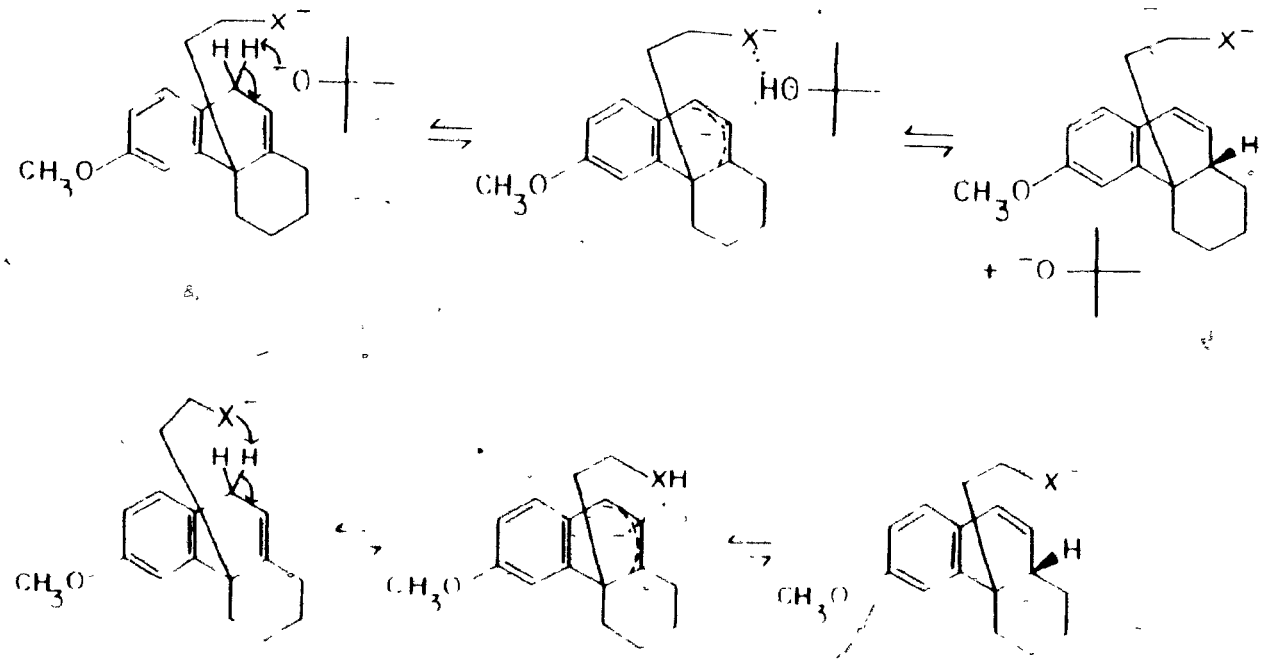

Figure XVII: Steric interactions in trans-hexahydrophenanthrene.

The 1,3-allylic proton transfer might proceed with a significant degree of intramolecularity.[64] A suprafacial proton transfer would give the cis isomer directly; moreover, the heteroatom on the 4a side chain might serve as an intramolecular proton carrier once it has been deprotonated by the t-butoxide anion. The latter possibility, involving a truly intramolecular proton transfer, would give the cis isomer directly. The reverse process would re-introduce the proton on the 10a position.

The cis-alcohol product was tosylated as was its isomeric precursor and the product 14 used as such without further purification. The IR spectrum of the tosylate showed no O-H absorption and its NMR spectrum appeared as a superposition of the separate spectra of the alcohol and the tosyl group.

Attempts were next made to displace the tosyl group with potassium ethyl thioxanthate, as was done with the unisomerized tosylate, but the resulting products could not be purified. Potassium thioacetate in boiling THF displaced the tosyl group within 6 hours to give a product which could be purified by flash chromatography. The major product, the acetylthia derivative 15, was thus obtained in 33% yield (based on alcohol 13).

The mass spectrum of this compound showed the parent ion at m/z 316 (30% abundance). A significant peak appeared at m/z 273 (70%), which can be accounted for by loss of the acetyl group. The base peak appeared at 213 as was the case for all the other analogues of this series. The large parent peak, and the peak at 273 strongly support the assigned structure.



Scheme X: The mechanism of the base-catalysed olefin isomerization.

The most distinguishing feature of the infrared spectrum of this compound was the carbonyl stretching mode at 1690 $cm^{-1}$ which is characteristic of thioesters.

The downfield region of the NMR of this thioester was uneventful; that region was similar to that of the alcohol starting material 13. The most important difference lay in the absence of the peaks assigned to the protons alpha to the hydroxyl group between 3.15 and 3.68 ppm as well as in the appearance of a multiplet between 2.3 and 3.25 ppm - integrating for two protons and attribuable to the protons alpha to the sulfur atom. A singlet belonging to the acetyl methyl group appeared at 2.25 ppm and integrated correctly. The 200 MHz spectrum of the compound is included in the appendix, but its features are essentially the same as those of the 60 MHz spectrum, except that the protons alpha to sulfur and the allylic proton appear separated from the other protons. The two appear as a broad triplet of doublets integrating for one proton between 2.8 and 3 ppm and a multiplet integrating for one proton between 2.3 and 2.6 ppm. It is clear, on that basis, that the desired structure was obtained.

Deprotection of the thiol function was achieved by treatment of the acetate with sodium methoxide in deaerated methanol-THF.[65] Although the acetate methyl group was absent in the resulting product (60 MHz NMR) the thiol resonance was not discernible. The aromatic region was modified somewhat but the olefinic and the methoxy peaks were unchanged. The deprotection reaction could be followed by TLC, though the results were diffucult to reproduce. Loss of the acetyl group required from 1 to 3 hours, but the Rf

of the product appeared similar to that of the starting material. After 3 hours in the presence of an excess of methoxide, a less polar material appeared which had an identical 60 MHz NMR spectrum to that of the higher Rf product. Several elution procedures were required in order to observe a difference in mobility between the more polar of the two products and the starting material. In either case, the product was used as such in the next step without further purification.

When the presumed thiol 16 thus obtained, was left in vacuo in a pyrex flask exposed to ambient light a new product slowly appeared. After four days, the double bond had disappeared (by NMR) and a new set of peaks appeared between 3.2 and 3.5 ppm. Unfortunately, the Rf of the product was again similar to that of the starting material so that the reaction could not be easily followed by TLC. Other methods of cyclization were attempted: the putative thiol was heated with AIBN in boiling $CCl_4$ while being exposed to UV light; also, irradiation at 254 nm at room temperature as a dilute solution in hexanes was tried; finally, irradiation at 254 nm, but in iso-octane was attempted. All of the above conditions led to the consumption of the styrene double bond of the substrate. However, none or little of the desired product could be detected by chromatographic analysis. Before adopting Nicolaou's method, a variety of procedures were tried for the liberation of the thiol function. The following attempts were made: lithium-aluminiumhydride in THF, ammonia in methanol and THF and aqueous sodium hydroxide in methanol and THF. None of these methods, nor others were as satisfactory as that of Nicolaou which involved treatment with sodium methoxide in methanol and THF.

Purification of product 17 by flash chromatography was eventually achieved and the 200MHz NMR spectrum, the mass and IR spectra of the product were obtained. Its formation could be accelerated by irradiating with a UV lamp and readily inhibited by shielding the compound from light. After irradiation and purification, the desired product was obtained in 16% yield.

The mass spectrum showed the parent ion at 274 (54% abundance). A significant M + 2 peak was also present (10%) as would be expected for a sulfur containing compound in view of the relatively abundant $^{34}S$ isotope (4.2%). In addition to the above peak, the expected base peak at m/z 213 was observed which, as before, is accounted for by the loss of the C15-S(17) chain.

The IR spectrum of the compound is similar, but not identical to the spectrum of 3-methoxy-thiaisomorphinan.

The 200 MHz NMR spectrum was also very similar to that of 3-methoxy-thiaisomorphinan; however, the differences are clear. In the case of the 3-methoxy-thiamorphinan 17 the aromatic protons gave rise to 8 peaks; whereas in the corresponding 3-methoxy-thiaisomorphinan 8 there were 5 distinct peaks. The methoxy group of the two isomers appeared to have similar chemical shifts: 3.76 and 3.78 in 7 and 17 respectively. The major spectral differences were found upfield from the methoxy group. The benzylic protons in 17 gave rise to a doublet of doublets, and a doublet as noted before (Table II). It would not be expected that the pattern should differ much since the dihedral angle between $H_9$, $H_{10\beta}$ and $H_{10\alpha}$ are nearly the same as in the isomorphinan system; in fact, $H_{10\beta}$ would be expected to couple to $H_9$,

and the same is true for $H_{10\alpha}$. The difference between the isomorphinan and the morphinan in this region lies in the chemical shift of these latter protons. In the isomorphinan, $H_{10\beta}$ and $H_{10\alpha}$ are centered at 3.24 and 3.56 ppm respectively; whereas in the morphinan they appear at 3.14 and 3.46 ppm respectively (0.1 ppm upfield); $H_9$ in the isomorphinan system appears at 2.78 ppm (0.08 ppm downfield of $H_9$ in the morphinan). Decoupling experiments in the case of the morphinan structure gave essentially identical results to the isomorphinan. That is decoupling $H_9$ simplified $H_{10\alpha}$ to a doublet. Decoupling $H_{10\alpha}$ simplified $H_9$ to a broad singlet and also affected $H_{10\beta}$. Decoupling $H_{10\beta}$ affected $H_{10\alpha}$ only. Below 2.8 ppm - the alkyl region - one sees the most significant differences between the two compounds. Although this region appears as two groups of multiplets in both compounds, the exact shape of these multiplets differs considerably. It would be expected that this region, where the protons suffer the greatest change in environment upon isomerization would also be the ones giving rise to the largest changes in the NMR spectrum. In summary, the 200 MH spectrum of 17 supports the structural assignment.

The $^{13}C$ NMR spectrum of 17 revealed 17 carbon resonances (Table III). This is in contrast to the aromatic resonances of the isomorphinan which were short of a band. The aromatic region is very similar to that of 3-methoxymorphinan.[52] The methoxy group can also be readily identified. The absence of a peak at 51.3 ppm for the methine carbon alpha to the nitrogen is noticeable. As was discussed before changing a nitrogen to a sulfur atom produces an upfield shift in the resonance frequency of the relevant carbon

TABLE II

Summary of Revelant 200 $MH_3$ Spectral

| | Methoxy-thiaisomorphinan | Methoxy-thiamorphinan |
|---|---|---|
| $H_9$ | 2.78 dJ = 8Hz. | 2.7 J = 8Hz. |
| $H_{10\beta}$ | 3.24 (3.2 / 3.28) J = 16Hz | 3.14 (3.09 / 3.18) J = 18Hz. |
| $H_{10\alpha}$ | 3.56 (3.52 d J = 8Hz / 3.60 d J = 8Hz) J = 16Hz. | 3.46 (3.42 J = 8Hz / 3.51 J = 8Hz) J = 18Hz. |
| $CH_3$ | 3.76 | 3.78 |

The same should be true of the methylene carbon 16.[53] None of the aliphatic carbons could be identified unambiguously at this point; however, the $^{13}C$ spectrum remains in full agreement with the proposed structure.

The formation of the thiamorphinan skeleton occurs most likely via a photochemically generated thiyl radical. The requirement for light in the reaction supports this contention. Cyclization reactions involving olefins and thiyl radicals has precedent, as was mentioned before.[55,58] The source of hydrogen atoms necessary for end product formation probably involves another molecule of thiol. The intermolecular reaction of a thiyl radical with an olefin is also known.[66] One would expect addition of a thiyl radical to a styrene double bond to occur on the beta carbon on the basis of stereoelectronic principles already documented.[45,67] A high concentration of hydrogen atoms as in hydrocarbon solvents might make attack of the double bond rate-limiting. Even if this step was not rate-limiting, the fact that the cyclization product is obtained may be the result of the greater thermodynamic stability of radicals at benzylic positions.[68] Thiyl radicals can also be generated photochemically from disulfides. Formation of the latter most probably competes with cyclization. One the major products, as detected by TLC, corresponds with the product of a reaction between the thiol and diazo-N,N-diethyl dicarboxylate. These are conditions for the formation of disulfides from thiols.[69] If, indeed, disulfides are formed, the ensuing unavailability of hydrogen atoms would favor alternative pathways. Another possible side reaction is de-sulfurization of the thiiyl radical, i.e. cleavage of the carbon-sulfur bond, leading to

TABLE III

Thiamorphinan C-13 Spectrum

| Chemical Shift | Assignment |
|---|---|
| 158.52 | aromatic (158.0) |
| 140.65 | aromatic (141.7) |
| 129.56 | aromatic (130.1) |
| 129.30 | aromatic (128.3) |
| 111.22 | aromatic (111.0) |
| 110.96 | aromatic (110.6) |
| 55.24 | CH O-$\phi$ ( 55.2) |
| 46.22 | CH ( 46.2) |
| 44.41 | $CH_2$ ( 42.9) |
| 38.41 | C ( 38.4) |
| 38.06 | CH ( 51.3) |
| 37.20 | $CH_2$ ( 37.1) |
| 35.65 | $CH_2$ ( 33.8) |
| 29.61 | $CH_2$ ( 39.2) |
| 26.93 | $CH_2$ ( 26.8) |
| 22.66 | $CH_2$ ( 26.8) |
| 22.31 | $CH_2$ ( 22.2) |

(spectrum of aza-morphinan)

carbon-centered radicals which could cyclize or dimerize.[70]

Demethylation of the phenyl ether group was achieved selectively, as before, with boron tribromide in dichloromethane. The 200 MHz NMR spectrum of the resulting product included a broad resonance at 4.6 ppm, and which integrated for one proton. This is characteristic of the phenolic hydroxyl.

The IR spectrum of the thiamorphinan thus produced in 40% yield, exhibited a hydroxyl O-H stretching mode at 3260 $cm^{-1}$

The parent ion in the mass spectrum of the product appeared at m/z 260 (65% abundance) together with the base peak at m/z 199, resulting from loss of the side chain functions. A peak at m/z 200 also appeared as it did in the spectra of most other compounds of this series.

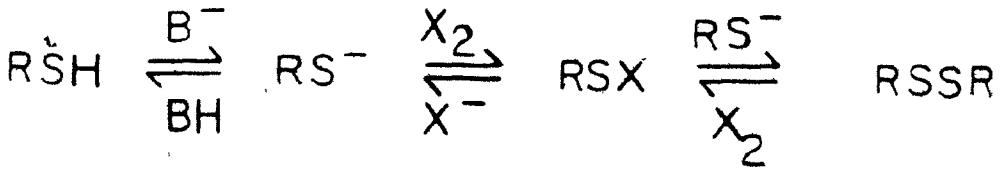
In conclusion 3-methoxy-17-deaza-17-thiamorphinan was successfully synthesized in an overall yield of 0.4% starting from 4a-aminoethyl-1,2,3,4, 4a,9-hexahydrophenanthrene. Having established the validity of this approach, it remains to improve the economics through revelant development work.

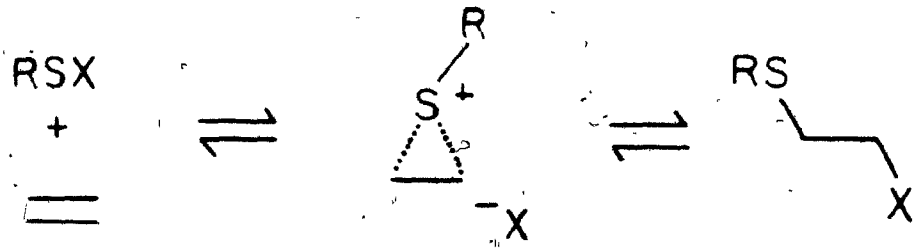
# CHAPTER 3

## Explorations, Suggestions for Further Work, and Conclusions

### 3.1 Exploratory Work and Results

In the previous chapter one sulfur atom was incorporated into a six-membered ring from either an intermediate radical or an intermediate anion. However, the sulfur atom can also function as an electrophilic group. Sulfenyl halides which are available from attack of the thiolate anion by electrophilic species such as the halogens readily react with olefins to give addition products as shown below.[71,72]




**Scheme XI:** Formation of sulfenyl halides (X = Cl, Br, I) and their reactions with olefins.

The predicted mode of attack of the halide ion involves that carbon atom which best stabilizes the developing carbocation. Since benzylic carbenium ions are well stabilized, the halide should enter at the benzylic position and be readily removable by reductive methods. This approach was explored using the thiol 11 under the conditions of Nicolaou with the target molecule shown below.[73]

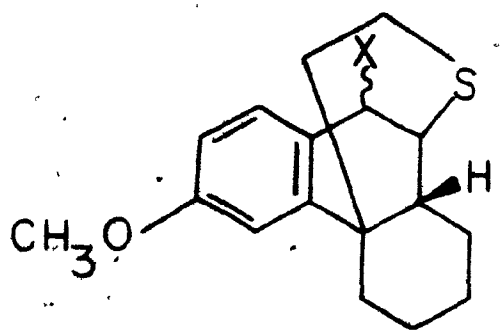



Figure XVII: Target molecule of sulfenyl halide cyclization (X = Cl, Br, I).

The thiol was dissolved in dichloromethane at -78°C and an excess of potassium carbonate was added. The mixture was treated with either an euivalent of iodine, bromine, or iodobenzene dichloride. This gave rise to mixtures of products in which the styrene double bond had disappeared by NMR. Analysis by TLC indicated that several products were produced in each case. The products resulting from chlorination or bromination were similar as ascertained by TLC and NMR. However, the product from the iodination

appeared different and one component could be purified by extensive chromatography. It showed a parent ion at m/z of 274 (33%) with the base peak appearing at 213 and a major peak at 213 (35%), also. A single proton appeared as an doublet at just under 4ppm in the 200 MHz NMR spectrum. A plausible structure is shown in Figure XIX where proton a may account for the observed doublet.[74] The sulfenyl halide approach was abandoned because of the complexity of the product mixtures and the undesirable nature of the one purified.

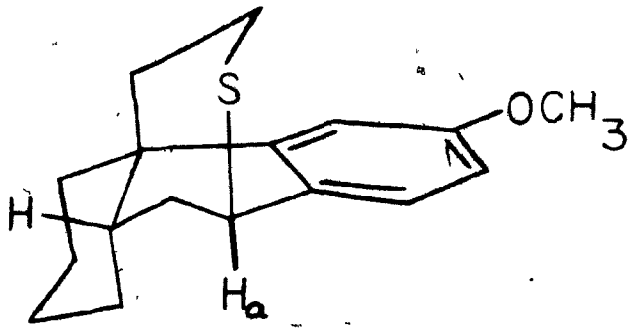


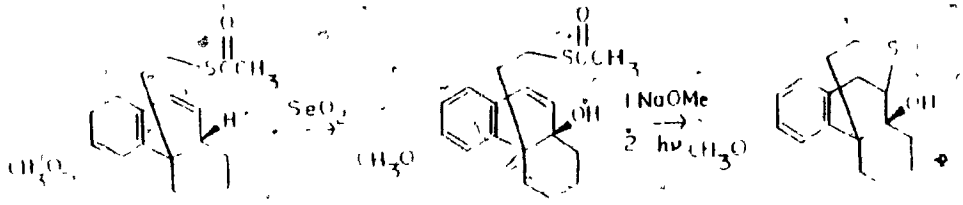

Figure XIX: Proposed structure of sulfenyl iodide cyclization product.

## 3.2 Suggestions for Further Work

Several other derivatives of potential interest may be synthesized from the intermediates produced. For example, the dimesylate may serve to generate oxa and phospha analogues of isomorphinans. From the isomerized tosylate, morphinan analogues containing heteroatoms other than nitrogen or sulfur may be obtainable in two steps by way of nucleophilic substitution of the tosylate followed by cyclization with the double bond. Free-radical conditions could be used in the formation of the phosphine analogue.

The aldehyde 3 opens up the possibility of generating carbon substituted analogues since the alpha carbon of the aldehyde can engage in a variety of reactions. Alternative syntheses of the aldehyde itself might be worthwhile developing.

Heteroatom analogues carrying a hydroxyl group at position 14 are interesting targets in view of the beneficial effect of that functionality in the morphinan series. Their synthesis may be approached using the "styrene-type" intermediates as shown below.




Scheme XII: The generation of 14-OH thiamorphinan derivatives.

Refinement of the key cyclization step is desirable and indeed is

necessary if certain derivatives are needed. A study of the effect of the irradiating wavelength would be worthwhile, as would the identification of the better radical initiators. Use of the disulfide, obtainable from the thiol, in cyclization reactions in the presence of hydrogen atoms may generate the desired product.

Clearly, the versability of the intermediates generated in this work should be exploited further.

## 3.3 Conclusions

The main goals of this study have been attained: 3-hydroxy-17-deaza-17-thiamorphinan and its isomorphinan analogue were synthesized in overall yields of 0.4% and 4% respectively from the amine 2. Their pharmacological properties will be of considerable interest. The synthetic methods were chosen so as to generate the desired stereochemistries unambiguously. Spectral evidence was presented in support of the structures. The stage is set for the development and generation of alkylated, oxygenated and phosphorylated analogues. 3-Methoxy-17-deaza-17-thiadehydrohasubanan was also synthesized.

# CHAPTER 4

# EXPERIMENTAL

## 4.1 General Experimental

Reagent grade solvents were used throughout unless otherwise specified. Dry tetrahydrofuran was obtained by refluxing in the presence of sodium and benzophenone. Other solvents were obtained dry either by standing over molecular sieves (dichloromethane, dimethylsulfoxide)[74], or commercially, (diethylether from Malinckrodt Canada Ltd., Toronto, and ethanol from Consolidated Alcohols Ltd., Toronto). Drying of organic solutions during workup was accomplished with sodium sulfate or magnesium sulfate.

p-Toluenesulfonylchloride was purified according to Fieser's method.[74] Potassium ethylthioxanthate was prepared by B. Gour.[75]

Solvent evaporation was carried out under reduced pressure (water aspirator).

A General Electric sunlamp, number 34, 275 watt, was used for ultraviolet irradiations.

Analytical thin layer chromatography was carried out on aluminium-backed sheets, precoated with Kieselgel $60F_{254}$, 0.2 mm thick, (Merck Co. Ltd., Darmstadt). Compounds were purified by flash chromatography,[76] on 32 - 63 (400 - 230 mesh) silica gel (British Drug Houses, Toronto). The crude mixtures were evaporated onto silica gel before being applied to the column.

Melting points were recorded in open capillary tubes on a Buchi SMP-20 and are uncorrected. Proton magnetic resonance were recorded on a Varian F-60, T-60A, or XL 200 spectrometer using TMS as a standard in deuteriochloroform. Chemical shifts are reported in parts per million on the $\delta$ scale. Infrared spectra were obtained on Beckman 29F, Acculab 8, or Pye-

Unicam SP-1000 spectrometers. Mass Spectra were provided by either Dr. J. Finkenbine of the Department of Chemistry, McGill University, or Professor O. Mamer at the Biomedical Mass Spectrometry Unit, McGill University.

4.2 Procedures

Synthesis of Aldehyde 3

The amine hydrochloride 1 (2.5 g, 8.6 mmol) was dissolved in $CH_2Cl_2$ (500 mL), and was extracted with 1N aqueous NaOH (3 x 220 mL) and water (200 mL). The organic phase was dried, filtered, and concentrated to give the amine 2 as a yellow oil. The amine 2 was dissolved in 1/1 ethanol-water (100 mL), and a solution of ninhydrin (6.0 g, 34mmol) in 1/1 ethanol-water (100 mL) was added with stirring under nitrogen. The clear yellow solution turned blue upon mixing the reagents. The flask was wrapped in aluminium foil to inhibit photochemical reactions. After 30 minutes $NaHCO_3$ (7.5 g) was added and stirring under nitrogen was continued for 24 hours. The resulting blue solution was filtered through celite, poured into water saturated with NaCl (200 mL) and extracted several times with ethyl acetate. The combined ethyl acetate extracts were washed with water saturated with NaCl, then dried, filtered, and concentrated to give a blue oil. Flash chromatography (9/1 hexanes-ethyl acetate) gave the aldehyde 3 as a colorless oil (1.09 g, 8.5 mmol) in 50% overall yield from 1.

3 mp = 72 – 73°C.

PMR ($CDCl_3$) δ 1.2 – 2.4 (br m, 9H, alkyl) 2.5 (dd J = 14, 2.5 Hz, 1H, $CH_2C$-(O)H) 3:17 (dd, J = 14, 3Hz, 1H, $CH_2C(O)H$) 3.3 (br m, 2H, allylic) 3.77 (s, 3H, $CH_3O$) 5.7 (br m, 1H, olefinic) 6.57 -7.1 (m, 3H, aromatic) 9.2 (dd, J = 3.5, 3.5 Hz, 1H, aldehydic). IR ($CHCl_3$) ν max 2718, 2815 (sh w, C(O) – H vibrations) 1712 (mw s, RC(O)4 stretch) 1610, 1574, 1500, 1460, 1444, (sh mw, w – s, aromatic C = C in plane skeletal vibrations) $cm^{-1}$. MS, m/e (90) $(M - CH_3C(O)H)^+$ 212 (100). No parent ion was observed.

Aldehyde Irradiation - Aromatization 3b

The aldehyde 3 (0.2009, 0.8 mmol) was dissolved in $CCl_4$, and azobisisobutyronitrile (0.019 g, 0.12 mmol) was added. The solution was heated at reflux overnight. The solvent was evaporated to give 60% of 3b (by NMR of the crude mixture). Flash chromatography (25/1 hexanes-ethyl acetate) gave pure naphtalene derivative 3b as an oil.

PMR ($CDCl_3$) δ 1.72 - 2.1 (m, 4H, aliphatic) 2.7 -3.15 (m, 4H, benzylic) 3.87 (s, 3H, $CH_3O\phi$) 6.7 - 7.15 (m, 3H, aromatic) 7.28 -7.67 (m, 2H, aromatic).

Unisomerized Alcohol 4

The aldehyde 3 (0.5091 g, 2.12 mmol) was dissolved in $CHCl_3$ (20 mL), and cooled to 0°C. Sodium borohydride (0.08 g, 2 mmol) was added to the solution, under nitrogen, as a slurry in anhydrous ethanol (20 mL). After 30 minutes the solution was poured into water (50 mL). Some IN aqueous HCl was added to the solution to render it clear, and the solution was extracted with $CHCl_3$ (3 x 50 mL). The combined organic extracts were washed with water, dried, filtered, and concentrated to give the alcohol 4, which was purified by flash chromatography (4/1 hexanes-ethyl acetate). The alcohol 4 (0.353 g, 1.4 mmol) was obtained in 70% yield as a clear colorless oil which was recrystallized from hexanes.

4 mp = 71 - 73°C.

PMR ($CDCl_3$) δ 1 - 2.3 (br m, 10H, alkyl) 2.3 - 2.83 (m, 1H, $CH_2OH$): 3.0 - 3.5 (br m, 3H, $CH_2OH$, allylic H) 3.77 (s, 3H, $CH_3O\phi$) 5.63 (br t, 1H, olefin) 6.52-7.05 (m, 3H, aromatic).

IR (neat) $\nu$ max 3385 (br s, OH stretch, intermolecular H-bond) 1607 (sh s) 1571 (br m) 1495 (sh s) 1458 (sh w) 1440 (br m - s, aromatic in plane C = C vibrations) $cm^{-1}$.

MS, m/z (%): $M^+$ 258 (7.3), $(M - H)^+$ 257 (32), $(M - H_2)^+$ 256 (72.5), $(M - CH_2CH_2OH)^+$ 213 (100), $(M - CH_3CH_2OH)^+$ 212 (75), $(CH_2COH)^+$ 43 (95), $(CH_3CH_2OH)^+$ 43 (43.1).

Oxidation of Unisomerized Alcohol: Diol 5

The alcohol 4 (0.224 g, 0.95 mmol) was dissolved in $CH_2Cl_2$ (10 mL) under nitrogen and 10 M borane-dimethylsulfide (1 mL) was added. After 24 hours $CH_2Cl_2$ (20 mL) and 10% aqueous sulfuric acid (7.5 mL) were added. After one hour, 15% aqueous sodium hydroxide (20 mL) was added, followed by 30 % aqueous hydrogen peroxide (20 mL) and the mixture was left for an additional 24 hours. The mixture was then extracted with ethyl ether which was washed with 15% aqueous sodium tartrate (3 X) and water. The organic phase was dried, filtered, and concentrated to yield the crude diol 5 (0.262 g), in 100% yield. Flash chromatography (2/1 ethyl acetate-hexanes) gave pure diol 5 in 40% yield (0.111 g, 0.40 mmol), as a white crystalline material.

PMR ($CDCl_3$) $\delta$ 1.1 - 4.3 (br m, 18H, alkyl) 3.78 (s, 3H, $CH_3O$) 6.57 - 7.13 (d, 3H, aromatic).

IR (neat) $\nu$ max 3300 (br s, OH stretch) 1600, 1570, 1490 (sh m - s, aromatic C - C vibration) 1400 ( br m, $CH_2$ scissoring, alkyl vibration).

MS, m/z (%) $(M - H_2O)^+$ 258 (1.7), $(M - H_2O - H_2)^+$ 256 (1.5), $(M - H_2O - CH_2CH_2OH)^+$ 213 (16.3), $(M - H_2O - CH_3CH_2OH)^+$ 212 (19.5). No parent ion was seen.

Mesylation of Diol: Dimesylate 6

The diol 5 (1.97 g, 7.1 mmol) was dissolved in dry pyridine (100 mL) and methane sulfonylchloride (3 mL) was added. After 24 hours at 0°C, the yellow solution was poured into water (400 mL) and extracted three times with $CH_2Cl_2$. The combined organic extracts were washed five times with 10% aqueous HCl, and once with water. The organic extracts were dried, filtered, and concentrated to give the dimesylate 6 (2.40 g, 5.55 mmol) as a yellow oil in 70% yield.

PMR ($CDCl_3$) δ 0.7 - 2.6 (br m, 13H, alkyl) 2.83 (s, 3H, $CH_3SO_2OR$) 3.72 (s, 3H, $CH_3O\phi$) 3.82 - 4.3 (br m, 2H, $CH_2OSO_2Me$) 4.63 - 5.18 (br m, 1H, $\underline{C}HOSO_2R$) 6.53 - 7.17 (br m, several peaks, 3H, aromatic).
IR ($CH_2Cl_2$) max 1330 - 1350 (br d s, assymetric $RSO_2OR$ stretch) 1170 (mw s, symmetric $RSO_2OR$ stretch ) $cm^{-1}$.

Cyclization of Dimesylate: Methoxy-thiamorphinan 7

The dimesylate 6 (2.4 g, 5.6 mmol) was dissolved in absolute ethanol (300 mL), and sodium sulfide nonahydrate (14.5 g, 60 mmol) was added under nitrogen. The heterogeneous solution was heated to reflux for twenty hours. After the solution was cooled, the ethanol was removed in vacuo, $CH_2Cl_2$ was added to the remaining yellow-white solid, and the heterogeneous mixture was ultrasonificated for 15 minutes. The $CH_2Cl_2$ was filtered through celite, leaving behind a yellowish powder ($S_8$). The filtrate was dried, filtered, and concentrated to give a yellowish oil, which, after flash chromatography (25/1 hexanes-ethyl acetate) gave the sulfide 7 (0.866 g, 3.1 mmol) as a

clear colorless oil in 56% yield. The sulfide 7 was recrystallized from hexanes.

7 mp = 73 - 74°C.

PMR ($CDCl_3$) δ 0.73 - 2.85 (m, 13H, alkyl) 3.03 ppm (br s, 1H, S-$CHR_2R_1$) 3.25 - 3.53 (br, 2H, benzylic) 3.7 (s, 3H, $CH_3O$) 6.45 - 7.05 (m, 3H, aromatic).

MS m/z (%) $M^+$ 274 (72), $(M - CH_2CH_2S)^+$ 214 (50), $(M - CH_3CH_2S)^+$ 213 (90), $(M - CH_2CH_2S - H)^+$ 212 (27), 84 (100).

Phenol: Hydroxythiaisomorphinan 8

The methyl ether 7 (0.446 g, 1.66 mmol) was dissolved in dry $CH_2Cl_2$ (10 mL) and 0.5 M boron tribromide in $CH_2Cl_2$ (20 mL) was added under argon at -60°C. The solution was left overnight. Water was added to the $CH_2Cl_2$ and after a few minutes two phases were diluted and separated after vigorous shaking. The organic phase was dried, filtered, and concentrated to give crude phenol 8 (0.440g, 1.7 mmol) in 100% yield. Flash chromatography ($CHCl_3$) gave pure phenol 8 as a white powder (0.26 g, 0.98 mmol) in 60% yield. The phenol was recrystallized from $CH_2Cl_2$ 8 mp 182.5 - 184°C.

PMR ($CDCl_3$) δ 0.73 - 2.88 (br m, 13H) 3.03 (br, 1H, S - $CHR_2R_2$) 3.25 - 3.53 (br, 2H, benzylic) 4.17 (br s, 1H, OH) 6.43 - 7.03 (m, 3H, aromatic).

IR (KBr disk) ν max 330 (br, alkyl, OH of phenol stretch) $cm^{-1}$.

MS, m/z $M^+$ 260 (40), $(M-CH_2CH_2S)^+$ 200 (37), $(M - CH_2CH_2S)^+$ 199 (71), $(M - CH_2CH_2S-H_2)^+$ 194 (24), 57 (100).

Deprotection of Ethyl thioxanthate and Cyclization:

Methoxy-thiadehydrohasubanan 12

The xanthate 10 (1.09 g, 3 mmol) was dissolved in THF (30 mL) under nitrogen and lithium aluminium hydride (0.1140 g, 33 mmol) was added. The solution was refluxed for 30 minutes, then cooled. The excess lithium aluminium hydride was destroyed by the addition of 1N aqueous HCl (2mL). The solution was filtered through celite under nitrogen onto sodium sulfate. The celite was washed with ether and the resulting filtrates were concentrated to give a yellow oil 11. Th oil was dissolved in $CCl_4$ (40 mL) and azobis-isobutyronitrile (0.025 g, 0.15 mmol) was added. The solution was refluxed with a UV lamp for six hours. Azobisisobutyronitrile was added at two hour intervals during reflux. The $CCl_4$ was removed in vacuo. Flash chromatography (9/1 hexanes-ethyl acetate) gave a mixture of methoxy-thiadehydrohasubanan 12 and methoxy-thiaisomorphinan 8. Flash chromatography of the mixture (25/1 hexanes-ethyl acetate) gave pure methoxy-thiadehydrohasubanan 12 and methoxy-thiaisomorphinan, 8. The yield of methoxy-thiadehydrohasubanan was 30% by NMR.

PMR ($CDCl_3$) $\delta$ 1.07 - 2.65 (br m, 10H, alkyl) 2.67 - 3.07 (m, 2H, $CH_2$-S) 3.82 (s, 3H, $CH_3O\phi$); 5.72 (d, J = 9 $H_z$, 1H, olefinic) 6.35 (d, J = 9 $H_z$, 1H, olefinic) 6.57 - 7.07 (m, 3H, aromatic).

Isomerized Alcohol 13

The alcohol, 4 (1,013 g, 3.93 mmol) was dissolved in dry DMSO (40 mL) under nitrogen, and potassium t-butoxide (1 g, 9.0 mmol) was added. After 48 hours more potassium t-butoxide (o.5 g, 4.5 mmol) was added to the solution. After 96 hours the solution was poured into water and extracted with $CH_2Cl_2$. The combined organic extracts were washed several times with water to give, upon drying, filtration, and concentration, the isomerized alcohol 13 (0.425 g, 1.65 mmol) as a yellow oil in 42% yield.

PMR ($CDCl_3$) δ 0.6 - 2.6 (br m, 12H, alkyl) 3.17 - 3.67 (m, 2H, $C\underline{H}_2OH$) 3.78 (s, 3H, $CH_3O\phi$) 5.75 (dd, J = 6 Hz, 9 Hz, 1H, olefin) 6.25 (d, J = 9 Hz, 1H, olefin), 6.48 - 7.07 (m, 3H, aromatic).

IR (neat) $\nu$ max 3380 (br s, OH stretch, intermolecular H-bond) 1602, 1563 (sh m, aromatic C - C in plane vibrations) 1487, 1470 1430, 1420 (br m, $CH_2$ scissoring) $cm^{-1}$.

MS, (%) $M^+$ 258 (30), $(M - H_2)^+$ 256 (30), $(M - CH_2CH_2OH)^+$ 213 (33), $(M - CH_3CH_2OH)^+$ 212 (40), 83 (100).

Tosylation of Isomerized Alcohol 13

The alcohol 13 (0.740 g, 3 mmol) was dissolved in dry pyridine (75 mL) and tosyl chloride (1.5 g, 8 mmol) was added to the solution at 0°C. After 12 hours the solution was poured into water and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ phase was washed several times with 1N aqueous HCl, dried, filtered, and concentrated to give the tosylate 14 as an oil which was used without further purification.

PMR ($CDCl_3$) δ 0.67 -2.37 (br, 11H, alkyl) 2.4 (s, 3H, $CH_3\phi SO_2$) 3.73 (s, 3H, $CH_3O\phi$) 3.53 - 4.33 (m, 2H, $\underline{CH_2}OSO_2\phi CH_3$) 5.67 (dd, J = 9 Hz, 6 Hz, olefin) 6.17 (d, J = 9 Hz, 1H, olefin) 6.47 - 7 (m, 3H, aromatic) 7.07 - 7.33 (d, 2H, tosyl, aromatic) 7.43 - 7.83 (m, 2H, tosyl, aromatic).
IR: 1170, 1355 ($SO_2$, symmetric, asymmetric stretch) $cm^{-1}$. No OH band.

**Synthesis of thiolacetate 15**

The tosylate 14 was dissolved in dry THF (50 mL), and potassium thiolacetate, (0.42 g, 3.7 mmol) was added. The mixture was refluxed under nitrogen for 6 hours. The resulting solution was filtered through celite and concentrated to give a reddish oil. Flash chromatography gave the thiolacetate 15 (0.3713 g, 1.3 mmol) as a colorless oil in 41% yield from the alcohol.

PMR ($CDCl_3$) δ 0.77 -2.77 (br,10 H, aliphatic) 2.25 (s, 3H, $\underline{CH_3}C(O)S\text{-}R$) 2.25 - 3.32 (m, 3H, $\underline{CH_2}S\ COCH_3$, CH = CH - $\underline{CH}$) 3.82 (s, 3H, $CH_3O\phi$) 5.78 (dd, J = 6 Hz, 9 Hz, 1H, olefinic) 6.3 (d, J = 9 Hz, 1H, olefinic) 6.57 - 7.05 (m, 3H, aromatic).
IR (neat) ν max: 1688 (br, s, R - $SC(O)CH_3$) $cm^{-1}$.
MS, m/z (%) $M^+$ 316 (30), $(M - COCH_3)^+$ 273 (70), $(M - CH_2CH_2\text{-}SC(O)CH_3)^+$ 213 (100).

Deprotection of Thiolacetate 16

Sodium (30 mg, 1.3 mmol) was added to degassed methanol (15 mL) under argon. After the sodium had dissolved, a solution of the thiolacetate 15 (180 mg, 0.6 mmol), in freshly distilled THF (10 mL) was added.

After two hours, the solution was poured into 1/1 saturated aqueous NaCl / 5% aqueous citric acid (40 mL), and extracted twice with ether. The ethereal phase was extracted twice with water saturated with NaCl, dried, filtered, and concentrated to yield the thiol 16 as a colorless oil.

PMR ($CDCl_3$) $\delta$ 0.77 - 2.8 (br, 14 H, alkyl) 3.8 (s, 3H $CH_3O\phi$) 5.78 (dd, J = 6Hz, 9 Hz, olefin) 6.3 (d, 1H, J = 9.5 Hz, olefin) 6.53 - 7.1 (m, 3H, aromatic).

Methoxy-thiamorphinan Synthesis 17 - Method A

The thiol 16 was left in vacuo and exposed to ambient light for five days. Flash chromatography (25/1 hexanes-ethyl acetate) yielded 17 as a colorless oil.

Methoxy-thiamorphinan Synthesis 17 - Method B

The thiol 16 was irradiated for 12 hours with ultra violet sunlamp under a high vacuum, to give 17 (56 mg, 0.2 mmol) as a colorless oil in 16% yield after flash chromatography (25/1 hexanes-ethyl acetate).

PMR ($CDCl_3$) $\delta$ 1.13 - 2.87 (br, 13H, alkyl) 2.97 (br, s, 1H, S - CH) 3.2 - 3.5 (br, 2H, benzylic) 3.8 (s, 3H, $CH_3O\phi$) 6.53 - 7.15 (br, 3H, aromatic).

MS, m/z (%) $M^+$ 274 (54), $(M-CH_2CHS)^+$ 213 (100).

Phenol from Methylphenol 18

The methoxy-thiamorphinan 17 (22mg, 0.08 mmol) was dissolved in $CH_2Cl_2$ (3 mL) under nitrogen and 0.5 M boron tribomide in $CH_2Cl_2$ (3 mL) was added at -60°C. The solution was allowed to warm to room temperature and left overnight. Water and $CH_2Cl_2$ were added to the solution and stirring was continued for 1 hour. The organic phase was dried, filtered, and concentrated to give a beige residue. Flash chromatography ($CHCl_3$) gave pure phenol 18 (8mg, 0.03 mmol) as a white powder in 40% yield.

IR (neat) $\nu$ max 3270 (vb s, H-O-$\phi$ stretch) $cm^{-1}$.

Amine Isomerization 2b

The amine 2a (2.85 g, 8.5 mmol) was dissolved in dry dimethyl sulfoxide (65 mL) under nitrogen with stirring. Potassium t-butoxide (2.85 g, 2.5 mmol) was added and after 3 days, more potassium t-butoxide (1g, 9 mmol) was added. After an additional 22 hours, the solution was poured into water (200 mL) and the aqueous layer washed with dichloromethane (4 x 250 mL). The combined organic extracts were dried, filtered, and concentrated to give a yellow oil. The oil was dissolved inether (200 mL) and washed with 10% aqueous HCl (3 x 150 mL). The aqueous extracts were made basic (pH 9) by the addition of solid sodium bicarbonate, and washed with dichloromethane (2 x 250 mL). The combined organic extracts were dried, filtered, and concentrated to give the isomerized amine 2b (1.93 g, 7.5 mmol) in 90% yield.

PMR ($CDCl_3$) $\delta$ 0.66 - 2.60 (m, 14H, alkyl) 3.8 (s, 3H, CH O) 5.8 (dd, J = 6 Hz, 9.5 Hz, 1H, olefinic) 6.25, 6.42 (d, J = 9.5 Hz, 1H, olefinic) 6.55 - 7.1 (m, 3H, aromatic).

Pyridinium Tetrafluoroborate 1b

The amine hydrochloride 1a (4.4 g, 17 mmol) was dissolved in absolute ethanol and 2,4,6-triphenylpyrilium tetrafluoroborate (6.73 g, 17 mmol) was added. The reaction was stirred overnight. The resulting solution was ultrasonificated for 12 hours to yield a light orange precipitate. The solid was filtered and washed with ether to yield 1b (7.6 g, 12 mmol) in 70% yield. The product could be recrystallized from absolute ethanol.

PMR ($CDCl_3$) 0.5 - 2.5 (br, 1oH, alkyl) 2.87 - 3.23 (br, 2H, benzylic) 3.67 (s, 3H, $CH_3O$) 3.67 - 4.6 (m, 2H, protons $\alpha$ to $N^+$) 5.27 (br t, 1H, olefinic proton) 6.3 - 7.1 (m, 3H, aromatic ring) 7.17 - 7.73 (br m, 17H, 2,4,6-triphenyl group and pyridinium ring protons).

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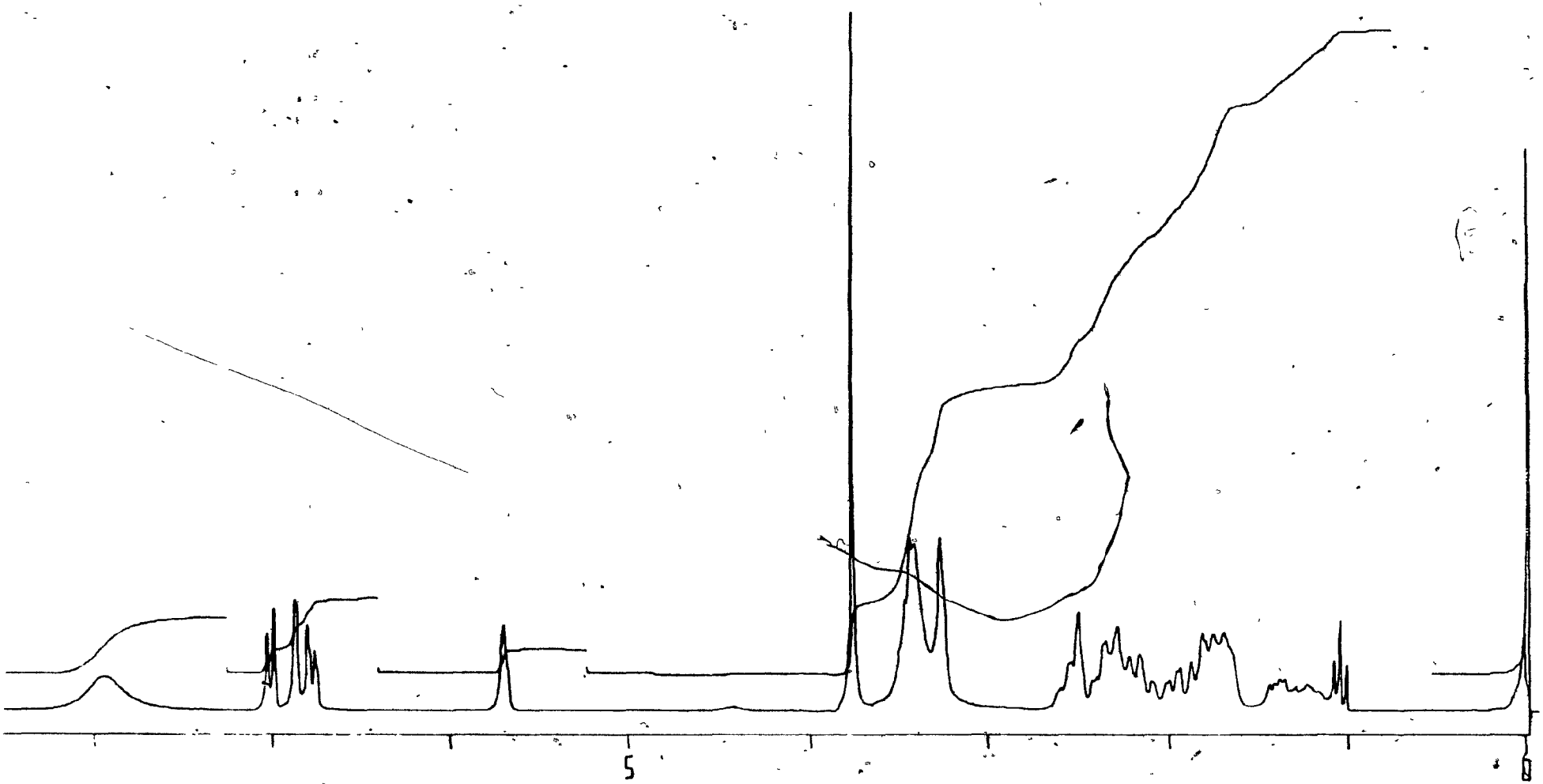
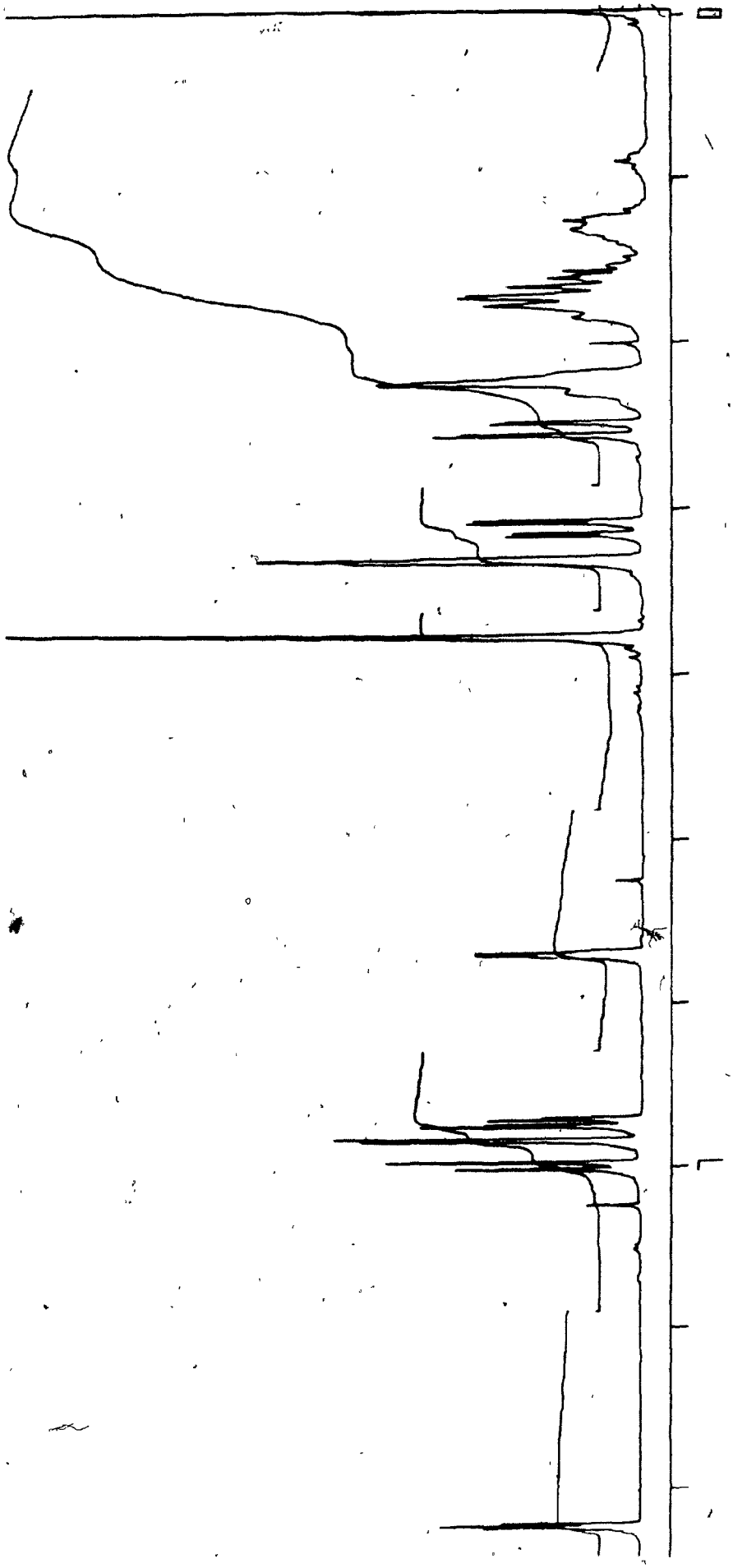
# APPENDIX

## SELECTED 200 MHz NMR SPECTRA

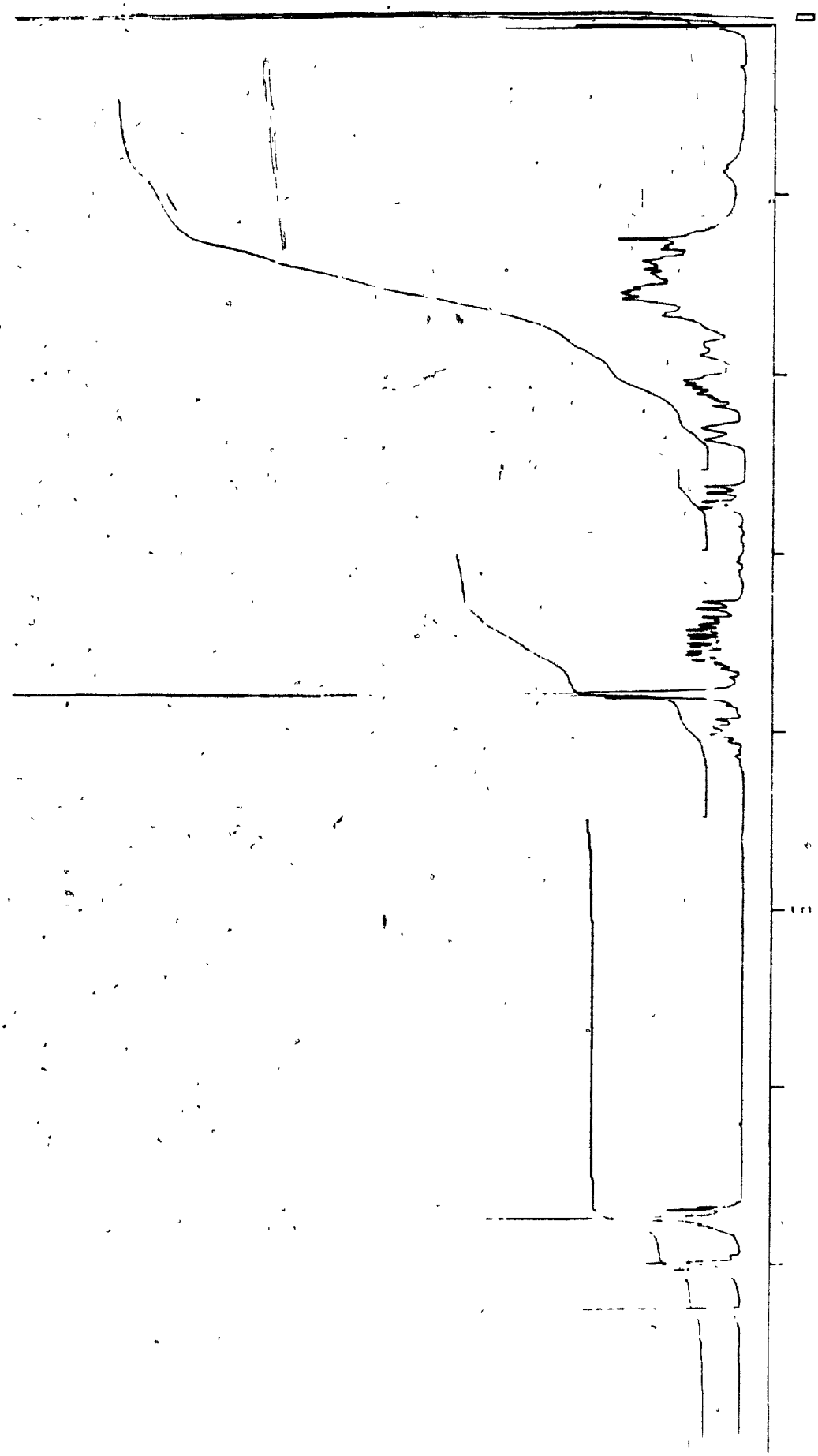

| | |
|---|---|
| Amine Hydrochloride | 1 |
| Aldehyde | 3 |
| Diol | 5 |
| Methoxy-thiaisomorphinan | 7 |
| Isomerized Alcohol | 13 |
| Thiolacetate | 15 |
| Methoxy-thiamorphinan | 17 |



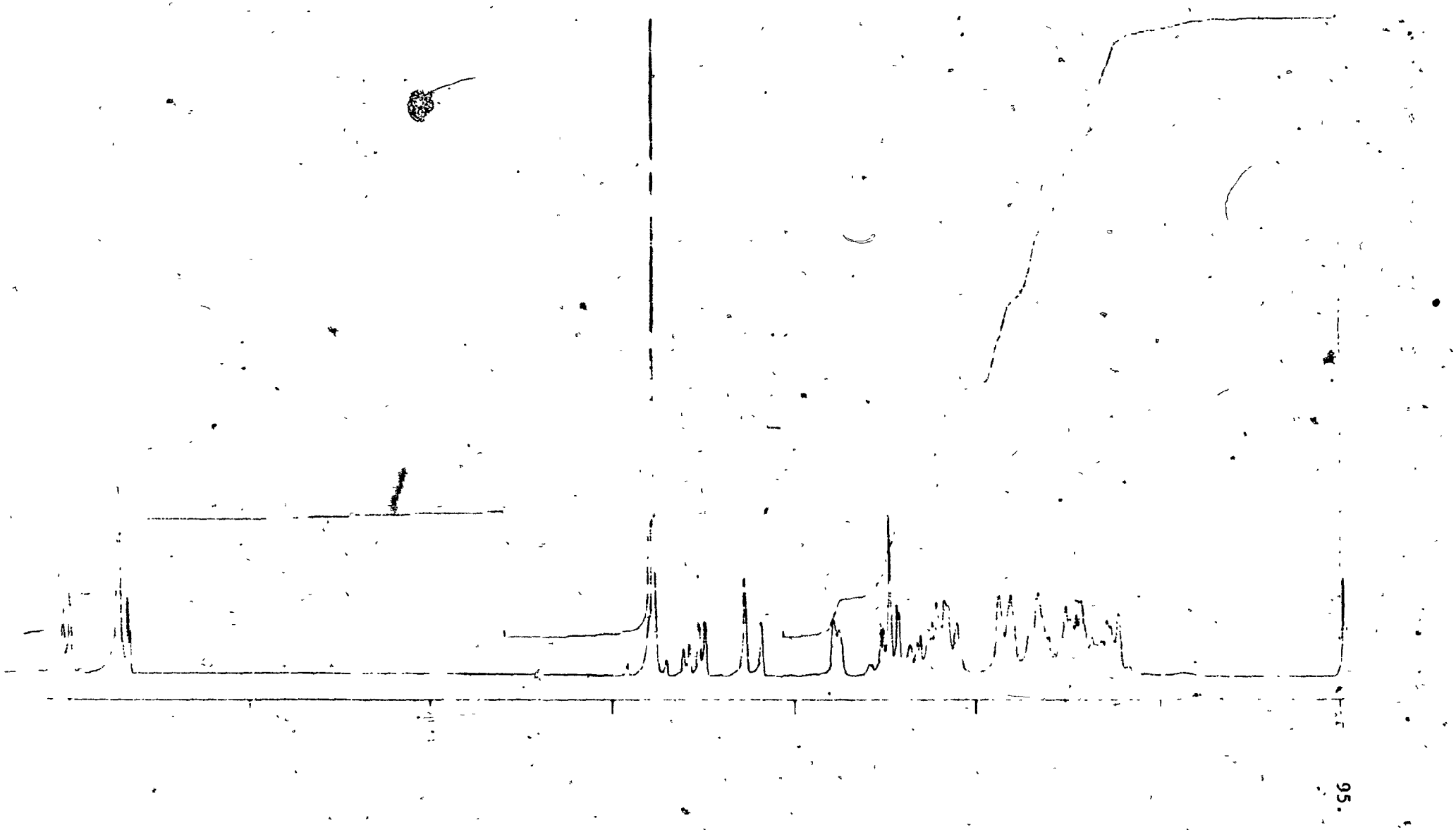

1 - Amine hydrochloride (Figure VI)



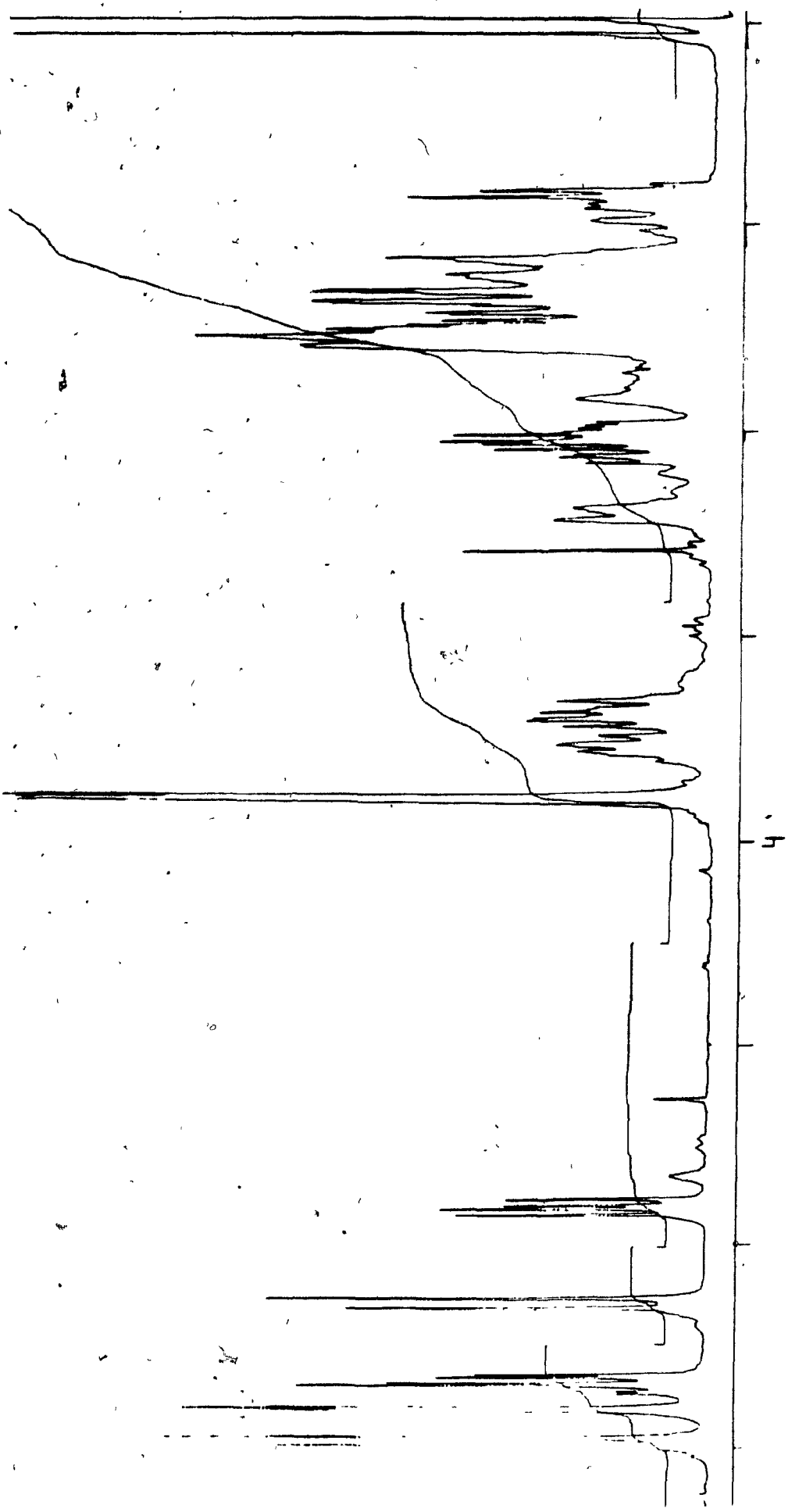
3 - Aldehyde



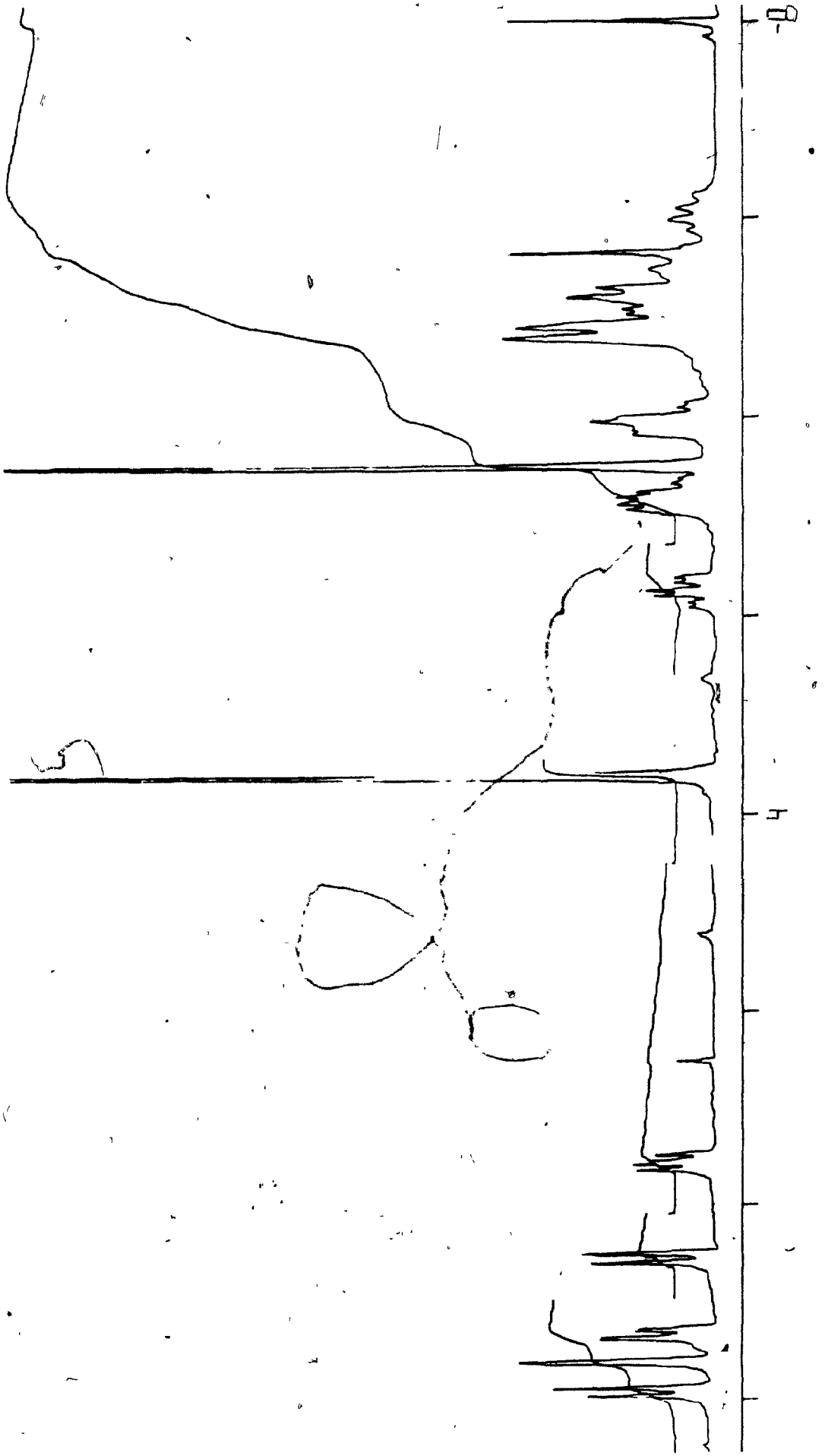
5 - Diol



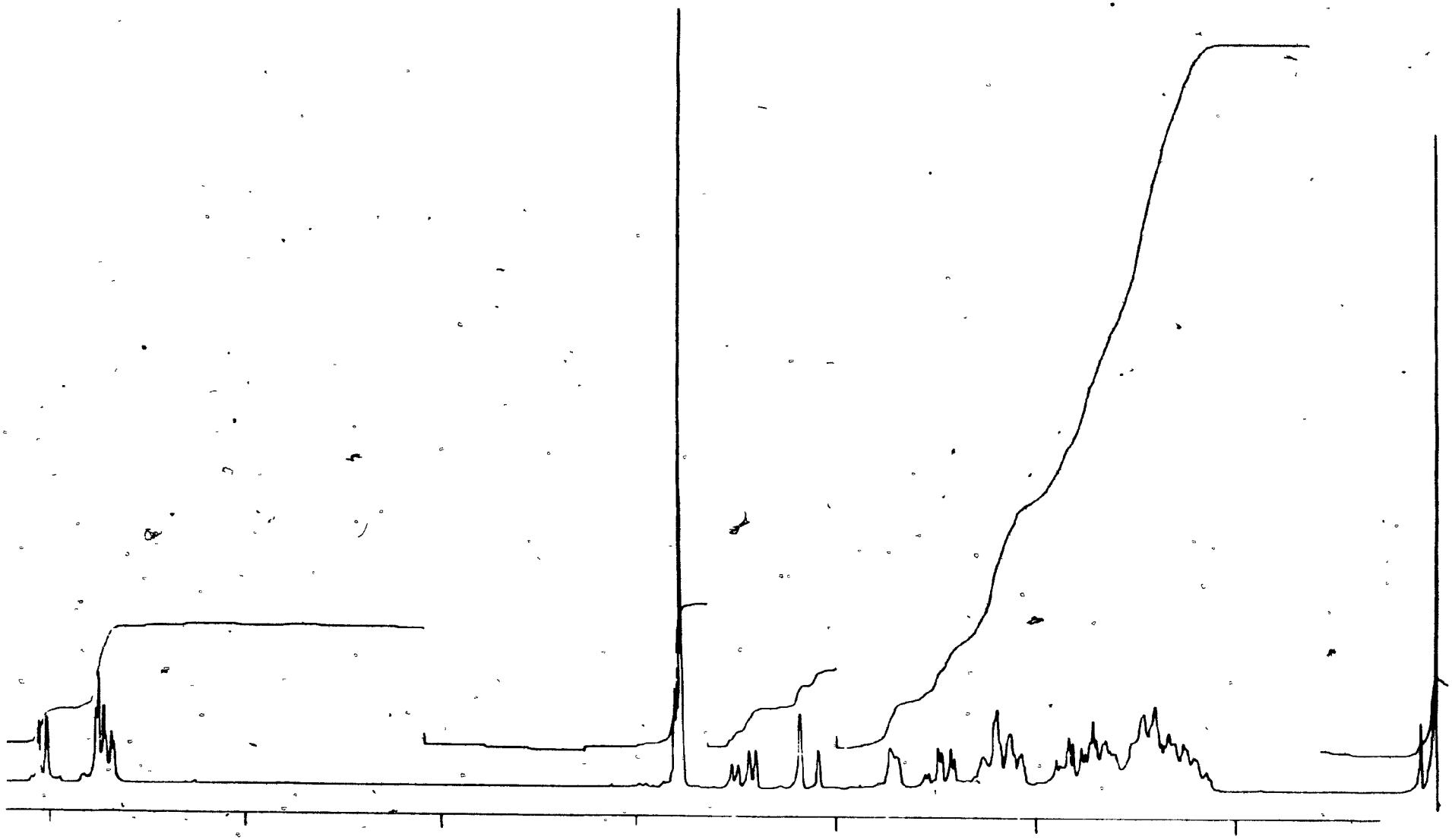
7 - Methoxy-thiaisomorphinan




13 - Isomerized alcohol




15 - Thiolacétate





17 - Methoxy-thiamorphinan