THE APPLICATION OF METALLATED ENAMINES TO THE SYNTHESIS OF MORPHINE ALKALOIDS

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1982

(Submitted May 24, 1982)

To My Parents

ACKNOWLEDGEMENTS

I would like to thank Dave Evans for his guidance, support and tolerance throughout the course of this work. His remarkable knowledge of and insight into chemistry provide a unique environment for research.

Rich Cherpeck deserves special mention for introducing me to the pleasures of alkaloid chemistry, as do Scott Biller and John Nelson for being exacting mentors. I would also like to thank everyone else who has contributed in making Caltech a stimulating place to do science.

Finally, special thanks to Gwen Anastasi and Dot Lloyd for invaluable assistance in the preparation of this manuscript.

ABSTRACT

Metallated enamines have been used to prepare a number of morphine-based analgesics, including efficient entry to the 4a-phenylisoquinolines and morphinans. Stereocontrolled formation of both cis and trans-fused perhydroisoquinolines has been accomplished by either kinetic or thermodynamic protonation of the corresponding octahydroisoquinoline. Reaction of 4a-phenyloctahydroisoquinolinium perchlorates with diazomethane afforded the expected aziridinium perchlorate with a component of direct cyclization to the morphinan structure also observed. Kornbloom oxidation to the α-amino-aldehyde was accomplished on treatment of the aziridinium salts with dimethylsulfoxide. The aldehydes were cyclized to the morphinan structure on reaction with boron trifluoride etherate, providing ready access to intermediates used by Gates in his pioneering total synthesis of morphine.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued) PAGE

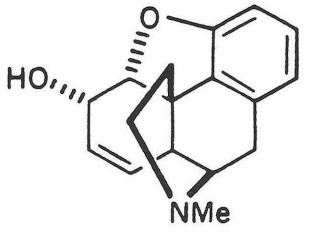
TABLE OF CONTENTS (continued) PAGE

TABLE OF CONTENTS (continued) PAGE

THE APPLICATION OF METALLATED ENAMINES TO THE SYNTHESIS OF MORPHINE ALKALOIDS

INTRODUCTION

Efforts aimed at the development of improved analgesics have established that structural subunits of morphine (1) exhibit useful analgesic activity in their own right,[1] as exemplified by morphinan (2), phenyl pipiperidine (4), and most recently, phenyldecahydroisoquinoline (3).[2] Each of these structures contains the 1-amino-3-phenylpropane functionality definitive of the qualitative structure-activity relationship known as the morphine rule.[1] Recent research in our



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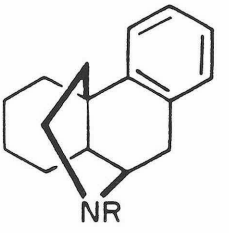

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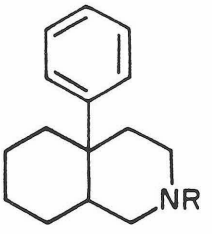

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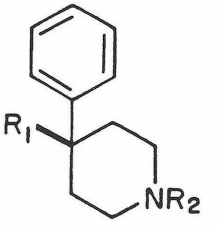


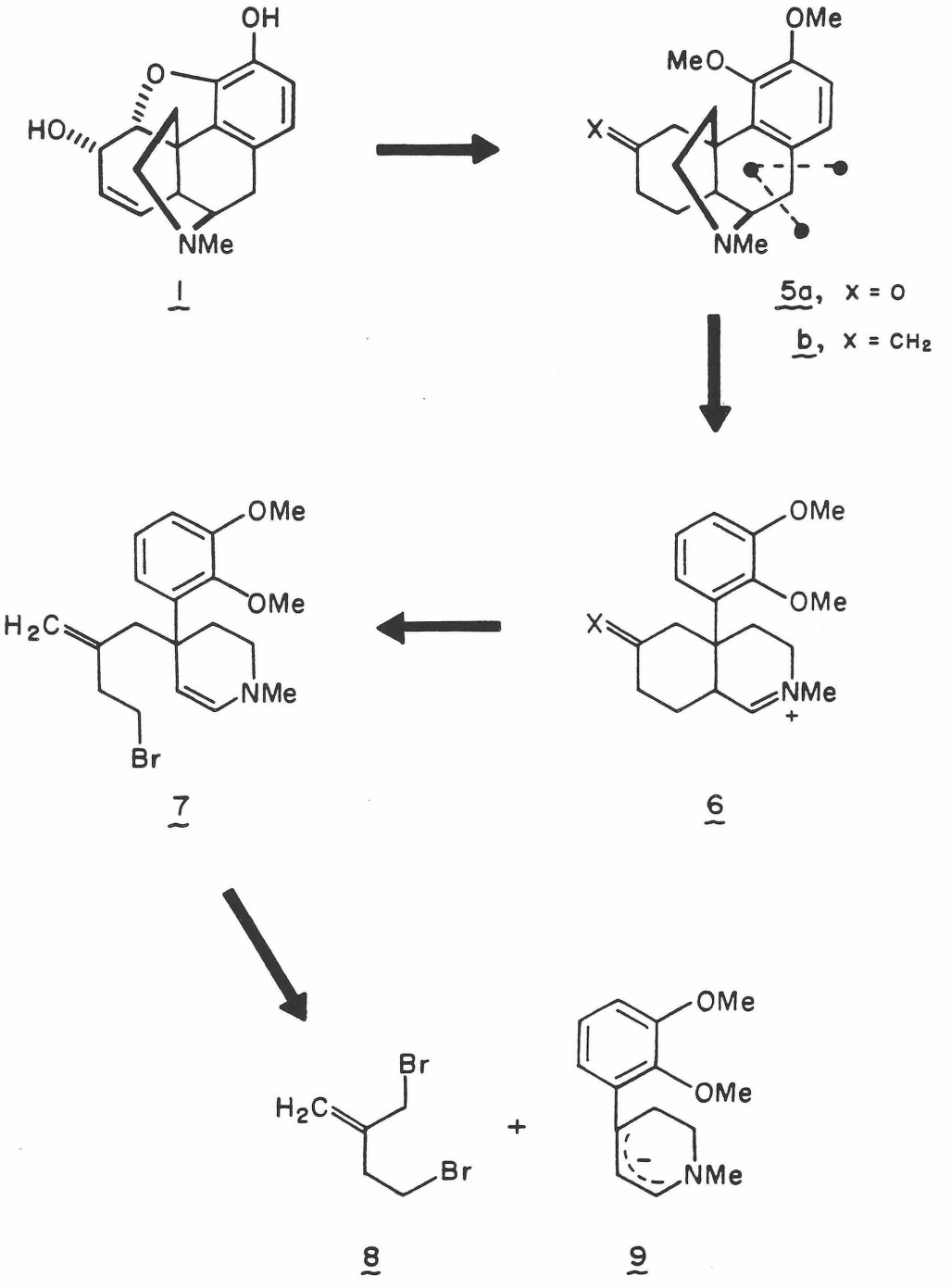
4

laboratories has demonstrated that metallated enamines provide expedient access to such morphine-based analgesics.[3] In this

report, the application of metallated enamines to alkaloid synthesis will be described in the context of a general route to a number of phenylpiperidine and decahydroisoquinoline analgesics, culminating in an approach to the morphine alkaloids.[4] The key elements of our plan of attack on morphine are illustrated retrosynthetically in Scheme I.

Our initial target has been morphinan 5, which comprises the fundamental architectural features of the morphine carbon skeleton and requires only well-documented functional group manipulations for ultimate conversion to the natural product.[4a,i-m] As originally proposed by Boekelheide in 1947,[5] dissection of the bridging methylene unit then reduces the problem to consideration of aryl-isoquinoline 6. Sequential disconnection about the ring fusion of 6 reveals an annelation process based on bis-alkylation of metallated enamine 9 by dibromide 8; wherein the double bond in 8 is intended to serve the dual function of providing regiocontrol via allylic activation as well as acting as a latent carbonyl unit. Of the five asymmetric centers found in morphine, control of relative stereochemistry at C5, C6 and C14 is well established from previous work,[4,6] so that the main stereochemical problem at hand will be introduction of the bridging methylene unit to the same face of the isoquinoline ring as the aryl substituent. Towards this end, it will also be desirable to achieve control of ring fusion geometry in 6.

Scheme I.



1

5a, X = O

b, X = CH_2

6

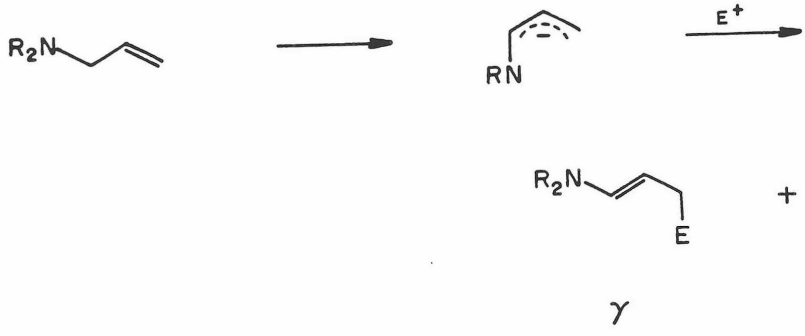
7

8

9

Utility of Metallated Enamines

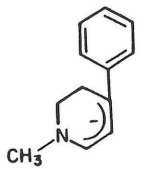
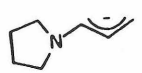
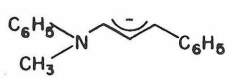
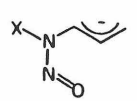
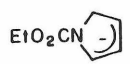
In conjunction with the development of this plan, the utilization of metallated enamines for the preparation of a number of morphine substructural analogues was investigated. The alkylation of metallated enamines (e.g. α-aminoallyl anions) has been examined previously with the aim of developing useful homoenolate equivalents.[8] Provided adequate regiochemical control can be obtained, alkylation at the γ-position followed by hydrolysis of the resulting enamine affords the desired homoenolate synthon (equation 1).



(1)

In general, N-alkyl- or N-arylallyl anions are reported to undergo alkylation exclusively at the γ-position in good yield (entries E-H, Table I).[8a-c] Alternatively, functionalization of nitrogen as an urethane or N-nitroso derivative provided the opposite sense of regiocontrol, giving rise to exclusive α-alkylation (entries I-K, Table I).[8d-e] The metallated enamine 10 desired for the present study has in fact been previously reported in the patent literature and found to undergo acylation at the γ-position exclusively (entry A, Table I).[8b]

TABLE I.

Entry	Allyl Anion[a]	Electrophile	γ/α[b,c]	Yield	Ref.
A		$ClCO_2Et$	>95:5	36	8b
B		$Br(CH_2)_4Cl$	>95:5	70	d
C		$CH_2{:}CHCH_2Br$	>95:5	70	d
D		8	>95:5	60	d
E		$n\text{-}C_4H_9Br$	>95:5	50	8a
F		$(CH_3)_3SiCl$	>95:5	70	8a
G		CH_3I	>95:5	76	8c
H		$(CH_3)_3SiCl$	>95:5	63	8c
I		CH_3I	<5:95	80	8d
J		$CH_3{:}CHCH_2I$	<5:95	83	8d
K		$n\text{-}C_4H_9Br$	<5:95	65	8e

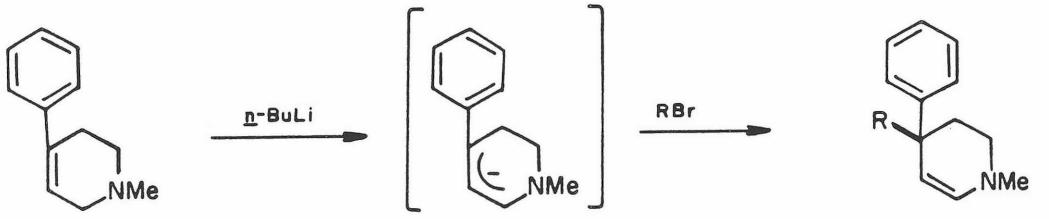
a Li counterion in all cases.

b α and γ relative to nitrogen.

c A single regioisomer was isolated in each case.

d See experimental section.

Tetrahydropyridine 10, on treatment with n-butyllithium in tetrahydrofuran at -10°C, afforded the metallated enamine 9, as a deep red solution, which underwent alkylation exclusively at the γ-position with a variety of alkyl halides giving endocyclic enamines 11a-11c in good overall yield (equation 2).[7]



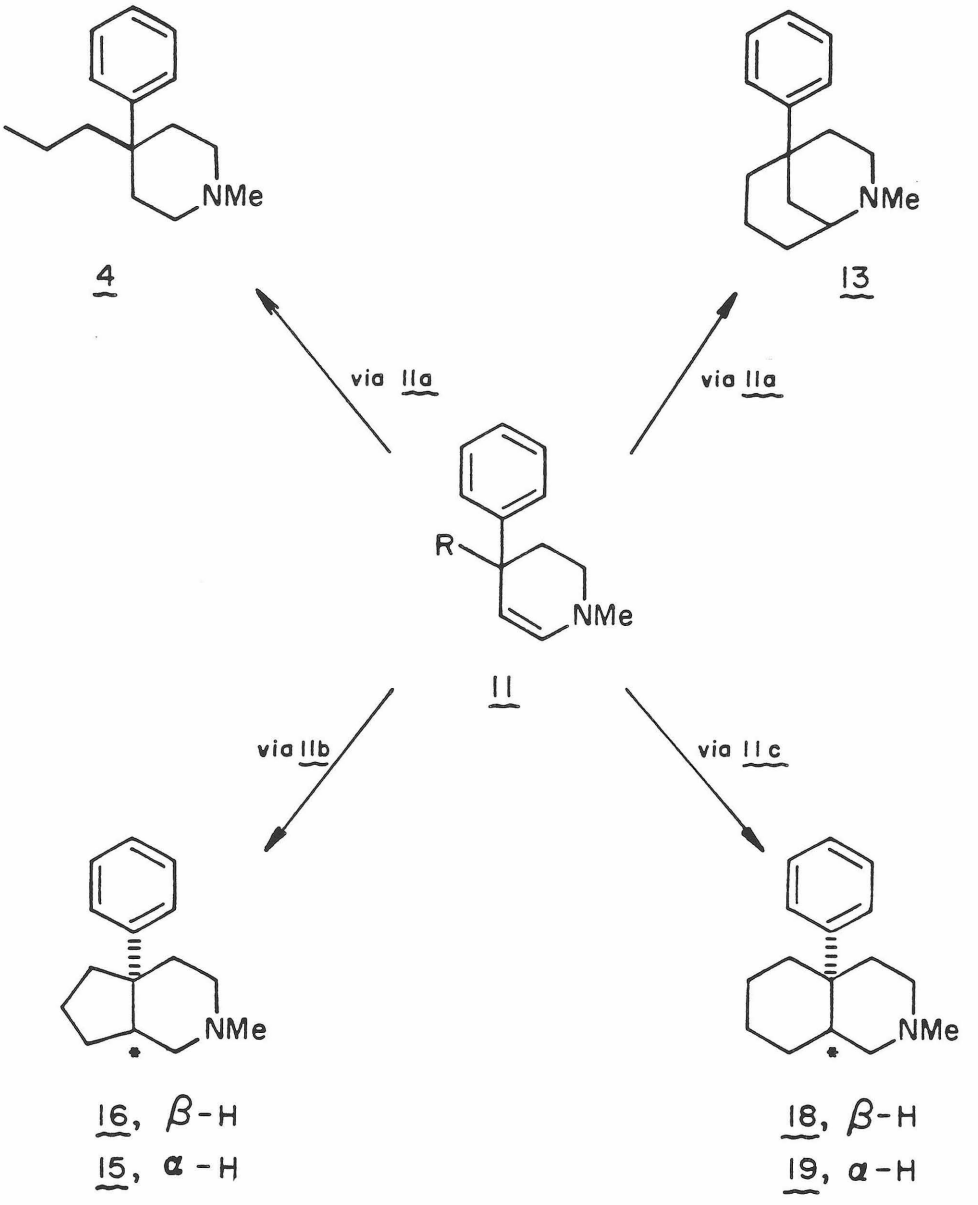
10 9 11 (2)

a, R = $CH_2CH=CH$, 77%
b, R = $(CH_2)_3Cl$, 70%
c, R = $(CH_2)_4Cl$, 70%

The versatility of these endocyclic enamines in the construction of simple morphine-based analgesics is illustrated in Scheme II. Compound 11a may be readily transformed to either phenylpiperidines or phenylmorphans in high yield. Similarly, intramolecular alkylation of 11b and 11c provides ready access to phenylpyrindines and phenylpiperidines, respectively.

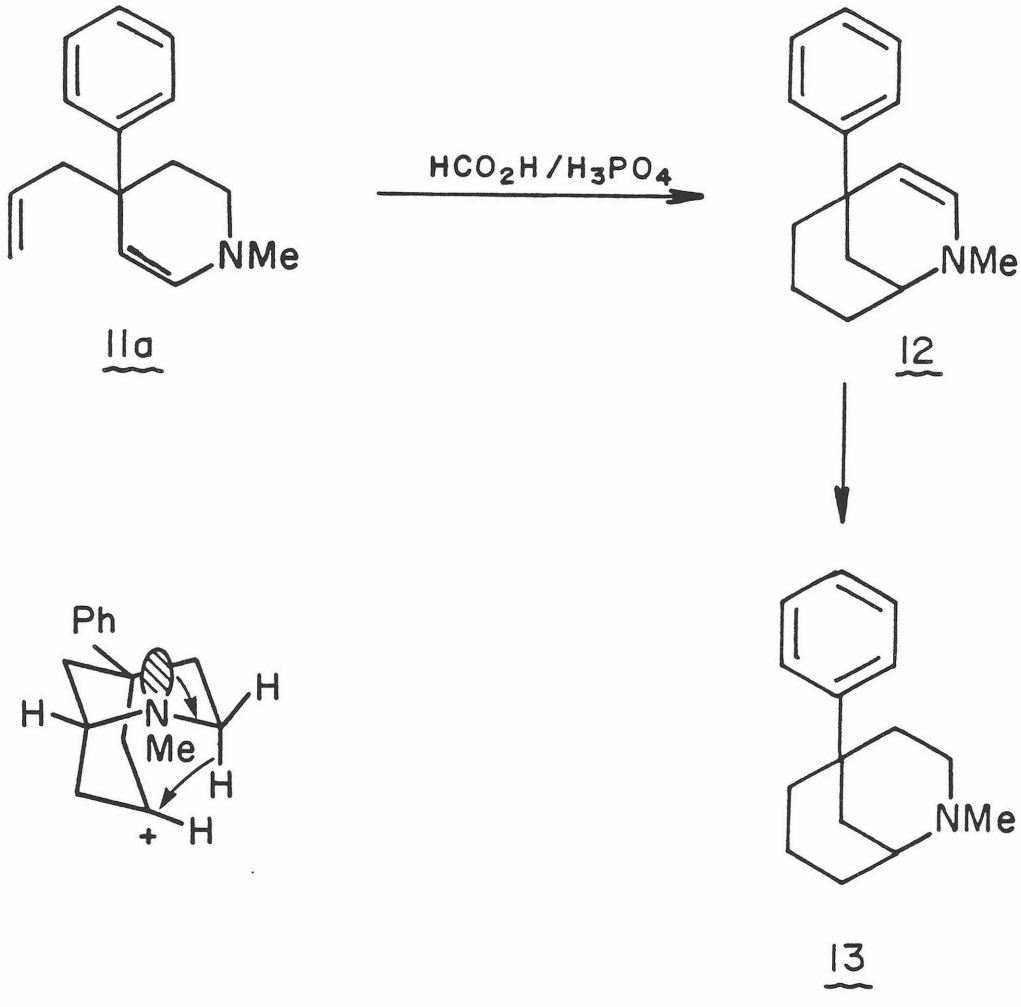
Allyl substituted 11a is obtained in 77% upon alkylation of 9 with allyl bromide. This versatile intermediate may be transformed into phenylpiperidine 4 ($R_1 = C_3H_7$, $R_2=CH_3$) by catalytic hydrogenation.[9] Alternatively, treatment of 11a with a 1:1 mixture of formic and phosphoric acids provided

Scheme II.


NMe
4
13
via IIa
via IIa
R
NMe
II
via IIb
via IIc
NMe
NMe
16, β-H
15, α-H
18, β-H
19, α-H

phenylmorphan 12 in 91% yield (Scheme III). This transformation

Scheme III.



11a 12 13

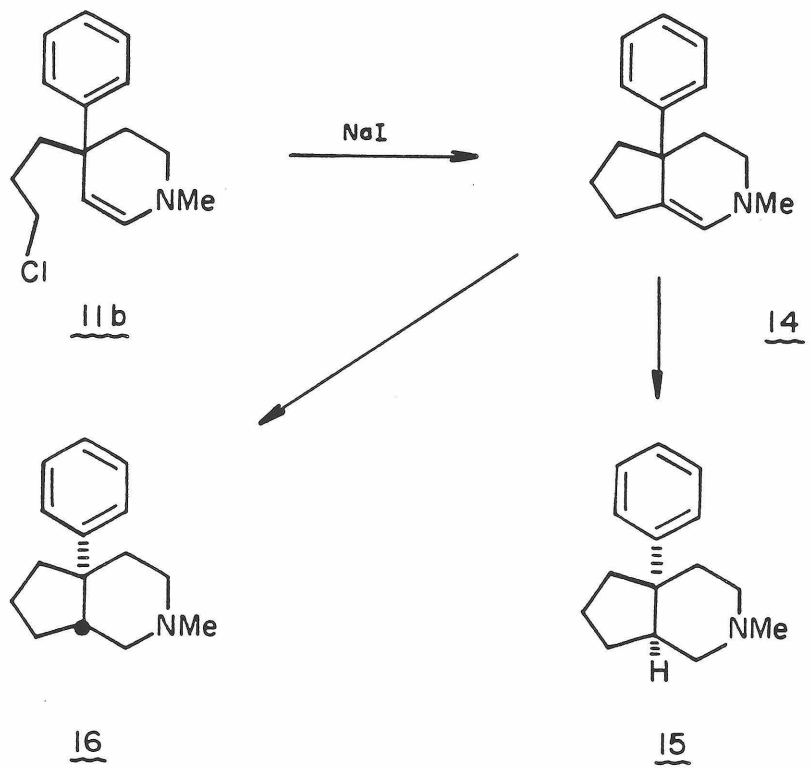
is viewed as proceeding via an immonium ion-olefin cyclization followed by a transannular hydride shift. Hydrogenation of 12 then gave the known phenylmorphan 13, previously prepared by a much longer route.[10]

Alkylation of metallated enamine 9 with α,ω-dihaloalkanes can be readily accomplished provided inverse addition of 9 to

a solution of the dihalide is employed. This operation is necessary to prevent competitive coupling of the halogen-bearing alkylation products (11b, 11c) with unreacted metallated enamine. Such undesired coupling products may comprise as much as 50% of the reaction mixture when direct addition of the alkyl dihalide to the metallated enamine is followed.

Inverse addition of 9 to a solution of four equivalents of 1-bromo-3-chloropropane (-50°C) in ethyl ether afforded the endocyclic enamine 11b, which on treatment with sodium iodide in refluxing acetonitrile for 24 hours afforded phenylpyrindine 14 in 70% yield. Hydrogenation of 15 then gave either cis- or trans-perhydropyrindines 15 or 16, depending on the catalyst employed; using 5% palladium on charcoal gave exclusively 15 (15:16 $\geq$ 95:5), while platinum oxide gave a slight predominance of 16 (16:15, 60:40). The assignment of ring-fusion stereochemistry in each case is based on comparison of ^{13}C-NMR spectra with the analogous cis- and trans-4a-phenylperhydroisoquinolines 18 and 19 of previously established configuration (vide infra). Specifically, the ^{13}C-resonance of C-7a occurs at lower field in the trans isomer than in the cis, while the resonance of the phenyl ipso-carbon occurs at higher field in the trans than in the cis isomer. Corresponding results are observed for C-8a and the phenyl ipso-carbon for 18 and 19 as well as for the parent cis- and trans-perhydroisoquinoline and

Scheme IV.

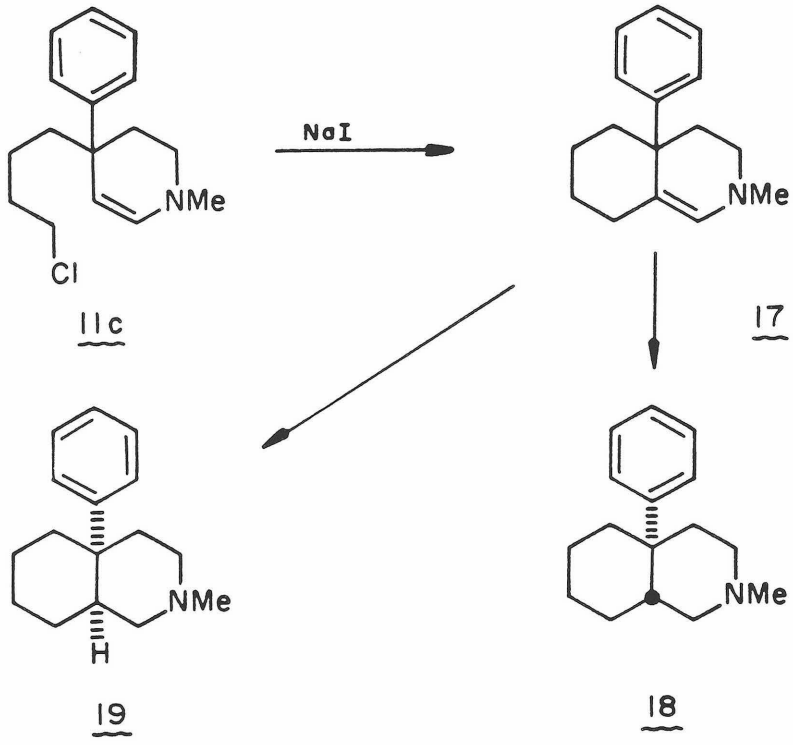


11b 14 16 15

decalin ring systems.[11,12] In the absence of further proof of ring-fusion configuration, the assignments for 15 and 16 must be considered tentative. The phenylpyrindines 14-15 so formed constitute a promising new class of analgesics.[13]

Access to the perhydroisoquinoline ring system is achieved by a homologous annelation sequence (Scheme V). Inverse

Scheme V.



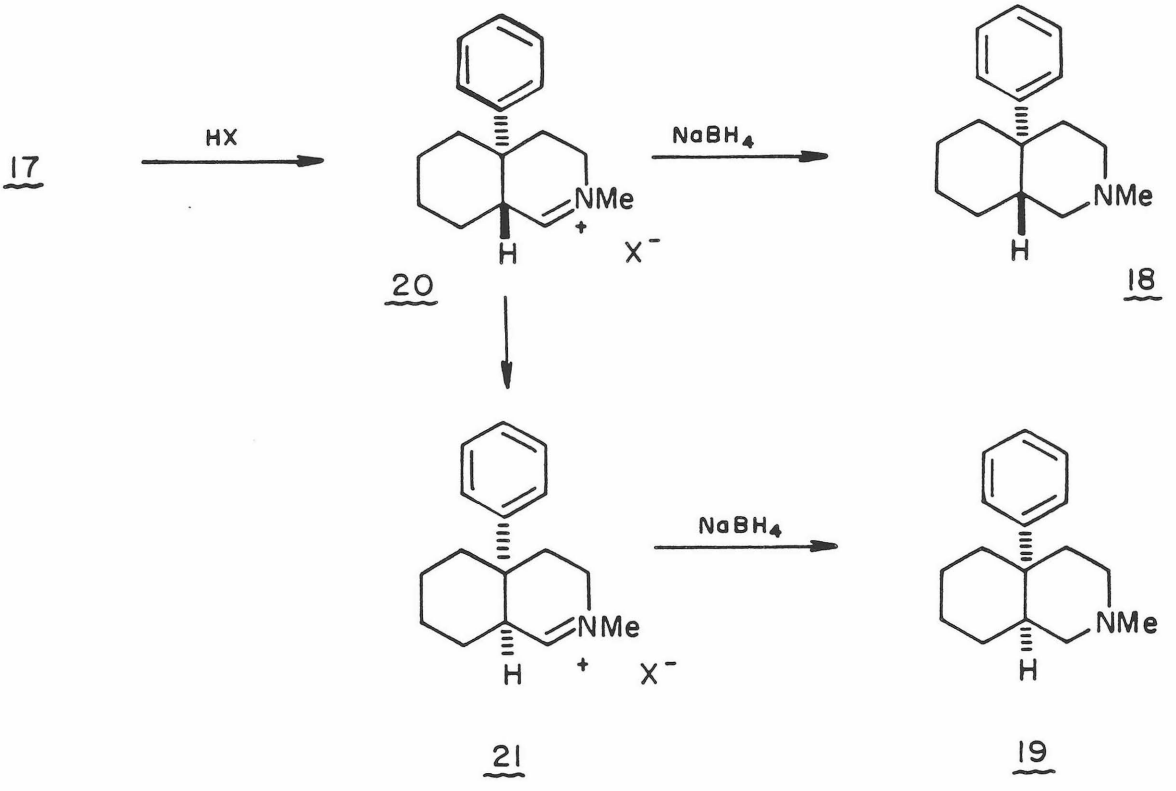
addition of 9 to a solution of four equivalents of 1-bromo-4-chloro-butane in ethyl ether gave endocyclic enamine 11c which is readily purified as its perchlorate salt, in a yield of 70%. Treatment of 11c with sodium

iodide in refluxing acetonitrile for 24 hours provided bicyclic enamine 17 in 60% overall yield from tetrahydropyridine 10 without intermediate purification of 11c. Either trans- or cis-perhydroisoquinolines 18 or 19 may be obtained with complete stereocontrol by catalytic hydrogenation over platinum oxide, the stereochemical outcome dependent on solvent choice. In ethanol, the reduction afforded exclusively trans-perhydroisoquinoline 18 (18:19 95:5), while in acetic acid only cis-perhydroisoquinoline 19 was found (19:18 ≥ 95:5).[14,16] This general approach to the 4a-phenylperhydroisoquinolines 18 and 19 is noteworthy for its directness in comparison with other published approaches.[14,16]

Formation and Reactions of Immonium Ions

For the utilization of bicyclic enamines such as 17 in the synthesis of morphinans, it was important that protonation give the corresponding immonium salt with well-defined ring-fusion stereochemistry. Treatment of a solution of 17 in ethyl ether with ethereal perchloric acid afforded exclusively the trans-fused isomer, 20 (Scheme VI), as determined by sodium borohydride reduction to 18 (18:19 ≥ 95:5). When 20 (oil) was dissolved in ethanol, after several days the cis-fused isomer, 21, gradually crystallized from solution (95% yield), with the stereochemistry again determined by sodium borohydride reduction (19:18 ≥ 95%). Examination of

Scheme VI.

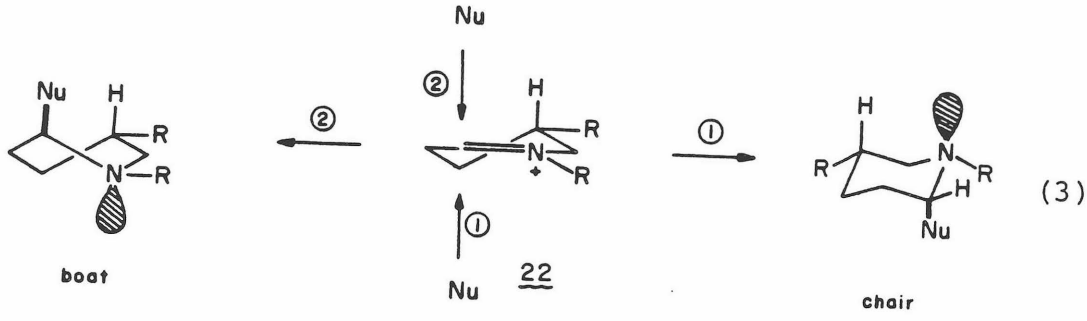


more soluble immonium salts (20, 21; x=Cl, OAC) demonstrated that 21 forms as the thermodynamic product and is not being produced as a consequence of lattice energy effects selectively crystallizing a small concentration of 21. Dichloromethane solutions of 20 (x=Cl) were observed by ^{13}C-NMR to

equilibrate to 21 (21:20, 97:3) without accompanying crystallization. Rates of equilibration were conveniently followed by this method and were found to vary with the basicity of the counterion. Solutions of the perchlorate salt of 20 in dichloromethane showed no formation of 21 after 48 hours, while in methanol (2 M, 25°C) an approximate half-life of 16 h was observed for equilibration of 20 to 21. Correspondingly, the approximate half-life for x=Cl (2 M solution in methanol, 25°C) was two hours, while for x=OAc (2 M, methanol, 25°C) equilibration occurred at a rate faster than the ^{13}C-NMR spectrum could be obtained ($T_{1/2} \leq 5$ min). These results correlate well with the dramatic solvent effects noted above in the hydrogenation of bicyclic enamine 17. It is concluded that 17 is the direct precursor to trans-fused perhydroisoquinoline 18 when the reaction is carried out in ethanol, while the thermodynamic cis-fused immonium salt 21 (x=OAc) is the species reduced in acetic acid. Stereocontrolled formation of either cis- or trans-fused 20 or 21 is thus readily accomplished by either kinetic or thermodynamic protonation of bicyclic enamine 18.[3,16]

Immonium salts 20 and 21 are appealing intermediates for morphinan synthesis, requiring only incorporation of the bridging methylene carbon. This carbon fragment could be appended onto the isoquinoline unit by nucleophilic addition to the immonium salt, provided that the addition can

be carried out in a stereoselective manner. In principle, stereoelectronic factors could provide the necessary stereochemical control element (equation 3). Given a conformationally



(3)

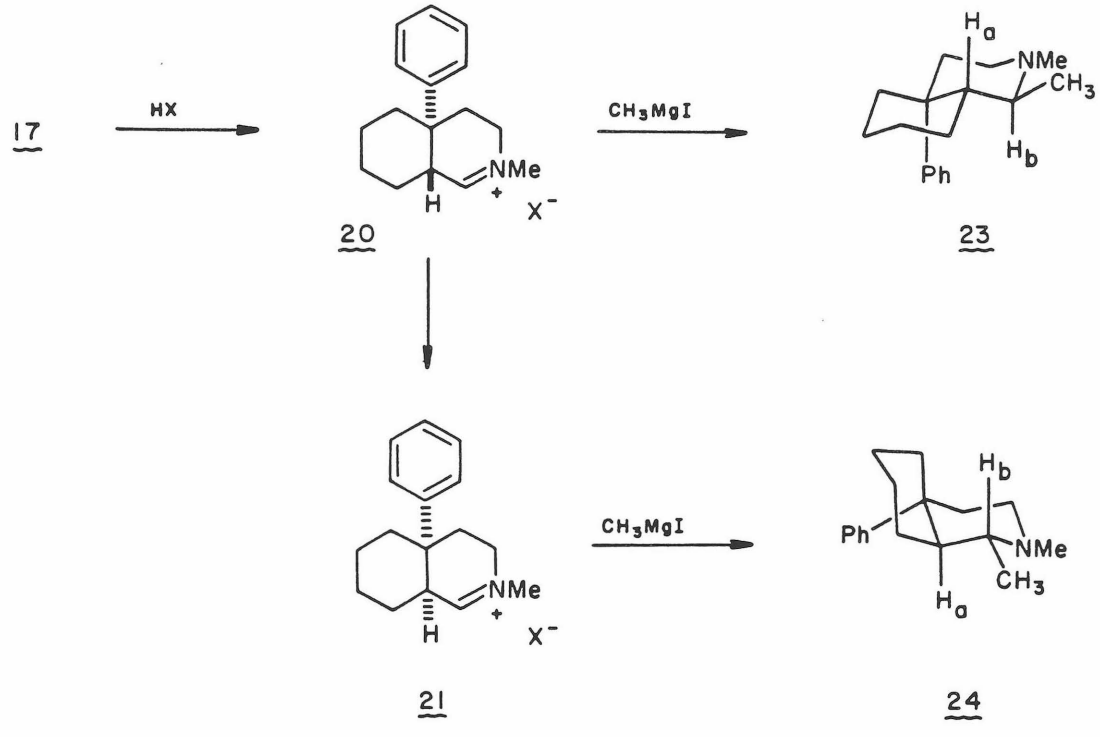
rigid cyclic immonium ion (22), maximum orbital overlap between the incoming nucleophile and the immonium π* orbital would result in an antiperiplanar alignment of nucleophile with the nitrogen lone pair.[17] Barring other overriding factors, addition to 23 should occur from the beta-face via a lower energy chair transition state, as opposed to the higher energy boat transition state. The expected product would thus be axially substituted. An excellent demonstration of this concept has been reported by Stevens in his elegant synthesis of the ladybug defense alkaloids, precoccinelline and coccinelline.[18]

However, at the outset of this work, the concept of stereoelectronic control in such additions was not yet well documented. If operative with immonium salts 20 and 21, stereoelectronic control would promote axial attack of the incoming nucleophile via the lower energy chair transition state, resulting in addition cis to the phenyl group, provided

such stereoelectronic factors can override the strong steric bias for addition opposite to the bulky phenyl substituent.

To test this point, the reactions of 20 and 21 with nucleophiles were investigated (Scheme VII). Treatment of

Scheme VII.



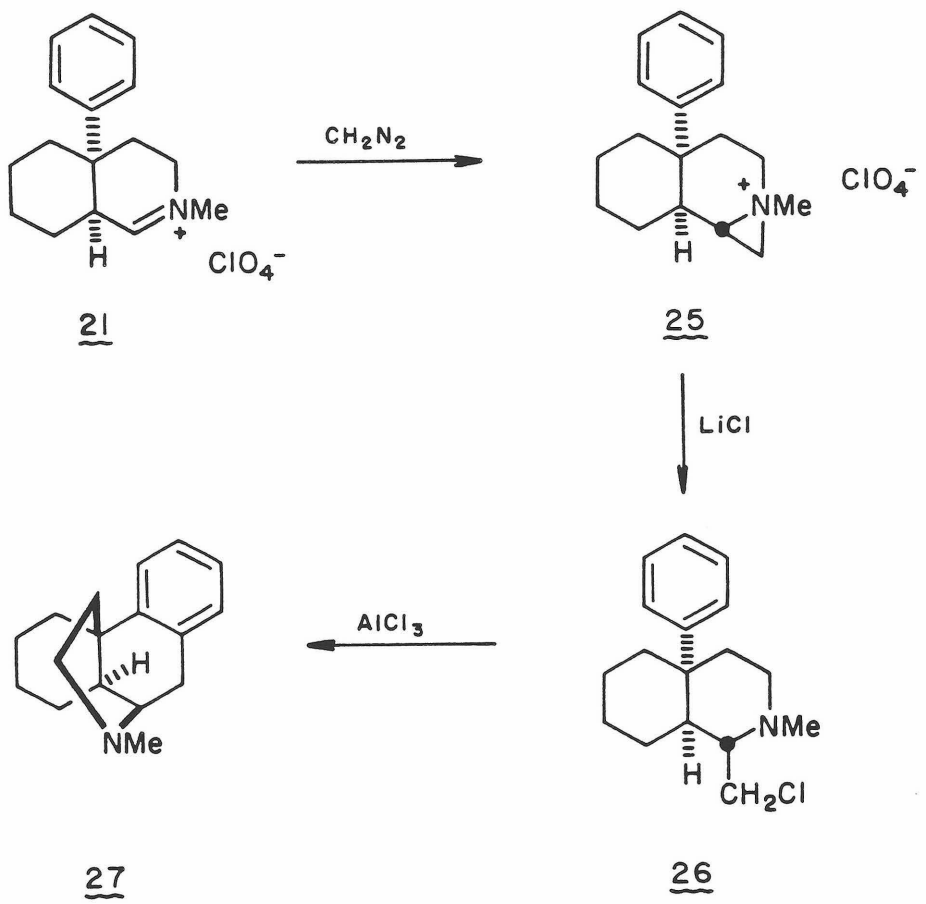
20 in tetrahydrofuran at -78°C with excess methylmagnesium iodide in ethyl ether resulted in formation of equatorial

methyl adduct 23, as indicated by J_{ab} = 10 Hz in ^{1}H-NMR, with none of the corresponding axial epimer found. In contrast to less encumbered examples,[18] this result demonstrates that nucleophilic addition via the higher energy boat-like transition state is feasible given a sufficient steric bias. The similar reaction of cis-fused 21 with methylmagnesium iodide, however, gave exclusive formation of 24 (J_{ab} = 10 Hz),[19] where a 1,3-cis relationship has been established between the phenyl and methyl substituents. If the methyl substituent was appropriately functionalized, this cis relationship would make possible cyclization to the morphinan skeleton.

Morphinan Synthesis via Aziridinium Salts

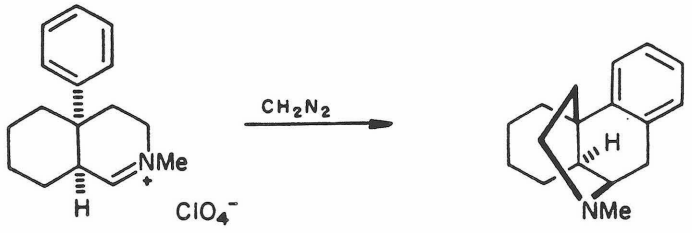
Towards this end, cis-fused immonium perchlorate 22 in dichloromethane at 0°C was allowed to react with ethereal diazomethane to give aziridinium perchlorate 25 in 85% yield as a single diastereomer after recrystallization from benzene/acetone (Scheme VIII).[20] In principle, aziridinium salt 25 could cyclize directly to the desired N-methylmorphinan 27; however, all attempts to thermally induce such a process have failed in our hands. In the event, regiospecific ring opening with lithium chloride in acetonitrile afforded a 98% yield of α-chloroamine 26. Ring closure to N-methylmorphinan 27 was then readily accomplished upon treatment of 26 with

Scheme VIII.



aluminum chloride in refluxing benzene, in an overall yield from 22 of 60%.[21] For purposes of verification, 27 was converted to its picrate and methiodide salts, whose melting points were found to be identical with those previously reported.[22] With a sample of morphinan 27 in hand, careful scrutiny of the reaction of immonium salt 22 with diazomethane revealed that a 15% yield of 27 was formed directly in

competition with aziridinium ion formation. An increase in the

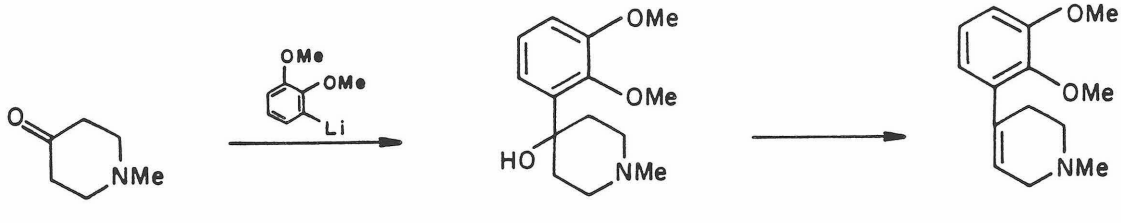


(4)

21 27

solvent polarity was found to dramatically enhance the amount of 27 so produced, with yields of 30% in acetone and 40% in methanol being obtained.

Having successfully demonstrated the feasibility of this approach for the preparation of simple morphinans, we next sought to apply it to compounds containing the aromatic oxygenation pattern found in morphine. The dimethoxyphenyl-tetrahydropyridine 30 required for the metallated enamine annelation process was prepared by a two-step sequence.



(5)

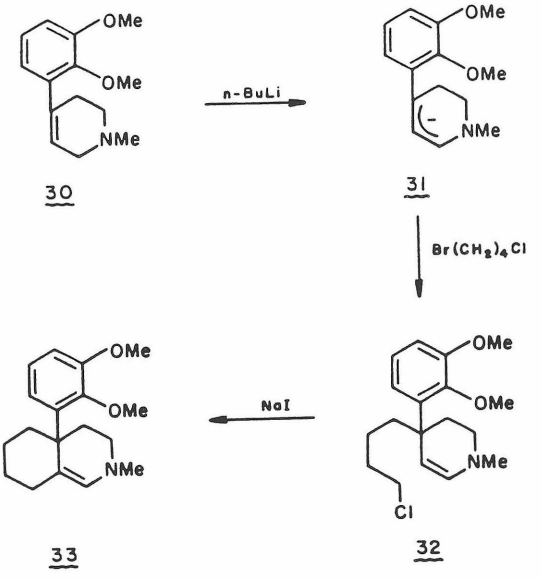
28 29 30

1,2-Dimethoxybenzene undergoes exclusive ortho-metallation upon treatment with n-butyllithium at room temperature in

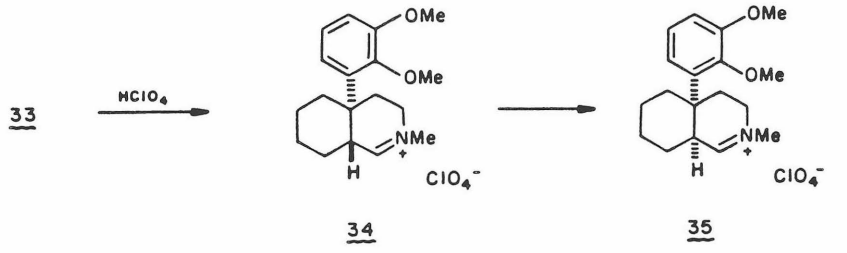
ethyl ether.[23] Addition of N-methyl-4-piperidone (28) in ether to a -10°C solution of dimethoxyphenyllithium so generated, afforded a 45-50% yield of 4-hydroxy-4-phenyl-piperidine 29, with the remainder of the mass balance accounted for by unreacted starting materials (due to competitive enolization) which are easily recovered for reuse in subsequent preparations. Dehydration with three equivalents of p-toluenesulfonic acid in refluxing toluene, with azeotropic removal of water, provided a 95% yield of the desired tetrahydropyridine 30.

The annelation process was then carried out as described for the unsubstituted phenyltetrahydropyridine 10. Metallation of 30 with n-butyllithium at -10°C in tetrahydrofuran afforded the allyl anion 31, with no competing aryl ring lithiation observed. Inverse addition of 31 to a -78°C solution of four

Scheme IX.



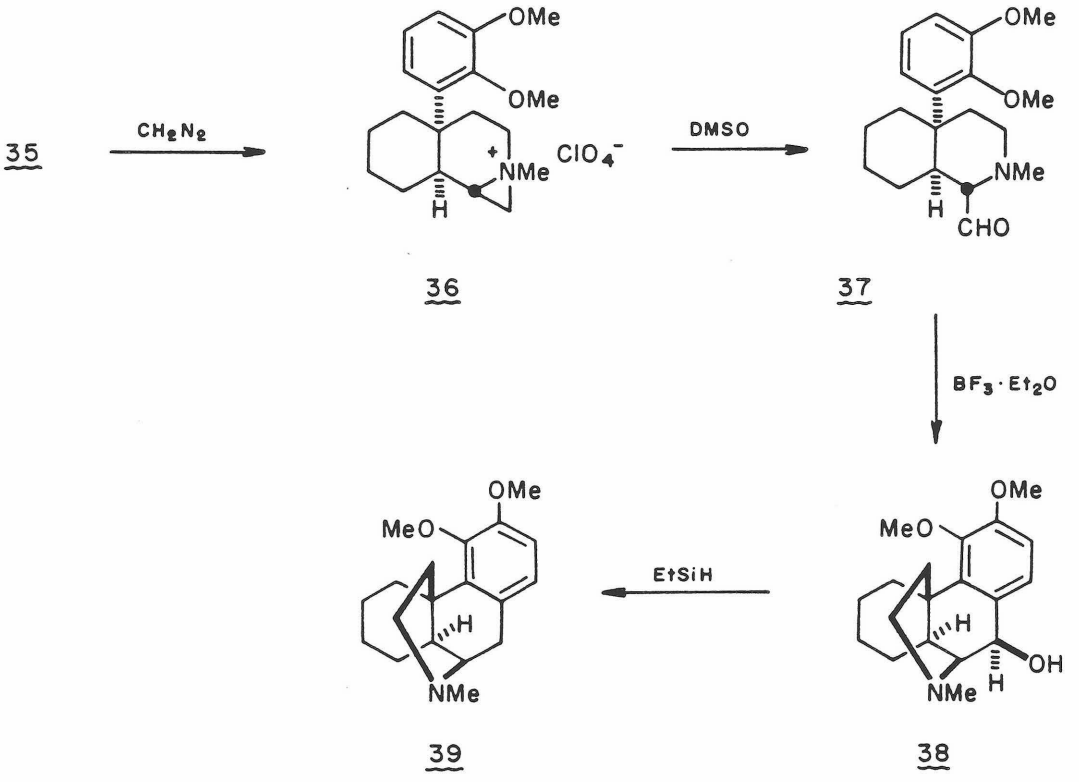
equivalents of 1-bromo-4-chlorobutane in ethyl ether afforded endocyclic enamine 32, which was directly cyclized by reaction with sodium iodide in refluxing acetonitrile to give a 54% yield of 33 after distillation. Protonation of 33 again gave a kinetic product 34, assumed to be trans-fused by analogy to the unsubstituted phenyl case above, which underwent equilibration to crystalline 35 (35:34 ≥ 97%). As the thermodynamic isomer, 35 was assumed to be cis-fused.



(6)

Reaction of 35 with diazomethane afforded aziridinium salt 36 as a single diastereomer. None of the corresponding dimethoxymorphinan 39 was found, even in more polar solvents, in direct contrast to the results noted above for the unsubstituted phenyl series. This observation may be a result of the ortho-methoxy substituent forcing a change in the rotomeric conformation of the aryl group. In order to minimize peri-interactions of the ortho substituent, the aryl group may orient itself with the methoxyl pointing away from the isoquinoline unit and the aryl ring bisecting the isoquinoline unit, effectively blocking approach of diazomethane in the conformer most likely to be giving direct

Scheme X.



morphinan formation in the substituted phenyl case (i.e. the conformer with aryl group axial to the nitrogen bearing ring).

At this point, milder cyclization conditions were desired which would be more compatible with the functionality required for the actual morphine synthesis.[24] Towards this end, it was anticipated that cyclization of α-aminoaldehyde 37

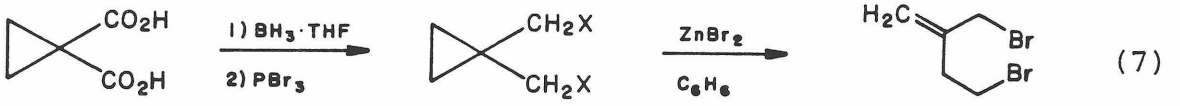
would take place under milder conditions than the harsh aluminum chloride process used above.[25] The regiospecific cleavage of aziridinium salts 25 and 36 with nucleophiles such as chloride or hydroxide suggested to us that a Kornbloom oxidation could be effected directly by reaction with dimethyl sulfoxide. Opening of the aziridinium ring with DMSO would liberate the basic nitrogen required for deprotonation and breakdown of the intermediate sulfoxonium salt.[3,26] Such was indeed the case. Simple treatment of 36 with excess dimethyl sulfoxide in anhydrous benzene at room temperature for 24 h afforded a 95% yield of the expected aldehyde 37. This exceptionally efficient oxidation of aziridinium salts deserves further attention as a potentially generalizable method for the construction of α-aminoaldehydes.

Surprisingly, reaction of 37 with boron trifluoride etherate in refluxing benzene produced morphinan 39 directly (40% yield), instead of the expected 10-hydroxymorphinan 38. Subsequently, it was observed that 38 is indeed produced upon treatment of 37 with $BF_3 \cdot Et_2O$ for approximately 1 minute at room temperature. In this way, 38 can be isolated in 90% yield as the 10β-hydroxy epimer exclusively. It is postulated that the observed reduction to 39 proceeds *via* $BF_3 \cdot Et_2O$ promoted ionization of the benzyl alcohol followed by hydride abstraction. It was gratifying to find that inclusion of a good hydride donor greatly improved the reduction. Reaction

of 37 with $BF_3 \cdot Et_2O$ and triethylsilane in refluxing benzene afforded an 80% yield of dimethoxymorphinan 39.[27] With the success of this reaction established, we were now equipped to tackle the synthesis of morphinans fully functionalized for elaboration into the natural product.

Synthesis of Morphine Alkaloids

In order to prepare morphinan and intermediate aryl isoquinoline structures functionalized at C-6 via a metallated enamine annelation process, an appropriately substituted dihalide synthon was required. 4-Bromo-2-bromomethyl-1-butene (8) appeared well suited for this purpose. The double bond would serve a dual role in providing regiocontrol in the alkylation process via allylic activation in addition to acting as a latent carbonyl unit. Towards this end, dibromide 8 was prepared in 60% overall yield from cyclopropane dicarboxylic acid (40).[28]



(7)

40

41, X = OH
42, X = Br

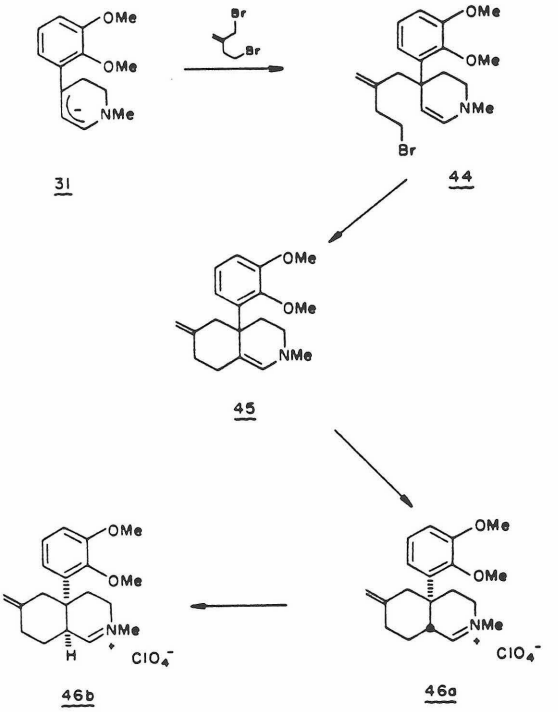
8

Borane reduction of 40 and subsequent bromination of diol 41 with phosphorous tribromide[29] afforded dibromide 42 in 72%

overall yield. Lewis acid-catalyzed cyclopropylcarbinyl rearrangement of 42 with zinc bromide in refluxing benzene then provided the desired 8 in 80% yield.[30] Scrupulously anhydrous conditions and sublimed zinc bromide are mandatory for efficient preparation of 8, a compound which is an appealing synthon for a variety of applications.

Inverse addition of metallated enamine 31 to a -78°C solution of two equivalents of 8 in ethyl ether gave endocyclic enamine 44 as a single regioisomer. Excess 43 is necessary to prevent coupling of 44 with 31, though the unreacted second equivalent was easily recovered for reuse later. While 44 in $CDCl_3$ was observed to undergo spontaneous cyclization to bicyclic enamine 45 over a period of several

Scheme XI.



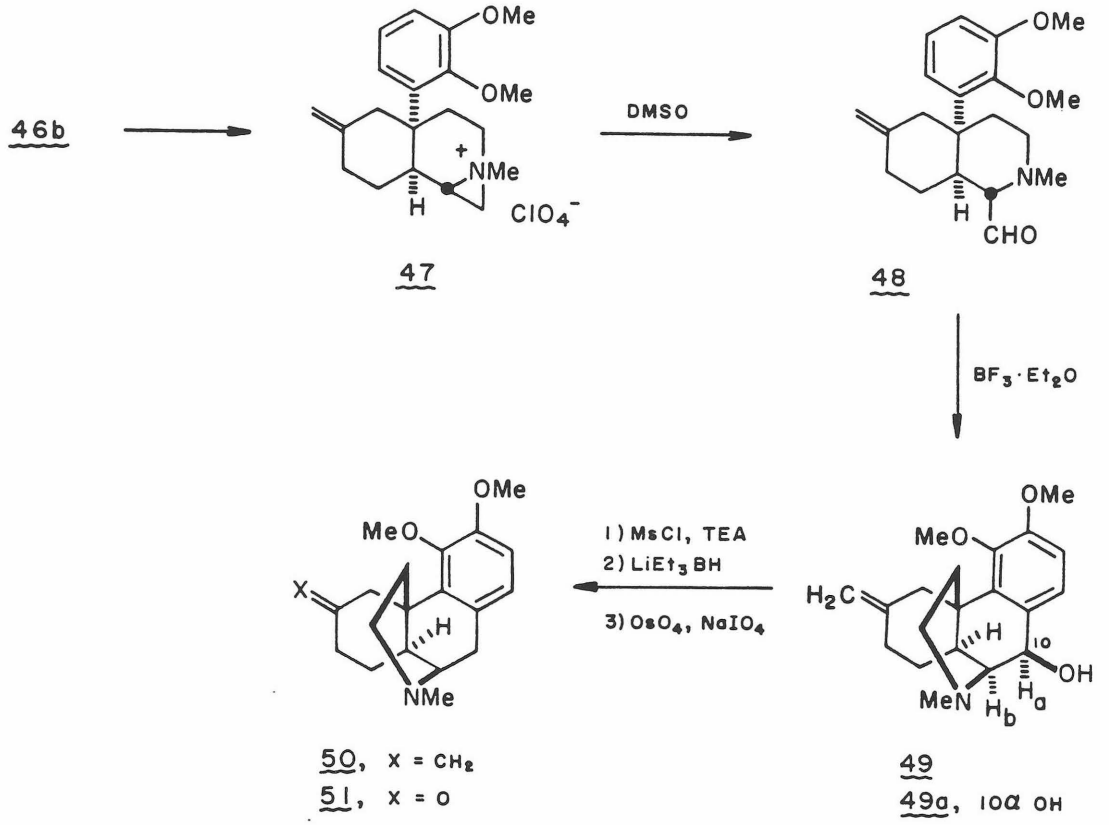
days, the highest yields for this process were obtained by heating 44 at reflux with sodium iodide and potassium carbonate in acetonitrile. Immediate kinetic protonation of the resulting bicyclic enamine 45 with perchloric acid gave directly the crystalline immonium salt 46a (assumed to be trans-fused, vide supra) in 60% overall yield from 30. Equilibration to the thermodynamically preferred cis isomer 46b (46b:46a = 95:5) then occurred upon dissolution in methanol at 50°C over 24 hours.[31]

Treatment of 46b with ethereal diazomethane afforded a 95% yield of aziridinium salt 47 as a single diastereomer. Oxidative cleavage of 47 was then accomplished upon reaction with dimethyl sulfoxide for 36 hours at room temperature in benzene to give aldehyde 48 in 95% yield. Cyclization of 48 with $BF_3 \cdot Et_2O$ at -10°C in toluene gave an 80% yield of 10-hydroxymorphinan 49 with almost exclusive formation of the 10β-hydroxy isomer shown in Scheme XII (10β:10α = 95:5).

The configurational assignment at the hydroxyl center is based on the coupling constant between Ha and Hb in the ^{1}H-NMR of 49 and 49a. For 49, J_{ab} = 6 Hz indicative of a pseudo-axial pseudo-equatorial relationship between the two protons. The Dreiding model of 49a reveals a dihedral angle of approximately 90° between H_a and H_b, which is consistant with J_{ab} ~ 0 Hz observed for this isomer.[32]

Attempted deoxygenation of 49 with triethylsilane and $BF_3 \cdot Et_2O$, as used previously, resulted in competitive exocyclic

Scheme XII.



to endocyclic isomerization of the double bond. Instead, the desired transformation was accomplished in a one-pot operation by sequential methanesulfonation of 49 in tetrahydrofuran followed by reduction of the derived mesylate with lithium triethylborohydride, affording a 90% yield of 50.[33,34]

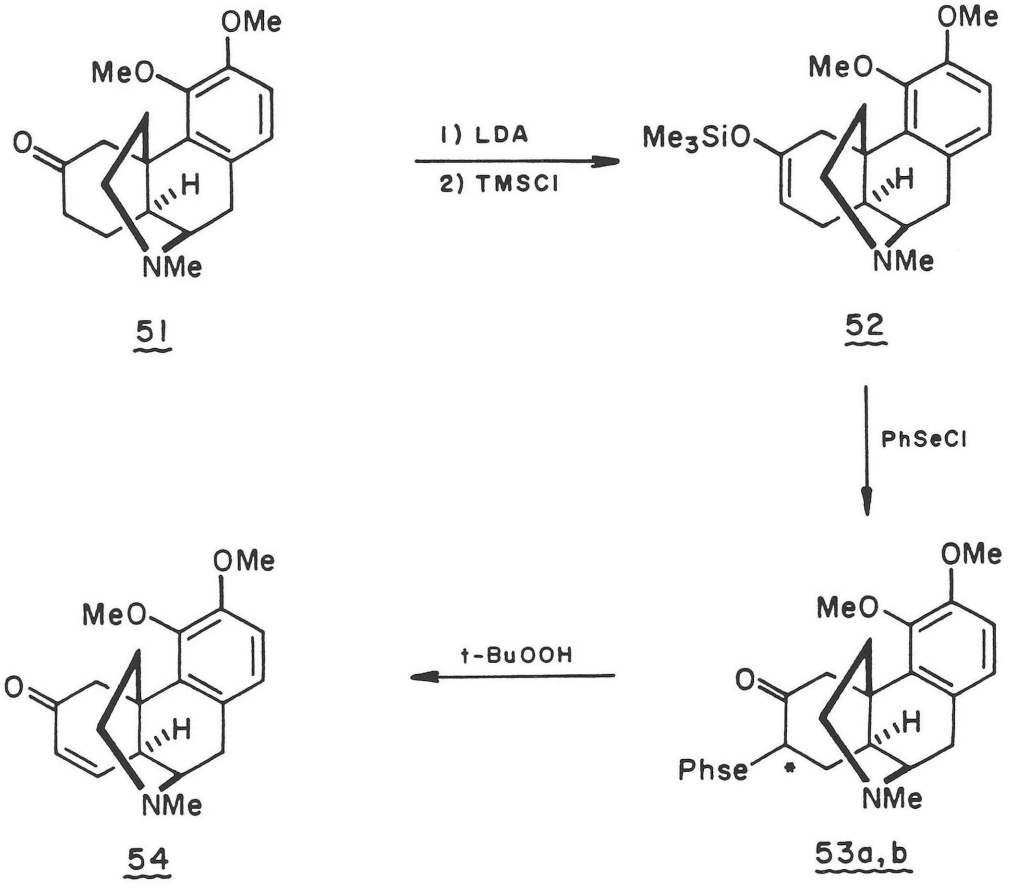
Morphinan 50 corresponds to the product expected from direct aryl cyclization upon reaction of immonium salt 46b with diazomethane. With an authentic sample of 50 in hand, it was possible to isolate approximately 0.1% of 50 out of the mother liquors remaining from recrystallization of aziridinium ion 47.

The small amount of morphinan noted in this instance is in marked constrast to earlier observations (vide supra) that this ring system could be directly constructed from immonium ions related to 11 upon treatment with diazomethane.[3] Again, this observation may be the result of a change in the rotomeric conformation of the aryl group caused by the ortho-methoxy substituent, as discussed above for immonium salt 35.

Intersection with the Gates total synthesis of morphine now required cleavage of 50 to give ketone 51, previously employed by Gates in his pioneering work on the preparation of the natural product.[4a] After investigating a variety of conditions, it was found that 51 was best prepared by Lemieux-Johnson oxidation of 50 using osmium tetroxide (0.05 equiv.) and sodium periodate (3 equiv.) in a solution of aqueous tetrahydrofuran and acetic acid,[35] which gave the Gates ketone 51 in 90% yield.[4a] Having intersected with the Gates approach, it was desired to convert 51 to its C-14 epimer 55 for purposes of structural validation.

Gates has previously demonstrated that C-14 configuration may be equilibrated via enones related to 54, thus producing the 14β-epimer 55 as the thermodynamically favored product.[6] Towards this end, ketone 51 was readily converted to enone 54 (Scheme XIII) by the usual selenylation, selenoxide elimination

Scheme XIII.



sequence.[36] Enolization of 51 at -78°C in tetrahydrofuran with lithium diisopropylamide followed by trapping with

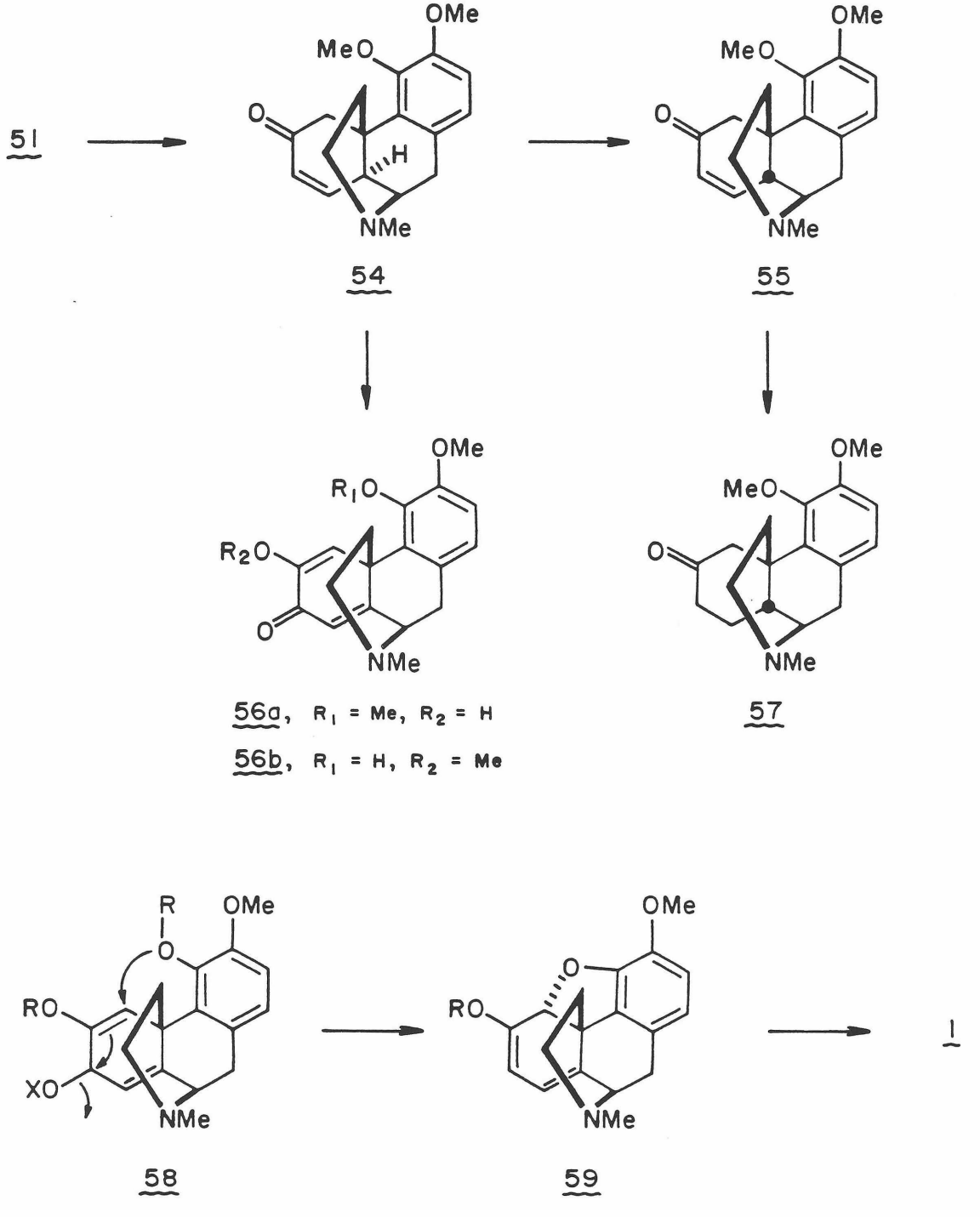
trimethylsilyl chloride provided silylenol ether 52, with no trace of its regioisomer observed.[37] Upon reaction with phenylselenyl chloride in benzene at room temperature, 52 gave 53 as a 1:1 mixture of selenide epimers in 60% yield from 51.[38] In contrast to the reported failure of enone formation via selenoxide elimination in closely related morphinan systems,[4ℓ,39] treatment of 53 with excess tert-butyl hydroperoxide in dichloromethane with one equivalent of trifluoracetic acid gave a 95% yield of enone 54.[36] The success of this reaction may be attributed to the use of tert-butyl hydroperoxide as the oxidizing agent.[36a] We find that this reagent shows no propensity to oxidize the tertiary nitrogen present (even unprotonated),[40] an observation which may be of importance for application to other alkaloidal systems.

Upon investigating the base-catalyzed epimerization of 54, it was found that upon treatment with potassium tert-butoxide, 54 was converted to diosphenol 56a. Further inquiry revealed that this interesting transformation proceeded best when one equivalent of oxygen was bubbled into the reaction mixture via a gas-tight syringe, though excess oxygen was clearly deleterious to the process (in its absence, it did not proceed at all).[41] Additionally, inclusion of sodium bisulfite in the reaction mixture afforded much cleaner product; however, this reagent was not required to effect the transformation. Optimum conditions were thus found to be

two equivalents of potassium tert-butoxide in dimethyl sulfoxide with tert-butyl alcohol along with one equivalent each of oxygen and sodium bisulfite, which gave 56a in 50% yield.[42] The close structural similarity of 56a to salutaridine (56b) suggests that it could be employed in a biogenetically patterned furan ring closure, as illustrated (Scheme XIV) by the known in vivo or in vitro conversion of salutaridinol (58) into thebaine (59),[4c-f,43] the direct biosynthetic precursor to codeine and morphine. However, the potential utility of 56a in such a process remains to be established.

Returning to the question of C14 inversion, treatment of 54 with aqueous potassium hydroxide allowed the anticipated epimerization to take place with a minimum of competing oxidation; providing the desired enone 55 (55:54 = 4:1) along with a small amount of 56a. Immediate hydrogenation of the reaction mixture followed by chromatographic separation afforded 14β-morphinan-6-one 57 in 40% yield along with 10% of 14α-epimer 51. The sample of (±) 57 so produced was found to be identical in all respects [^{1}H-NMR (500 MHz), ^{13}C-NMR, IR, MS, TLC] with a sample of authentic (+) 57 prepared by degration from (-) morphine and generously provided by A. Brossi and H. Schmidhammer.[45]

Scheme XIV.


51
OMe
MeO
O
H
NMe
54
55
R1O
R2O
56a, R1 = Me, R2 = H
56b, R1 = H, R2 = Me
57
R
RO
XO
58
59
1

Experimental Section

Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on either a Varian Associates EM-390 (90 MHz) or a JOEL-FX-90Q (90 MHz) spectrometer and are reported in ppm on the δ scale from internal tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, coupling constant (Hz), and interpretation. 500 MHz ^{1}H magnetic resonance spectra were recorded on a Bruker WM-500 spectrometer at the Southern California Regional NMR Facility. ^{13}C magnetic resonance spectra were recorded on either a JOEL-FX-90Q (22.5 MHz) or a Varian Associates XL-100 (25.5 MHz) and are reported in ppm from tetramethylsilane on the δ scale. Multiplicities are reported using the format given above. Mass spectral analyses were performed by either the California Institute of Technology Microanalytical Laboratory on a Dupont 21-492B spectrometer or by the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln, on a Kratos MS-50 TA spectrometer. Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Flash chromatography was performed according to the general procedure of Still[46], employing either EM Reagents 40-63 μm Silica Gel 60 or Whatman 37-53 μm Silica Gel LPS-2. Medium pressure liquid chromatography was performed using EM Reagents LoBar Silica Gel 60 prepacked columns with a Fluid Metering Inc. Model RP lab pump. Thin-layer chromatography was performed using EM Reagents 0.25 mm Silica Gel 60 plates.

When necessary, solvents and reagents were dried prior to use. Diethyl ether, tetrahydrofuran and benzene were distilled from sodium metal/benzophenone ketyl. Triethylamine, t-butyl alcohol, dimethyl sulfoxide, diisopropylamine, dichloromethane and trimethylsilyl chloride were distilled from calcium hydride. Methanesulfonyl chloride was distilled from phosphorous pentoxide. Potassium t-butoxide and zinc bromide were purified by sublimation. All other reagents were used as received.

1-Methyl-4-phenyl-4(2-propenyl)-1,2,3,4-tetrahydropyridine (11a).[7] To a -10°C solution of 20.50 g (120 mmol) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (10) in 300 mL of anhydrous THF was added, dropwise, 75 mL of 1.6 M n-butyllithium in hexane. After the addition was complete, the mixture was stirred for 10 min. at -10°C, then cooled to -30°C. The resulting deep red solution was transferred via cannula into a -50°C solution of 14.40 g (120 mmol) of allyl

bromide in 250 mL of ethyl ether. The mixture was rapidly warmed to 0°C followed by careful addition of 500 mL of brine. The organic layer was separated, diluted with 2 L of ether, washed with brine, dried (k_2CO_3) and evaporated under vacuum. Distillation afforded 19.50 g (77%) of the title compound: bp 101-105°C/0.1 mm; IR ($CHCl_3$) 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ7.40 (m, 5H, ArH), 6.06 (d, 1H, J = 8 Hz, CH=C<u>H</u>N), 5.52 (m, 1H, C<u>H</u>=CH_2), 5.00 (m, 2H, CH=C<u>H_2</u>), 4.60 (d, 1H, J = 8 Hz, C<u>H</u>=CHN), 2.65 (s, 3H, NC<u>H_3</u>), 2.90-1.97 (m, 6H, aliphatic) ppm.

<u>Anal</u>. calcd. for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.15; H, 8.71; N, 6.34.

<u>1-Methyl-4-phenyl-4-propyl-piperidine (4)</u>.[7] A solution of 1.00 g (4.7 mmol) of <u>11a</u> in 50 mL of ethanol was hydrogenated over 0.5 g 5% Pd/C at 60 psi for 4 h at room temperature. Filtration and evaporation under vacuum gave 1.00 g (100%) of the title compound: ^{1}H-NMR ($CDCl_3$) δ7.28 (m, 5H, ArH), 2.23 (s, 3H, NC<u>H_3</u>), 2.77-0.70 (m, 15H, aliphatic) ppm.

A hydrochloride salt was prepared: mp 208-209 (lit. 204-206).[9]

<u>2-Methyl-5-phenyl-2-azoniabicyclo[3.3.1]non-2-ene perchlorate (12)</u>.[7] A solution of 1.00 g (4.7 mmol) of <u>11a</u> in 2.5 mL of 85% phosphoric acid and 2.5 mL of 90% formic acid was stirred at room temperature for 66 h. The mixture was poured into 180 mL of ice water and basified by dropwise

addition of 50% aqueous sodium hydroxide. The product was extracted into ethyl ether and the combined extracts were washed with brine, dried (k_2CO_3) and evaporated under vacuum: IR ($CHCl_3$) 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ7.32 (m, 5H, ArH), 6.11 (d, 1H, J = 8 Hz, NC<u>H</u>=CH), 4.30 (d, 1H, J = 8 Hz, NCH=C<u>H</u>), 3.19 (m, 1H, NC<u>H</u>$(CH_2)_2$), 2.74 (s, 3H, NC<u>H</u>$_3$), 2.94-1.14 (m, 8H, aliphatic) ppm.

The residue was dissolved in ethyl ether and the perchlorate salt was prepared by dropwise addition of a 1:1 solution of 70% perchloric acid and ethanol, using congo red as the end point indicator. The resulting solid was recrystallized from ethanol to give 1.34 g (91%) of the immonium salt of 12: mp 164-165; IR (kBr) 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ8.97 (s, 1H, C<u>H</u>=N^+), 7.43 (m, 5H, ArH), 4.37 (m, 1H, $(CH_2)_2$C<u>H</u>N^+), 3.28 (m, 2H, C<u>H</u>$_2$CH=N^+), 2.42-1.37 (m, 8H, aliphatic) ppm.

<u>Anal</u>. calcd. for $C_{15}H_{20}NClO_4$: C, 57.42; H, 6.42; N, 4.46. Found: C, 57.22; H, 6.32; N, 4.46.

<u>2-Methyl-5-phenyl-2-azabicyclo[3.3.1]-nonane (13)</u>.[7]

A solution of 12 (1.00 g, 4.7 mmol) in 200 mL of ethanol was hydrogenated for 4 h at 60 psi using 0.5 g of 5% pd/c. Filtration and evaporation of the solvent gave 1.00 g (100%) of the title compound: ^{1}H-NMR ($CDCl_3$) δ7.30-6.43 (m, 5H, ArH), 2.18 (s, 3H, NC<u>H</u>$_3$), 3.00-1.29 (m, 13H, aliphatic) ppm.

Anal. calcd. for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.43; H, 9.70; N, 6.71.

A hydrochloride salt of 14 was prepared and recrystallized from acetone: mp 235-237 (lit. 239-240).[10]

Anal. calcd. for $C_{15}H_{22}NCl$: C, 71.55; H, 8.81, N, 5.56. Found: C, 71.88; H, 8.65; N, 5.64.

2-Methyl-4a-phenyl-2,3,4,4a,5,6-hexahydro-2-pyrindine (14).[7] To a -10°C solution of 25 gm (0.14 mol) of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (10) in 450 mL of dry THF was added, dropwise, 90 mL (0.14 mol) of 1.6 M n-Butyllithium in hexane. The mixture was stirred for 10 min after completion of the addition, then cooled to -30°C. The resulting deep red solution was transferred via cannula into a -50°C solution of 73.30 gm (0.47 mol) of 1-Bromo-3-chloropropane in 300 mL ethyl ether. After the addition, the mixture was rapidly warmed to -20°C and 500 mL of ice cold brine was added. The organic layer was separated and washed with cold water. The product was extracted into three, 400 mL portions of cold 1 N HCl. After washing with ether, the extracts were made basic by dropwise addition of 50% NaOH (keeping the temperature at 0°C). The product was extracted into 2.5 L ether, dried over k_2CO_3 and evaporated to dryness (at 10°C or below). The residue was immediately dissolved in 2.5 L acetonitrile; 52.50 gm (0.35 mol) sodium iodide was added and the mixture was refluxed for 24 h. At the end of this period, the solvent was evaporated and the residue

partitioned between 800 mL 1 N NaOH and 1 L of ether, with vigorous stirring for 45 min. The ether layer was separated, washed with brine, dried (k_2CO_3), and evaporated. Distillation gave 21.50 gm (70%) of enamine 14: bp 110-112°C (0.075 mm); IR ($CHCl_3$) 1657 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ7.34 (m, 5H, ArH), 5.93 (s, 1H, N-C<u>H</u>=C), 2.58 (s, 3H, N-C<u>H</u>$_3$), 2.91-1.17 (m, 10H, aliphatic) ppm.

<u>Anal</u>. calcd. for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.74; H, 8.72; N, 6.28.

<u>cis-2-Methyl-4a-phenyl-octahydro-2-pyrindine (15)</u>.[7] A solution of 0.50 gm (2.3 mmol) of enamine 14 and 0.5 gm of 5% Pd/C in 50 mL ethanol was hydrogenated at 60 psi for 4 h at room temperature. Filtration and evaporation gave 0.50 gm (quantitative) of the title compound (15): ^{1}H-NMR ($CDCl_3$) δ7.28-7.00 (m, 5H, ArH), 2.24 (s, 3H, N-C<u>H</u>$_3$), 2.76-1.37 (m, 13H, aliphatic) pp; ^{13}C-NMR ($CDCl_3$) δ14.82 (s), 128.0 (d), 126.5 (d), 125.4 (d), 57.0 (t), 52.5 (t), 46.7 (s), 46.6 (q), 42.6 (d), 37.6 (t), 34.4 (t), 28.0 (t), 20.8 (t) ppm.

The HBr salt of 16 was prepared and recrystallized from 1.5:1 isopropyl ether-isopropanol: mp 209-210°C.

<u>Anal</u>. calcd. for $C_{15}H_{22}NBr$: C, 60.81; H, 7.49; N, 4.73. Found: C, 60.55; H, 7.49; N, 4.57.

<u>trans-2-Methyl-4a-phenyl-octahydro-2-pyrindine (16)</u>.[7] 5.00 gm (3 mmol) of enamine 14 and 0.50 gm PtO_2 in 50 mL ethanol was hydrogenated at 60 psi for 4 h at room temperature.

The mixture was filtered and evaporated to dryness. NMR and HPLC (Waters Associates μPorasil 4mm x 30 cm column, 97:3 $CHCl_3/CH_3OH$ and 0.01% $NH_2CH_2CH_2OH$, flow rate 100 mL/h) indicated a mixture of approximately 40% cis 15 and 60% 16. The mixture was dissolved in ether and made acidic with excess ethereal HBr. After evaporation, the residue was recrystallized from 30 mL isopropanol and 70 mL isopropyl ether, yielding 2.60 gm (38%) of cis 15 · HBr.

The filtrate was evaporated and the residue taken up in water. This was made strongly basic with 1 N NaOH. The product was extracted into ether, washed with water, dried (k_2CO_3), and evaporated to give 2.57 gm crude trans 16. The product was further purified by conversion to its picrate salt (2.76 gm picric acid) and recrystallized from ethanol to give 2.70 gm (26%) 16 · picrate: mp 167-168°C.

Anal. calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44; N, 12.61. Found: C, 56.99; H, 5.65; N, 12.46.

Stirring over NH_4OH and extraction into ether afforded the free base of 16 (NMR and HPLC confirmed the absence of cis 15): ^{1}H-NMR ($CDCl_3$) δ7.54-7.04 (m, 5H, ArH), 2.27 (s, 3H, N-CH_3), 3.14-1.30 (m, 13H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ145.2 (s), 137.9 (d), 129.0 (d), 127.6 (d), 125.1 (d), 55.4 (t), 52.0 (t), 49.2 (d), 47.8 (s), 45.9 (a), 43.1 (t), 41.1 (t), 25.5 (t), 21.1 (t) ppm.

The maleate salt of 16 was prepared and recrystallized from ethyl acetate: mp 113-114°C.

Anal. calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.66; H, 7.82; N, 3.98.

1-Methyl-4-(4-chlorobutyl)-4-phenyl-1,2,3,4-tetrahydropyridine (11c). To a -10°C solution of 5 gm (28.9 mmol) tetrahydropyridine 11 in 100 mL dry THF was added 20 mL (32 mmol) of 1.6 M n-butyllithium, dropwise. Ten min. after the addition was complete, the solution was cooled to -30°C and added, via cannula, to a -78°C solution of 17 gm (99 mmol) 1-bromo-4-chlorobutane in 60 mL ethyl ether. The reaction was warmed to -20°C and 100 mL ice cold brine added. The organic layer was separated and washed with cold water, followed by extraction with three, 90 mL portions of cold 1 N HCl. After washing once with ether, the combined acid extracts were made basic by addition of 50% sodium hydroxide, maintaining the temperature at 0°C. The product was extracted into three, 200 mL portions of ether, dried (k_2CO_3) and evaporated under vacuum to give 7.10 gm crude tetrahydropyridine 11c: IR ($CHCl_3$) 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ7.43-6.97 (m, 5H, ArH), 5.93 (d, 1H, J = 8.4 Hz, N-C<u>H</u>=C), 4.53 (d, 1H, J = 8.4 Hz, N-C=C<u>H</u>), 2.53 (s, 3H, N-C<u>H</u>$_3$), 3.53-1.00 (m, 12H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ149.4 (s), 136.7 (d), 127.9 (d), 127.2 (d), 125.4 (d), 102.5 (d), 46.3 (t), 44.7 (t), 42.7 (a), 42.4 (t), 40.0 (s), 37.1 (t), 33.3 (t), 21.6 (t) ppm.

The perchlorate salt was prepared by adding a 1:1 solution of 60% perchloric acid and ethanol to the enamine 11c in

ether. Recrystallization of the resulting precipitate from ethanol gave 7.4 gm (70%) of yellow crystals: mp 170-172°C.

Anal. calcd. for $C_{16}H_{23}NCl_2O_4$: C, 52.75; H, 6.36; N, 3.97. Found: C, 52.77; H, 6.12; N, 3.73.

N-Methyl-4a-phenyl-3,4,5,6,7,8-octahydroisoquinoline (17). To a -10°C solution of 15 g (86 mmol) of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (10) in 250 mL of anhydrous THF was added 60 mL (90 mmol) of 1.50 M n-butyllithium in hexane. Ten min after the addition was complete, the solution was cooled to -30°C and added to a -78°C solution of 49 g (286 mmol) of 1-bromo-4-chlorobutane in 180 mL of ethyl ether over 30 min. The reaction was rapidly warmed to -20°C and 300 mL of ice cold brine added. The organic layer was separated and washed with cold water, followed by extraction with three, 250-mL portions of cold 1 N aqueous hydrochloric acid. After washing once with ethyl ether, the combined acid extracts were made basic by addition of 50% aqueous sodium hydroxide solution, while maintaining the temperature at 0°C. The product was extracted into three, 600-mL portions of ethyl ether, dried over anhydrous potassium carbonate and the solvent was carefully evaporated under vacuum, keeping the temperature at 10°C or below. The residue was immediately dissolved in 1.5 L of acetonitrile, 32 g (214 mmol) of sodium iodide was added, and the reaction was refluxed for 24 h under an argon atmosphere. After removing the solvent under vacuum, the residue was partitioned

between 500 mL 1 N aqueous sodium hydroxide and 600 mL of ethyl ether. The ether layer was separated, washed with brine, dried over anhydrous potassium carbonate and the solvent removed under vacuum. Distillation at 100°C (0.025 mm) gave 11.7 g (60%) of colorless oil: IR ($CHCl_3$) 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ7.36 (m, 5H, ArH), 5.88 (s, 1H, =CH-), 2.34 (s, 3H, N-NCH_3), 2.82-1.00 (m, 12H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ147.6, 132.8, 127.1, 125.1, 113.3, 45.8, 42.9, 41.5, 39.9, 30.3, 28.3, 22.9 ppm.

Anal. calcd. for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.26; H, 9.12; N, 6.23.

N-Methyl-4a-phenyl-3,4,5,6,7,8,8a-trans-octahydroisoquinoliumperchlorate (20). To a solution of 100 mg (0.44 mmol) octahydroisoquinoline 18 in 3 mL anhydrous ethyl ether was carefully added ethereal perchloric acid, until the solution tested blue on congo red paper (pH ~3). Evaporation of the solvent under vacuum gave a colorless oil: IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.91 (br, 1H, +N=CH-), 7.59-6.95 (m, 5H, ArH), 3.83 [s, 3H, =N(CH_3)-], 3.31-1.05 (m, 13H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 182.3, 139.0, 129.3, 127.1, 126.7, 51.3, 48.7, 47.0, 40.4, 38.8, 37.2, 26.4, 21.6 ppm.

N-Methyl-4a-phenyl-3,4,6,7,8,8a-cis-octahydroisoquinoliniumperchlorate (21). To a solution of 100 mg (0.44 mmol) octahydroisoquinoline 17 in 3 mL of ethyl ether was carefully

added a mixture of 60% aqueous perchloric acid diluted with an equal part of absolute ethanol, until the solution tested blue on congo red paper (pH ~3). The solution was evaporated under a stream of nitrogen until most of the ether was removed. Additional ethanol was added and the solution was warmed on a steam bath until the oil layer dissolved. Upon standing for several days, there was obtained 137 mg (95%) of white crystalline perchlorate: mp 162-163°C; IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.91 (br, 1H, +N=C<u>H</u>-), 7.29 (m, 4H, ArH), 3.71 [s, 3H, =N(C<u>H</u>$_3$)-], 2.69-1.05 (m, 13H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 182.2, 143.6, 129.2, 127.1, 125.2, 51.0, 49.1, 42.5, 36.1, 34.1, 31.1, 25.6, 24.4, 21.2 ppm.

<u>Anal</u>. calcd. for $C_{16}H_{22}N\cdot ClO_4$: C, 58.63; H, 6.76; N, 4.27. Found: C, 58.24; H, 6.69; N, 4.15.

<u>trans-2-Methyl-4a-phenyl-decahydroisoquinoline (18)</u>. <u>Method A.</u>[7] Enamine <u>17</u> (0.50 g, 2.2 mmol) in 50 mL ethanol was hydrogenated for 4 h at room temperature using 0.5 g PtO_2 and 60 psi hydrogen. The mixture was filtered and evaporated to give 0.50 g (100%) of the title compound, which crystallized on standing: mp 67-69°C; IR ($CHCl_3$) 3000-2800, 1590, 1460, 1442 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.64-7.07 (m, 5H, ArH), 2.20 (s, 3H, NC<u>H</u>$_3$), 2.84-0.88 (m, 15H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 145.0 (s), 130.0 (d), 127.6 (d), 124.9 (d), 58.5 (t), 52.0 (t), 46.4 (d), 46.2 (a), 43.7 (t), 41.4 (s), 27.2 (t), 27.0 (t), 22.2 (t) ppm.

Anal. calcd. for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found: C, 83.64; H, 9.85; N, 5.85.

An HBr salt of 18 was prepared and recrystallized from ethyl acetate-ethanol: mp 210-212°C.

Anal. calcd. for $C_{16}H_{24}NBr$: C, 61.94; H, 7.80; N, 4.51. Found: C, 61.69; H, 7.69; N, 4.47.

A picrate salt of 18 was prepared and recrystallized from ethanol: mp 218.5-220 (Lit. 218.5-220°C).[14]

Anal. calcd. for $C_{22}H_{26}N_4O_7$: C, 57.76; H, 5.51; N, 12.25. Found: C, 57.50; H, 5.69; N, 12.44.

Method B. To a 0°C solution of 200 mg (0.61 mmol) of trans-immonium salt 20 in 20 mL of methanol was added 116 mg (3.05 mmol) of sodium borohydride. After 30 min, the excess borohydride was quenched by the addition of 10 mL of 1 N aqueous hydrochloric acid. The residue remaining after evaporation of the solvent under vacuum was taken up in 30 mL of 1 N aqueous hydrochloric acid. After washing with ethyl ether, the acid solution was neutralized by careful addition of 50% aqueous sodium hydroxide. This suspension was extracted with three, 20 mL portions of dichloromethane. The combined extracts were washed with brine, dried (k_2CO_3) and evaporated under vacuum to give 140 mg (100%) of the title compound as a colorless oil. The ^1H and ^{13}C-NMR were identical with material prepared by Method A.

cis-2-Methyl-4a-phenyl-decahydroisoquinoline (19). Method A.[7] Enamine 17 (2.00 g, 8.8 mmol) in 100 mL of acetic acid was hydrogenated at 60°C and 60 psi for 15 h over 0.20 g PtO_2. The mixture was then filtered and evaporated. The residue was dissolved in water and made strongly basic with 1 N sodium hydroxide. The product was extracted into ether, washed with brine, dried over k_2CO_3 and evaporated under vacuum to give 2.00 g (100%) of the title compound. Gas chromatography (OV-1, 150°-260°C at 10°/min) showed very little of the trans isomer present: ^{1}H-NMR ($CDCl_3$) δ 7.17-7.67 (m, 5H, ArH), 2.28 (s, 3H, NCH_3), 2.80-1.06 (m, 15H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 148.5 (s), 128.3 (d), 126.1 (d), 125.3 (d), 57.5 (t), 52.6 (t), 46.6 (q), 39.5 (s), 37.3 (d), 26.9 (t), 22.5 (t) ppm.

A HBr salt of 19 was prepared and recrystallized from acetone-isopropanol: mp 219.5-221.5°C (lit. 222-224°C).[14]

A picrate salt of 20 was prepared and recrystallized three times from ethanol: mp 160-162 (lit. 144-146).[14]

Method B. The title compound was prepared from cis-immonium salt 21 by the same procedure (Method B) as trans-2-methyl-4a-phenyl-decahydroisoquinoline (18) in 95% yield. The ^{1}H and ^{13}C-NMR spectra were identical with material prepared by Method A.

trans-1α,2-Dimethyl-4aα-phenylperhydroisoquinoline (23). To a -78°C solution of 2.18 g (6.66 mmol) of trans-immonium salt 20 in 25 mL of anhydrous tetrahydrofuran was added 15 mL

(41 mmol) of 2.75 M methylmagnesium iodide in ether. After warming to room temperature, the reaction was stirred for 4.5 h. Excess Grignard reagent was quenched by the addition of 50 mL of 1 N aqueous tetrasodium ethylenediaminetretracetate (EDTA). This mixture was extracted with three, 50 mL portions of dichloromethane. After washing with brine, the combined extracts were dried (k_2CO_3) and the solvent evaporated under vacuum, to give a 3:1:1 mixture of 23:24:17, respectively. Chromatography at medium pressure over silica gel (EM Laboratories, size B LoBar column; eluted with hexane and chloroform, 80:20, saturated with ammonia) afforded 920 mg (57%) of the title compound as a colorless oil: IR ($CHCl_3$) 3100-2800, 1490, 1455, 1375, 1260, 1180, 1160, 1028, 1014 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.56-7.01 (m, 5H, ArH), 2.61 (d, d, 1H, J = 10 Hz, J = 6 Hz, NC<u>H</u>CH_3), 2.22 (s, 3H, NC<u>H</u>$_3$), 1.14 (d, 3H, J = 6 Hz, NCHC<u>H</u>$_3$), 2.51-1.05 (m, 13H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 145.3 (s), 130.1 (d), 127.5 (d), 124.9 (d), 59.2 (d), 52.6 (t), 52.2 (a), 44.2 (d), 43.8 (t). 43.5 (t), 42.5 (s), 27.7 (t), 24.5 (t), 21.7 (t), 17.9 (a) ppm.

<u>Exact mass</u> calcd. for $C_{17}H_{25}N$: 243.199. Found: 243.199.

<u>cis</u>-1α,2-Dimethyl-4aα-phenylperhydroisoquinoline (24). The title compound was prepared by the same procedure as used above for <u>trans</u>-dimethylperhydroisoquinoline 23. Starting with 200 mg (0.610 mmol) of <u>cis</u>-immonium salt 21, 140 mg (95%) of

the title compound was obtained as a colorless oil: IR ($CHCl_3$) 3100-2800, 1490, 1462, 1442, 1362, 1262, 1242, 1149, 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.52 (m, 5H, ArH), 2.61 (dd, 1H, J = 10 Hz, J = 5 Hz, NC<u>H</u>CH_3), 2.31 (s, 3H, NC<u>H</u>$_3$), 1.18 (d, 3H, J = 5 H, NCHC<u>H</u>$_3$), 2.28-1.05 (m, 13H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 148.7 (s), 128.3 (d), 125.8 (d), 125.2 (d), 57.0 (d), 52.8 (s), 43.7 (a), 43.5 (d), 42.5 (t), 40.8 (t), 27.5 (t), 24.1 (t), 22.6 (t), 20.7 (t), 17.2 (a) ppm.

<u>Exact mass</u> calcd. for $C_{17}H_{25}N$: 243.199. Found: 243.200.

<u>(4a , 8a , 8b)-2-Methyl-4a-phenyldecahydroazirino [1,2,-a]isoquinolinium perchlorate (25)</u>. To a 0°C solution of 460 mg (1.40 mmol) of <u>cis</u>-immonium perchlorate <u>21</u> in 20 mL of anhydrous dichloromethane was added ethereal diazomethane,[47] dropwise, until the yellow color persisted. Immediate gas evolution was observed. The cooling bath was removed and excess diazomethane evaporated under a stream of nitrogen. When the yellow color had dispersed, the remaining solvent was evaporated under vacuum, to give 457 mg of a white solid. ^{13}C-NMR showed this to be a mixture of aziridinium salt <u>25</u> and morphinan <u>27</u> in a ratio of 85:15, as determined by ^{1}H-NMR integration of the NCH_3 signals. Recrystallization from benzene/acetone gave 407 mg (85%) of the title compound as white needles: IR (CH_2Cl_2) 3060-2870, 1446, 1090 cm^{-1}; ^{1}H-NMR (CD_3CN) δ 7.46-7.05 (m, 5H, ArH), 3.63 (m, 2H, NC<u>H</u>$_2$),

3.19 (s, 3H, $NC\underline{H}_3$), 3.13-1.53 (m, 14H, aliphatic) ppm; ^{13}C-NMR (CD_3CN) δ 145.0 (s), 129.4 (d), 126.9 (d), 126.5 (d), 51.5 (a), 51.0 (d), 50.9 (t), 43.6 (t), 36.7 (s), 35.4 (d), 33.5 (t), 31.2 (t), 26.9 (t), 21.8 (t), 21.6 (t) ppm.

Anal. calcd. for $C_{17}H_{24}NO_4Cl$: C, 59.74; H, 7.08; N, 4.10. Found: C, 59.76; H, 6.94; N, 3.99.

(1α, 4aα, 8aα)-1-(Chloromethyl)-2-methyl-4a-phenyldecahydroisoquinoline (26). A room temperature solution of 1.10 gm of an 85:15 mixture of aziridinium salt 25 (2.86 mmol) and N-methylmorphinan 27 (0.5 mmol), and 685 mg (16.3 mmol) of lithium chloride in 30 mL acetonitrile was stirred for 1 h. The solvent was evaporated under vacuum and the residue taken up in 50 mL dichloromethane. This solution was washed once with 30 mL water, dried (Na_2SO_4), and evaporated under vacuum, to give 880 mg of a colorless oil. Separation by flash chromatography (3:1, hexane and ethyl acetate, 2.5% triethylamine) gave 770 mg (97%) of the title compound and 73 mg of morphinan 27. The β-chloroamine 26 was induced to crystallize from a solution of hexane placed in a freezer for several weeks: mp 68-70°C; IR ($CHCl_3$) 3000-2800, 1462, 1152, 1090 cm^{-1}; ^{1}H-NMR (CD_3CN) δ 7.49-6.98 (m, 5H, aromatic), 3.73 (m, 2H, $C\underline{H}_2Cl$), 2.28 (s, 3H, $NC\underline{H}_3$), 3.32-1.16 (m, 14H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 148.2 (s), 128.4 (d), 125.8 (d), 125.4 (d), 61.8 (d), 52.5 (t), 43.4 (t), 43.1 (d), 40.4 (s), 37.8 (a), 23.7 (t), 22.4 (t), 21.1 (t) ppm.

Anal. calcd. for $C_{17}H_{24}NCl$: C, 73.49; H, 8.71; N, 5.04. Found: C, 73.40; H, 8.64; N, 4.95.

(14α)-17-Methylmorphinan (27). A solution of 385 mg of an 85:15 mixture of β-chloroamine 26 and morphinan 27 (1.20 mmol of 26) and 800 mg (6 mmol) of aluminum trichloride in 20 mL of anhydrous benzene was refluxed for 2 h. Upon cooling to room temperature, 20 mL 10% aqueous sodium hydroxide was added and the mixture was stirred for 15 min. The aqueous phase was separated (reserving the organic phase) and extracted with two, 20 mL portions of dichloromethane. The combined organic extracts were washed once with 30 mL water, dried (Na_2SO_4), and evaporated to give 326 mg of a brown oil. Flash chromatography (1:3, ethyl acetate and hexane, 1.5% triethylamine) afforded 210 mg (60%) of the title compound as a colorless oil: IR ($CHCl_3$) 3060-2800, 1585, 1446, 1376, 1280, 1156 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.28-7.03 (m, 4H, ArH), 2.31 (s, 3H, NCH_3), 3.26-0.83 (m, 16H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 146.3 (s), 137.5 (s), 127.5 (d), 125.6 (d), 125.4 (d), 123.9 (d), 58.8 (d), 47.5 (t), 43.1 (a), 42.1 (d), 36.0 (t), 34.4 (s), 31.7 (t), 27.7 (t), 26.7 (t), 26.2 (t), 22.4 (t) ppm.

A picrate salt was prepared: 210-213°C (lit. 210-212.5).[22]

Anal. calcd. for $C_{23}H_{26}N_4O_7$: C, 58.72; H, 5.57; N, 11.91. Found: C, 58.52; H, 5.46; N, 11.79.

A methiodide salt was also prepared: mp 233-236 (lit. 233-236).[22]

4-(2,3-Dimethoxyphenyl)-4-hydroxyl-1-methylpiperidine (29). To 35 g (254 mmol) of o-dimethoxybenzene in 250 mL of anhydrous ethyl ether at room temperature was added dropwise, 115 mL (203 mmol) of 1.75 M n-butyllithium in hexane. A yellow solution was formed initially, followed by precipitation of o-dimethoxyphenyllithium. After stirring for 2 h, the reaction was cooled to -10°C and 21 g (186 mmol) of 1-methyl-4-piperidone in 100 mL of anhydrous ethyl ether was added dropwise and stirred for 6 h. The excess lithium reagent was quenched by addition of 150 mL of H_2O. The organic layer was separated and extracted with three, 150-mL portions of 1 N aqueous hydrochloric acid. The combined acid extracts were washed with 200 mL of ethyl ether, cooled to 0°C and neutralized by the dropwise addition of 50% aqueous sodium hydroxide. The resulting suspension was extracted with three, 300-mL portions of dichloromethane. The combined extracts were washed with water followed by brine, dried over anhydrous potassium carbonate and the solvent removed under vacuum yielding 25 g of crude alcohol, as a mixture with 1-methyl-4-piperidone as evidenced by NMR, IR and TLC. Recrystallization from hexane afforded 21.0 g (83.5 mmol, 45%) of the alcohol as a white crystalline solid: mp 72-73°C; ^{1}H-NMR ($CDCl_3$) δ 7.07-6.73 (m, 3H, aromatic), 4.19 (s, 1H, OH), 3.93 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.30 (s, 3H, N-CH_3), 2.80-1.73 (broad m, 8H) ppm; IR ($CHCl_3$) 3520, 1590, 1575, 1490 cm^{-1}.

Exact mass calcd. for $C_{14}H_{21}NO_3$: 251.152. Found: 251.153.

N-Methyl-4-(2,3-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine (30). A solution of 20 g (80 mmol) of N-methyl-4-(2,3-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine (29) and 46 g (2 mmol) of p-toluenesulfonic acid in 600 mL toluene was refluxed with azeotropic removal of water for 2 h. The reaction mixture was extracted with four, 250 mL portions of 1 N aqueous hydrochloric acid. The combined extracts were washed with 500 mL ethyl ether, neutralized by careful addition of 50% aqueous sodium hydroxide, and extracted with four, 250-mL portions of dichloromethane. After washing once with brine, and drying over k_2CO_3 the dichloromethane was evaporated under vacuum to give a yellow oil. Molecular distillation at 98°C (0.004 mm) yielded 17.5 g (95%) of a colorless oil: IR ($CHCl_3$) 1590, 1575, 1460, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.81 (m, 3H, aromatic), 5.75 (t, 1H, J = 0.5 Hz, =C<u>H</u>-), 3.80 (s, 3H, OC<u>H</u>$_3$), 3.71 (s, 3H, OC<u>H</u>$_3$), 3.11 (m, 2H, aliphatic), 2.62 (m, 4H, aliphatic), 2.4 (s, 3H, NC<u>H</u>$_3$) ppm.

Exact mass calcd. for $C_{14}H_{19}NO_2$: 233.1417. Found: 233.1409.

N-Methyl-4a-(2,3-dimethoxyphenyl)-3,4,5,6,7,8-octahydroisoquinoline (33). The title compound was prepared by the same procedure described for octahydroisoquinoline (17).

Following this procedure, 12 g (30) gave 8 g (54%) of 33 after bulb-to-bulb distillation at 150°C (0.004 mm): IR ($CHCl_3$) 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.84 (m, 3H, aromatic), 5.75 (s, 1H, =CH-), 3.83 (s, 6H, OCH_3), 2.51 (s, 3H, NCH_3), 2.91-1.05 (m, 12H, aliphatic) ppm.

Exact mass calcd. for $C_{18}H_{25}NO_2$: 287.189. Found: 287.188.

N-Methyl-4a-(2,3-dimethoxyphenyl)-3,4,5,6,7,8,8a-cis-octahydroisoquinolinium perchlorate (35). The title compound was prepared by the same procedure as that described for perchlorate (21), with one modification. After dissolving the initially formed salt in hot ethanol, it was necessary to maintain the solution at 50°C overnight while the cis-immonium salt formed. Upon cooling to room temperature, the product was collected by filtration. Starting with 150 mg (0.52 mmol) of (33), there was obtained 195.5 mg (97%) of white crystalline (35): mp 169-170°C; IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H, +N=CH-), 7.19-6.68 (m, 3H, aromatic), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.71 (s, 3H, NCH_3), 3.5-1.05 (m, 13H, aliphatic) ppm; ^{13}C-NMR (CD_3CN) δ 182.2, 154.5, 148.0, 136.6, 124.8, 120.2, 113.2, 61.0, 56.4, 51.8, 49.2, 43.2, 37.7, 33.7, 28.0, 26.7, 25.1, 22.2 ppm.

Anal. calcd. for $C_{18}H_{26}ClNO_6$: C, 55.74; H, 6.76; N, 3.61. Found: C,55.51; H, 6.84; N, 3.57.

(4aα, 8aα, 8bβ)-4a-(2,3-Dimethoxyphenyl)-2-methyl-decahydroazirino[1,2-a]isoquinolinium perchlorate (36). To a 0°C solution of 1.33 g (3.43 mmol) of cis-immonium perchlorate 35 in 50 mL of dichloromethane was added ethereal diazomethane,[47] dropwise, until the yellow color persisted. Immediate gas evolution was observed. The cooling bath was removed and excess diazomethane evaporated under a stream of nitrogen, until the yellow color dispersed. Evaporation under vacuum of the remaining solvent gave 1.38 g (100%) of the title compound as a white crystalline solid: mp 184-186°C; ^{1}H-NMR (CD_3CN) δ 6.94 (m, 3H, ArH0, 3.81 (s, 6H, OCH_3), 3.31 (s, 3H, NCH_3), 3.78-1.50 (m, 16H, aliphatic) ppm; ^{13}C-NMR (CD_3CN) δ 154.7, 149.2, 137.7, 124.4, 121.0, 112.9, 60.7, 56.4, 52.3, 51.1, 45.0, 37.9, 35.2, 32.8, 31.3, 27.5, 22.8, 22.1 ppm.

Anal. calcd. for $C_{19}H_{28}NClO_6$: C, 56.80; H, 7.03; N, 3.49. Found: C, 56.92; H, 6.99; N, 3.85.

(1α, 4aα, 8aα)-1-Carboxaldehyde-2-methyl-4a-(2,3-dimethoxyphenyl)-decahydroisoquinoline (37). A room temperature solution of 150 mg (0.373 mmol) of aziridinium perchlorate 36 and 2 mL of anhydrous dimethyl sulfoxide in 10 mL of anhydrous benzene was stirred for 24 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture extracted with three, 15 mL portions of dichloromethane. The combined extracts were washed with five, 15 mL portions of water, dried

(Na_2SO_4), and evaporated under vacuum to give 125 mg (95%) of the title compound: IR ($CHCl_3$) 3000-2800, 1722, 1590, 1570, 1460, 1418, 1288, 1260, 1058, 1000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.36 (m, 1H, CHO), 6.99-6.69 (m, 3H, ArH), 3.82 (s, 6H, OCH_3), 2.22 (s, 3H, NCH_3), 3.03-1.23 (m, 14H, aliphatic) ppm; ^{13}C-NMR (C_6D_6) δ 203.1, 154.4, 149.7, 140.0, 123.5, 120.8, 111.4, 71.8, 59.8, 55.4, 50.3, 44.9, 40.9, 40.4, 34.9, 24.7, 23.2, 21.8 ppm.

Exact mass calcd. for $C_{19}H_{27}NO_3$: 317.199. Found: 317.199.

(10β, 14α)-3,4-Dimethoxy-10-hydroxy-17-methylmorphinan (38). To a room temperature solution of 144.8 mg (0.457 mmol) of carboxaldehyde 37 in 10 mL of anhydrous benzene was added 280 μL (2.28 mmol) of boron trifluoride etherate. After stirring for 1 min, the reaction was quenched by addition of 10 mL of 10% aqueous sodium hydroxide. The mixture was stirred for 15 min, then the aqueous phase was extracted with three, 15 mL portions of dichloromethane. The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated under vacuum. Flash chromatography (7:3, hexane and ethyl acetate, 2.5% triethylamine) afforded 130 mg (90%) of the title compound as a colorless oil: IR ($CHCl_3$) 3300, 3000-2800, 1590, 1570, 1475, 1288, 1270, 1105, 1078, 1060, 1046, 1040, 1010, 1000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.29 (d, 1H, J = 9 Hz, ArH), 6.84 (d, H, J = 9 Hz, ArH),

4.57 (d, 1H, J = 6 Hz, ArCHOH), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.67 (br s, 1H, OH), 2.73 (s, 3H, NCH_3), 3.07-1.03 (m, 14H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 152.3 (s), 146.9 (s), 138.0 (s), 135.5 (s), 123.6 (d), 111.1 (d), 68.3 (d), 63.3 (d), 60.4 (a), 55.7 (a), 47.2 (d), 46.6 (t), 42.9 (a), 38.6 (t), 35.7 (t), 29.6 (t), 26.7 (t), 23.8 (t), 22.9 (t), ppm.

Exact mass calcd. for $C_{19}H_{27}NO_3$: 317.199. Found: 317.198.

(14α)-3,4,-Dimethoxy-17-Methylmorphinan (39). To a room temperature solution of 100 mg (0.313 mmol) of carboxaldehyde 37 in 10 mL of anhydrous benzene was added 100 μL (0.813 mmol) of boron trifluoride etherate, followed by 60 μL (0.377 mmol) of triethylsilane. After heating at reflux for 2h, the reaction was cooled to room temperature and 10 mL of 10% aqueous sodium hydroxide added. The mixture was stirred for 15 min, then the aqueous phase was extracted with three, 15 mL portions of dichloromethane. The combined organic extracts were washed once with water, dried (Na_2SO_4) and evaporated under vacuum. Flash chromatography of the residue (7:3, hexane and ethyl acetate, 2.5% triethylamine) gave 75 mg (80%) of the title compound as a colorless oil: IR ($CHCl_3$) 3000-2800, 1575, 1460, 1420, 1284, 1260, 1218, 1060, 1002 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 6.75 (d, 1H, J = 9 Hz, ArH), 6.56 (d, 1H, J = 9 Hz, ArH), 3.71 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.21 (s, 3H, NCH_3), 3.30 (m, 16H, aliphatic) ppm.

Exact mass calcd. for $C_{19}H_{27}NO_2$: 301.204. Found: 301.204.

A perchlorate salt was prepared and found to be a monohydrate: mp 121-122.5.

Anal. calcd for $C_{19}H_{30}NClO_7$: C, 54.35; H, 7.15; N, 3.33. Found: C, 54.03; H, 7.08; N, 3.33.

1,1-bis-hydroxymethylcyclopropane (41). To a -10°C solution of 100 gm (769 mmol) of cyclopropane-1,1-dicarboxylic acid in 1 L of anhydrous tetrahydrofuran was added, dropwise, 2.2 L of 1 M borane • THF complex, over a 2 h period.[28] The cooling bath was removed, allowing the mixture to warm to room temperature. After 6 h, the mixture was again cooled to 0°C and 1.5 L of methanol was slowly added (caution: vigorous gas evolution). A distillation head was placed on the reaction vessel and 2.8 L of solvent was distilled off, to concentrate the reaction volume to approximately 1.9 L. Five additional times, 1.5 L methanol was added and distilled off (to remove $B(OCH_3)_3$). Evaporation of the remaining solvent and distillation gave 75.14 gm (96%) of the title compound, whose physical properties are identical to those reported:[48] bp 125°C/10 mm; IR (CCl_4) 3400, 3080, 3007 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.08 (br s, 2H, O<u>H</u>), 3.53 (br s, 4H, C<u>H</u>$_2$OH), 0.49 (s, 4H, -C<u>H</u>$_2$-), ppm; ^{13}C-NMR ($CDCl_3$) δ 68.0, 24.2, 8.6 ppm.

1,1-bis-bromomethylcyclopropane (42). To a 0°C solution of 68 g (664 mmol) of 1,1-bis-hydroxymethylcyclopropane (41)

in 1 L of dichloromethane was slowly added 75 mL (2.6 g, 800 mmol) of phosphorous tribromide dissolved in 200 mL of dichloromethane, followed by 10 mL (15 g, 90 mmol) of 48% aqueous hydrobromic acid. After stirring for 96 h at room temperature, quenching was accomplished by the addition of 1 L of water and sufficient aqueous sodium hydroxide to adjust the pH $\geq$8. This mixture was stirred for 30 min, then the aqueous phase was extracted with two, 500 mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum. The residue was taken up in 1.5 L of ethyl ether, the solution saturated with HBr gas, and stirred for 8 h; 300 mL of water was added and the mixture basified with 50% aqueous sodium hydroxide. Extraction of the aqueous phase with two, 500 mL portions of ether, washing of the combined extracts with brine, drying ($MgSO_4$), evaporation and distillation under vacuum gave 112.9 g (75%) of the title compound whose physical properties are identical with those reported:[49] bp 67°C/5 mm; IR (CH_2Cl_2) 3050-2900, 1428, 1328, 1254, 1222, 1054, 1021, 966, 958, 879 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.50 (s, 4H, $C\underline{H}_2Br$), 0.90 (s, 4H, $-C\underline{H}_2-$) ppm.

4-Bromo-2-bromomethyl-1-butene (8). A solution of 28.0 g (124 mmol) of sublimed zinc bromide and 28.0 g (122 mmol) of 1,1-bis-bromomethylcyclopropane (42) in 400 mL of anhydrous benzene was refluxed for 24 h. Upon cooling to room temperature, the solution was filtered through a celite pad and

washed with three, 250 mL portions of saturated aqueous bicarbonate. The solution was dried ($MgSO_4$), evaporated under vacuum, and distilled, giving 22.3 g (80%) of the title compound, whose physical properties are identical with the literature report[30]: bp 65°/5 mm; IR ($CHCl_3$) 3100-2880, 1640, 1438, 1260, 1140, 924 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.29 (s, 1H, $\underline{H}C=C$), 5.05 (s, 1H, $\underline{H}C=C$), 3.96 (s, 2H, $BrC\underline{H}_2C=C$), 3.49 (t, 2H, J = 6 Hz, $BrC\underline{H}_2CH_2$), 2.77 (t, 2H, J = 6 Hz, $BrCH_2C\underline{H}_2$) ppm; ^{13}C-NMR ($CDCl_3$) δ 142.1, 117.5, 36.5, 35.8, 30.1 ppm.

trans-4a-(2,3-Dimethoxyphenyl)-2-methyl-6-methylidene-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium perchlorate (46a).

To a -10°C solution of 23 g (100 mmol) of tetrahydropyridine 30 in 300 mL anhydrous THF was added, dropwise, 65 mL (110 mmol) of 1.7 M n-butyllithium. After stirring for 15 min, the solution was cooled to -30°C and transferred via cannula into a -78°C solution of 49.9 g (220 mmol) of dibromide (8) in 50 mL of anhydrous ether. The reaction was rapidly warmed to -20°C and 300 mL of ice cold brine added. The organic layer was separated and extracted with three, 600 mL portions of cold 1 N aqueous hydrochloric acid. After washing once with ether, the combined acid extracts were made basic by addition of 50% aqueous sodium hydroxide, while maintaining the temperature at 0°C. The product was extracted into three, 600 mL portions of ether, dried (K_2CO_3), and the solvent evaporated under vacuum keeping the temperature below 10°C. The residue was

immediately dissolved in 2.5 L of acetonitrile with 37.5 g (250 mmol) of sodium iodide and 28 g (202 mmol) of potassium carbonate, and then refluxed for 45 min. After filtration and solvent evaporation, the residue was taken up in 200 mL of ether; to this solution was added a 1:1 mixture of 60% aqueous perchloric acid and methanol, until the solution tested blue on congo red paper (pH<3). Scratching of the oily precipitate then induced crystallization. Trituration, with 20% methanol in ether, of the collected solid afforded 24 g (60%) of the title compound: IR (CH_2Cl_2) 3050-2840, 1690, 1576, 1460, 1418, 1260, 1095 cm^{-1}; ^{1}H-NMR (CD_3CN) δ 8.67 (br s, 1H, C$\underline{H}$=N^+), 6.97-6.41 (m, 3H, ArH), 4.52 (m, 2H, C$\underline{H}_2$=C), 3.87 (s, 3H, OC$\underline{H}_3$), 3.81 (s, 3H, OCH_3), 3.46 (br s, 3H, NC$\underline{H}_3$), 3.73-1.83 (m, 11H, aliphatic) ppm; ^{13}C-NMR (CD_3CN) δ 182.4, 154.6, 148.8, 145.1, 131.2, 123.9, 122.3, 113.7, 111.8, 61.3, 56.5, 52.4, 48.8, 47.7, 43.0, 35.2, 34.7, 27.0 ppm.

Anal. calcd for $C_{19}H_{26}NO_6Cl$: C, 57.07; H, 6.54; N, 3.50. Found: C, 56.91; H, 6.60; N, 3.41.

Partition of immonium salt 46a between dichloromethane and 1 N aqueous sodium hydroxide, followed by solvent evaporation and bulb to bulb distillation (135°C/0.005 mm) afforded 4a-(2,3-dimethyoxyphenyl)-2-methyl-6-methylidene-2,3,4,4a,5,6,7,8-octahydroisoquinoline (45) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 6.91-6.69 (m, 3H, ArH), 5.80 (s, 1H, C=C$\underline{H}$N), 4.50 (s, 2H, C$\underline{H}_2$=C), 3.74 (s, 3H, OC$\underline{H}_3$), 3.80 (s, 3H, OC$\underline{H}_3$), 2.52

(s, 3H, NCH_3), 3.42-1.63 (m, 10H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 153.2, 147.7, 147.3, 138.9, 133.7, 125.1, 122.0, 112.8, 110.9, 108.4, 60.2, 55.7, 46.7, 46.2, 44.5, 42.7, 37.8, 36.1, 31.8 ppm.

Exact mass calcd. for $C_{19}H_{25}NO_2$: 299.189. Found: 299.190.

(4aα, 8aα, 8bβ)-4a-(Dimethoxyphenyl)-2-methyl-6-methylidene-decahydroazirino-[1,2-a]isoquinolinium perchlorate (47). Trans-immonium perchlorate 46a (15 g, 37.5 mmol) was equilibrated by dissolution in 1 L of methanol with stirring at 55°C for 24 h. Evaporation of the solvent gave cis-4a-(2,3-dimethoxyphenyl)-2-methyl-6-methylidene-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium perchlorate (46b)(cis:trans, 95:5)[50]: ^{1}H-NMR (CD_3CN) δ 8.63 (br s, 1H, $CH{=}N^+$), 7.06-6.75 (m, 3H, ArH), 4.81 (m, 2H, $CH_2{=}C$), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.49 (br s, 3H, NCH_3), 3.73-1.80 (m, 11H, aliphatic) ppm; ^{13}C-NMR (CD_3CN) δ 181.4, 154.6, 148.9, 144.6, 136.2, 124.8, 120.2, 113.7, 111.9, 61.2, 56.5, 52.2, 49.3, 43.1, 42.6, 39.3, 33.2, 27.6, 27.1 ppm.

To a 0°C solution of the cis immonium salt 46b in 200 mL anhydrous dichloromethane was added ethereal diazomethane, until the yellow color persisted. Immediate gas evolution was observed, followed shortly afterward by formation of a copious precipitate. Excess diazomethane was evaporated under a stream of nitrogen, then the remaining solvent was removed

under vacuum. Trituration of the residue with cold ethyl ether gave 14.8 g (95%) of the title compound as a tan solid; mp 186-188°C; IR (CH_2Cl_2) 3060-2840, 1575, 1465, 1420, 1255, 1090, 1000 cm^{-1}; ^{1}H-NMR (CD_3CN) δ 7.02-6.87 (m, 3H, ArH), 4.81 (m, 2H, $C\underline{H}_2$=C), 3.79 (s, 6H, $OC\underline{H}_3$), 3.07 (s, 3H, $NC\underline{H}_3$), 3.72-1.67 (m, 14H, aliphatic) ppm; ^{13}C-NMR (CD_3CN) δ 154.5, 148.8, 145.7, 138.3, 124.1, 121.3, 113.3, 111.4, 60.8, 56.5, 53.5, 50.8, 50.7, 46.2, 43.3, 39.4, 34.8, 30.4, 27.6 ppm.

Anal. calcd. for $C_{20}H_{28}NClO_6$: C, 58.04; H, 6.82; N, 3.38. Found: C, 58.08; H, 6.85; N, 3.44.

Flash chromatography (1:1, hexane and ethyl acetate, 0.25% triethylamine) of the mother liquors from trituration of aziridinium salt 47 afforded 9.4 mg (0.08%) of morphinan 50.

(1α, 4aα, 8aα)-4a-(Dimethoxyphenyl)-2-methyl-6-methylidene-decahydroisoquinoline-1-carboxaldehyde (48). A solution of 4.0 g (9.7 mmol) of aziridinium salt 47 and 20 mL (280 mmol) of anhydrous dimethyl sulfoxide in 100 mL of benzene was stirred at room temperature for 36 h. The mixture was then mixed with 100 mL saturated aqueous sodium bicarbonate for 15 min. After extraction of the aqueous phase with two, 100 mL portions of dichloromethane, the combined organic phases were washed with three, 100 mL portions of water, dried (Na_2SO_4) and evaporated, giving 3.04 g (95%) of the title compound: IR (CH_2Cl_2) 3060-2800, 1729, 1576, 1462, 1422, 1270, 1062, 1005 cm^{-1}; ^{1}H-NMR (C_6D_6/CD_3CN) δ 9.29 (d, 1H, J = 5 Hz, C$\underline{H}$O), 7.08-6.62 (m, 3H,

ArH), 4.68 (s, 2H, $C\underline{H}_2$=C), 3.75 (s, 3H, $OC\underline{H}_3$), 3.42 (s, 3H, $OC\underline{H}_3$), 2.19 (s, 3H, $NC\underline{H}_3$), 3.28-1.35 (m, 12H, aliphatic) ppm.

Exact mass calcd. for $C_{20}H_{27}NO_3$: 329.199. Found: 329.198.

(10β, 14α)-3,4-Dimethoxy-10-hydroxy-6-methylidene-17-methyl-morphinan (49). To a -10°C solution of 403.6 mg (1.22 mmol) of carboxalde 48 in 50 mL toluene and 15 mL dichloromethane was added, dropwise, 380 µL (3.09 mmol) of boron trifluoride etherate. After 2 h, the reaction was quenched by addition of 30 mL of 10% aqueous sodium hydroxide and stirred for 1 hr more. The aqueous phase was extracted with two, 25 mL portions of dichloromethane and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to give a brown oil. Filtration through silica gel (6 gm, silica gel 60, 60-200µ; ethyl acetate, 0.5% triethyl amine) gave 318 mg (80%) of a colorless oil composed of the title compound and a trace of the 10α-hydroxy epimer 49a.

In a separate experiment, 1.64 g (4.98 mmol) of a mixture of carbinol epimers were separated by flash chromatography (ethyl acetate, 0.5% triethylamine) to give 1330 mg of 10 β-hydroxy-morphinan 49 and 67 mg of 10α-hydroxy-morphinan 49a (49:49a, 95:5).

For 49: IR (CH_2Cl_2) 3600, 3080-2800, 1600, 1480, 1260, 1100, 1060, 1005 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 7.62 (d, 1H, J = 9 Hz,

ArH), 6.61 (d, 1H, J = 9 Hz, ArH), 4.85 (m, 2H, $C\underline{H}_2$=C), 4.67 (d, 1H, J = 6 Hz, ArC$\underline{H}$OH), 3.82-3.75 (m, 1H, H_{52}), 3.72 (s, 3H, OC$\underline{H}_3$), 3.33 (s, 3H, OC$\underline{H}_3$), 2.42 (s, 1H, NC$\underline{H}_3$), 2.63-1.14 (m, 12H, aliphatic) ppm; ^{13}C-NMR (C_6D_6) δ 152.7, 147.4, 137.0, 123.9, 111.8, 110.0, 69.4, 63.3, 60.0, 55.4, 47.1, 46.6, 45.5, 42.4, 40.3, 35.4, 30.3, 25.2 ppm.

Exact mass calcd. for $C_{20}H_{27}NO_3$: 329.1992. Found: 329.1991.

For 49a: IR (CH_2Cl_2) 3600, 3020-2800, 1600, 1480, 1260, 1060, 1005 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 7.07 (d, 1H, J = 9 Hz, ArH), 6.56 (d, 1H, J = 9 Hz, ArH), 4.91 (br s, 2H, $C\underline{H}_2$=C), 4.33 (br s, 1H, ArC$\underline{H}$OH), 3.88-3.74 (m, 1H, H_{52}), 3.70 (s, 3H, OC$\underline{H}_3$), 3.35 (s, 3H, OC$\underline{H}_3$), 2.30 (s, 3H, NC$\underline{H}_3$), 2.83-1.37 (m, 12H, aliphatic) ppm; ^{13}C-NMR (C_6D_6) δ 153.4, 147.8, 134.8, 111.5, 110.2, 72.4, 65.8, 63.9, 60.0, 55.4, 48.0, 44.8, 43.1, 39.2, 37.8, 35.1, 29.2, 28.6 ppm.

Exact mass calcd. for $C_{20}H_{27}NO_3$: 329.1992. Found: 329.1992.

(14α)-3,4-Dimethoxy-17-methyl-6-methylidene-morphinan (50). To a -10°C solution of 1.31 g (3.98 mmol) of 10-hydroxy-morphinan 49 (containing approximately 5% 49a) in 75 mL THF was added 850 μL (617 mg, 6 mmol) of triethylamine followed by 350 μL (518 mg, 4.5 mmol) of methanesulfonyl chloride. After 1 h, during which time the solution had become heterogeneous, 20 mL of 1 M lithium triethylborohydride in THF was

added. Immediate gas evolution was observed along with clearing of the reaction mixture. The cooling bath was removed and 1.5 h later, 50 mL of methanol was carefully added. The mixture was cooled to 0°C and 10 mL of 3 N aqueous sodium hydroxide was added, followed by 10 mL of 30% aqueous hydrogen peroxide (caution: a very exothermic reaction results). Heating at reflux was then carried out after the initial vigorous reaction had subsided. Additional portions of 10 mL 3 N NaOH and 10 mL 30% H_2O_2 were added at 2 h intervals over a 10 h period, then the mixture was refluxed for 8 h more. Upon cooling to room temperature, the solution was concentrated under vacuum, diluted with 100 mL of water and extracted with three, 10 mL portions of dichloromethane. Drying (Na_2SO_4) of the combined extracts, evaporation, and filtration through silica gel (10 g, 60-230 μm; ethyl acetate, 0.5% triethylamine) afforded 1.12 g (90%) of the title compound: IR (CH_2Cl_2) 3080-2800, 1480, 1280, 1060, 1040 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 6.73 (d, 1H, J = 9 Hz, ArH), 6.54 (d, 1H, J = 9 Hz, ArH), 4.93 (br s, 2H, $C\underline{H}_2$=C), 3.97-3.83 (m, 1H, C=CC$\underline{H}$), 3.73 (s, 3H, $OC\underline{H}_3$), 3.38 (s, 3H, $OC\underline{H}_3$), 2.19 (s, 3H, $NC\underline{H}_3$), 3.12-1.33 (m, 13H, aliphatic) ppm; ^{13}C-NMR (C_6D_6) δ 151.9 (s), 149.1 (s), 148.0 (s), 138.4 (s), 132.0 (s), 123.2 (d), 111.5 (d), 110.0 (t), 60.1 (a), 58.7 (d), 55.6 (a), 48.2 (t), 45.2 (t), 43.1 (a), 43.0 (d), 38.8 (s), 35.1 (t), 30.0 (t), 28.8 (t), 28.7 (t) ppm.

Exact mass calcd. for $C_{20}H_{27}NO_2$: 313.2043. Found: 313.2036.

A picrate salt was prepared and recrystallized from chloroform-methanol: mp 201.5-203.5.

Anal. calcd. for $C_{26}H_{30}N_4O_9$: C, 57.56; H, 5.57; N, 10.33. Found: C, 57.40, H, 5.57; N, 10.26.

(14α)-3,4-Dimethyl-17-methyl-morphinan-6-one (51). To a 0°C solution of 2.44 g (7.78 mmol) of 6-methylene-morphinan 50 in 60 mL of tetrahydrofuran and 20 mL glacial acetic acid was added 2.9 mL (0.39 mmol) of 0.135 M aqueous osmium tetrroxide and 47 mL (23.5 mmol) of 0.5 M aqueous sodium periodate. The solution was allowed to gradually warm to room temperature, accompanied by formation of a copious white precipitate. The precipitate was removed by filtration and washed with glacial acetic acid. After concentration of the filtrate under vacuum, the residue was diluted with 100 mL of water and extracted with three, 75 mL portions of dichloro-methane. The combined extracts were washed with 150 mL of water, dried (Na_2SO_4) and evaporated under vacuum. Filtration through silica gel (10 g, 60-230 μm; ethyl acetate, 0.5% triethylamine) afforded 2.23 g (90%) of the title compound: IR (CH_2Cl_2) 3060-2800, 1700, 1480, 1420, 1265, 1150, 1089, 1058, 1036 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 6.71 (d, 1H, J = 9 Hz, ArH), 6.50 (d, 1H, J = 9 Hz, ArH), 3.93 (dd, J = 15 Hz, J = 1.5 Hz, H_{52}), 3.77 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.11 (s, 3H,

$OC\underline{H}_3$), 3.06-1.38 (m, 13H, aliphatic) ppm; ^{13}C-NMR (C_6D_6) δ 209.6 (s), 151.9 (s), 148.7 (s), 136.8 (s), 131.1 (s), 123.2 (d), 111.8 (d), 60.0 (a), 57.8 (d), 55.6 (a), 51.9 (t), 47.9 (t), 42.8 (a), 41.7 (d), 40.8 (t), 40.4 (s), 3.13 (t), 28.5 (t), 26.9 (t) ppm.

Exact mass calcd. for $C_{19}H_{25}NO_3$: 315.1836. Found: 315.1831.

Anal. calcd. for $C_{25}H_{28}N_4O_{10}$: C, 55.14; H, 5.18; N, 10.15. Found: C, 54.92; H, 5.12; N, 10.29.

(14α)-3,4-Dimethoxy-7-ene-17-methyl-6-trimethylsilyloxy-morphinan (52). A solution of lithium diisopropylamide (LDA) was prepared by adding 590 µL (1.02 mmol) of 1.7 M n-butyl-lithium in hexane to a -30°C solution of 190 µL (1.36 mmol) of diisopropylamine in 40 mL of anhydrous THF and stirring for 15 min. To the LDA solution (cooled to -78°C) was added 214 mg (0.678 mmol) of morphinan-6-one (51) dissolved in 4 mL of THF. After 30 min, 1 mL of a solution of 1.75 mL (13.8 mmol) of trimethylsilylchloride and 0.9 mL (6.46 mmol) of triethyl-amine in 7.3 mL THF, was added all at once. The cooling bath was then removed and when the mixture had warmed to room temperature, 20 mL of saturated aqueous sodium bicarbonate was added, followed by vigorous stirring for 20 min. Dilution of the aqueous phase with 20 mL of water, extraction with dichloromethane, drying (Na_2SO_4) of the combined organic phases, and evaporation under vacuum gave 252 mg (96%) of

the title compound: IR (CH_2Cl_2 3060-2800, 1685, 1600, 1482, 1275, 1190, 1165, 1150, 1086, 1058 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 6.72 (d, 1Hz, J = 9 Hz, ArH), 6.52 (d, 1H, J = 9 Hz, ArH), 5.08 (m, 1H, OC=C<u>H</u>), 3.77 (s, 3H, OC<u>H</u>$_3$), 3.38 (s, 3H, OC<u>H</u>$_3$), 2.43 (s, 3H, NC<u>H</u>$_3$), 3.55-1.18 (m, 12H, aliphatic), 0.28 (s, 9H, Si(C<u>H</u>$_3$)$_3$) ppm; ^{13}C-NMR (C_6D_6) δ 151.9, 149.1, 149.0, 138.0, 131.4, 123.2, 113.2, 111.6, 101.6, 60.0, 57.2, 55.6, 53.4, 48.5, 42.8, 42.3, 41.8, 38.9, 38.6, 36.7, 30.9, 28.7, 25.9 ppm.

<u>Exact mass</u> calcd. for $C_{22}H_{33}NO_3Si$: 387.2231. Found: 387.2223.

<u>(7α, 14α)-3,4-Dimethoxy-17-methyl-7-phenylselenomorphinan-6-one (53a) and (7β, 14α)-3,4-dimethoxy-17-methyl-7-phenyl-seleno-morphinan-6-one (53b)</u>. To a room temperature solution of 338.1 mg (0.87 mmol) silyl enol ether <u>52</u> in 50 mL of benzene was added 167 mg (0.87 mmol) of phenylselenyl chloride in 3 mL of benzene. After 15 min, 50 mL of saturated aqueous sodium bicarbonate was added and the aqueous phase was extracted with two, 50 mL portions of dichloromethane. The combined extracts were dried (Na_2SO_4), evaporated under vacuum, and filtered through silica gel (6 g, 60-200 μ; 1:1 hexane and ethyl acetate, 0.5% triethylamine) to give 240 mg (60%) of a 1:1 mixture of epimeric selenides. IR (CH_2Cl_2) 3050-2800, 1694, 1595, 1574, 1478, 1450, 1425, 1250, 1055, 1035 cm^{-1}.

Flash chromatograph (1:1 hexane and ethyl acetate, 0.5% triethylamine) afforded a pure sample of each C-7 epimer of unassigned stereochemistry.

For epimer A: ^{1}H-NMR (C_6D_6) δ 7.58 (m, 2H, sePhH), 6.90 (m, 3H, sePhH), 6.70 (d, 1H, J = 9 Hz, ArH), 6.50 (d, 1H, J = 9 Hz, ArH), 4.09 (m, H, SeCH), 3.75 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 2.11 (s, 3H, NCH_3), 3.87-1.53 (m, 12H, aliphatic) ppm.

For epimer B: ^{1}H-NMR (C_6D_6) δ 7.52 (m, 2H, sePhH), 6.95 (m, 3H, sePhH), 6.60 (d, 1H, J = 9 Hz, ArH), 6.49 (d, H, J = 9 Hz, ArH), 4.04 (m, 1H, SeCH), 3.58 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.13 (s, 3H, NCH_3), 3.63-1.53 (m, 12H, aliphatic) ppm.

Exact mass calcd. for $C_{25}H_{29}NO_3Se$: 471.1314. Found: 471.1315.

(14α)-3,4-Dimethoxy-7-ene-17-methyl-morphinan-6-one (54). A solution of 239.8 mg (0.51 mmol) of a 1:1 mixture of selenides 53a and 53b in 30 mL dichloromethane was stirred with 40 μL (0.51 mmol) of trifluoracetic acid and 300 μL (2.55 mmol) of 90% t-butyl hydroperoxide, at room temperature for 3 days. Saturated aqueous sodium bicarbonate (30 mL) was added. After vigorous stirring for 30 min, the organic phase was dried (Na_2SO_4) and evaporated under vacuum to give 143.8 mg (90%) of the title compound: IR (CH_2Cl_2) 3065-2850, 1672, 1482, 1280, 1150, 1098, 1060, 1040, 1022 cm^{-1}; ^{1}H-NMR (CD_3CN) δ

6.94 (dd, 1H, J = 10 Hz, S = 1 Hz, CHC=CC=O), 6.84 (s, 2H, ArH), 6.02 (dd, 1H, J = 10 Hz, J = 3 Hz, C=CHC=O), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.27 (s, 3H, NCH_3), 3.72-1.16 (m, 10H, aliphatic) ppm.

Exact mass calcd. for $C_{19}H_{23}NO_3$: 313.1679. Found: 313.1675.

3,4-Dimethoxy-6-hydroxy-morphinan-5,8-diene-7-one (56a). To a suspension of 64.3 mg (0.21 mmol) enone 54, 50 mg (0.45 mmol) potassium t-butoxide, and 21.0 mg (0.2mmol) sodium bisulfite in 3 mL dimethyl sulfoxide and 0.5 mL t-butyl alcohol was added 4.7 mL (0.21 mmol) oxygen via a gas tight syringe, with immediate formation of a deep red color. After 5 min, 30 mL of water was added and the mixture was extracted with three, 25 mL portions of dichloromethane. The combined extracts were washed with three, 30 mL portions of water, dried (Na_2SO_4) and evaporated to give 33.5 mg (50%) of the title compound: IR (CH_2Cl_2) 3425, 3058-2820, 1670, 1650, 1620, 1482, 1422, 1260, 1218, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.54 (s, 1H, C=CH), 6.88 (s, 2H, ArH), 6.45 (s, 1H, C=CH), 3.94 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.48 (s, 3H, NCH_3), 3.5-1.74 (m, 7H, aliphatic) ppm; ^{13}C-NMR ($CDCl_3$) δ 181.8, 165.0, 152.1, 147.3, 146.9, 131.9, 123.0, 122.6, 120.2, 111.8, 61.3, 60.6, 55.9, 46.4, 43.9, 41.6, 38.4, 32.9 ppm.

Exact mass calcd. for $C_{19}H_{21}NO_4$: 327.1471. Found: 327.1463.

(14β)-3,4-Dimethoxy-17-methyl-morphinan-6-one (57) was prepared by base-catalyzed equilibration of (14α)-morphinan 54 to (14β)-morphinan 55 and subsequent hydrogenation. A room temperature solution of 38 mg (0.12 mmol) (14α)-morphinan 54 and 1.2 mL of 0.1 M aqueous potassium hydroxide in 3 mL of methanol was stirred for 23 h. Dilution with 10 mL of aqueous sodium bicarbonate, extraction with three, 20 mL portions of dichloromethane, drying (Na_2SO_4), and evaporation under vacuum gave 36.8 mg of a mixture of crude enones (14β: 14α, approximately 80:20).[6] This mixture was immediately hydrogenated at 1 atm with 5 mg of 5% Pd/C in 2 mL of methanol, for 24 h. Filtration, evaporation of the filtrate, and flash chromatography (ethyl acetate, 2.5% triethylamine) afforded 15 mg (40%) of (14β)-morphinan 57 along with 4 mg of (14α)-morphinan 51. The ^1H, ^{13}C-NMR and IR spectra, as well as the TLC mobility, of 57 were identical with an authentic sample.[45]

For (14β)-3,4-dimethoxy-7-ene-17-methylmorphinan-6-one (55): ^1H-NMR (CD_3CN) δ 6.81 (dd, 1H, J = 10 Hz, J = 3 Hz, C<u>H</u>=CC=O), 6.76 (s, 2H, ArH), 5.77 (dd, 1H, J = 10 Hz, J = 3 Hz, C=C<u>H</u>C=O), 3.91 (m, 1H, H_{52}), 3.62 (s, 3H, OC<u>H</u>$_3$), 3.59 (s, 3H, OC<u>H</u>$_3$), 2.34 (s, 3H, NC<u>H</u>$_3$), 3.22-1.28 (m, 9H, aliphatic) ppm.

Exact mass calcd. for $C_{19}H_{23}NO_3$: 313.1679. Found: 313.1676.

For (14β)-morphinan 57: IR (CH_2Cl_2) 3060-2800, 1706, 1600, 1480, 1260, 1050 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 6.76 (br s, 2H, ArH), 3.99 (dd, 1H, J = 14 Hz, J = 2.5 Hz, H_{52}), 3.94 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.41 (s, 3H, NCH_3) ppm; ^{13}C-NMR ($CDCl_3$) δ 210.5, 151.5, 148.9, 130.4, 130.2, 122.9, 111.4, 60.3, 57.0, 55.8, 51.3, 46.5, 45.6, 42.6, 41.5, 41.1, 40.0, 27.0, 24.0 ppm.

Exact mass calcd. for $C_{14}H_{25}NO_3$: 315.1836. Found: 315.1830.

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stereochemistry assigned to 19 was confirmed by X-ray analysis.[15] As described in the discussion on pyridines 16 and 17, ^{13}C-NMR was also found useful for assignment of cis versus trans ring fusion.[11,12]

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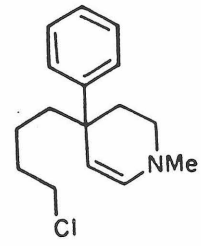
APPENDIX I

IR and ^{1}H NMR Spectral Catalog

Page 41



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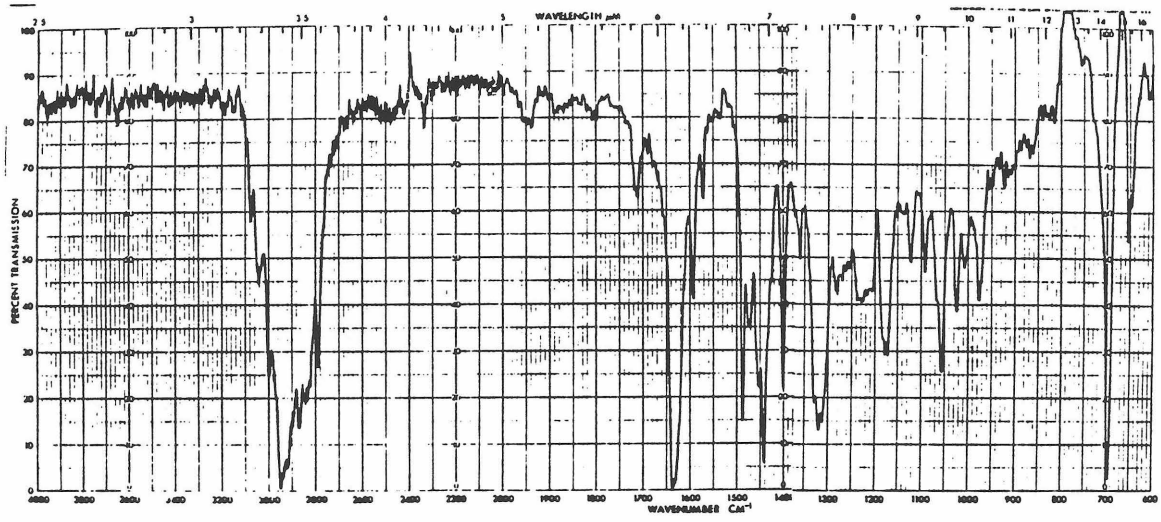

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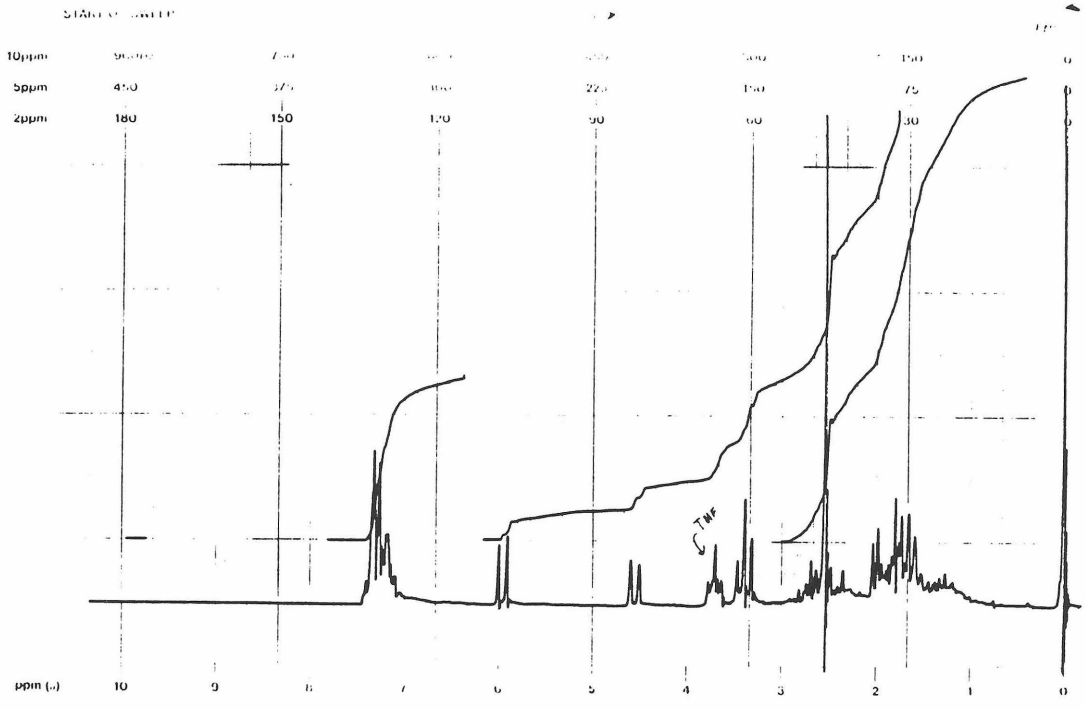
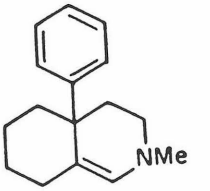


Page 42



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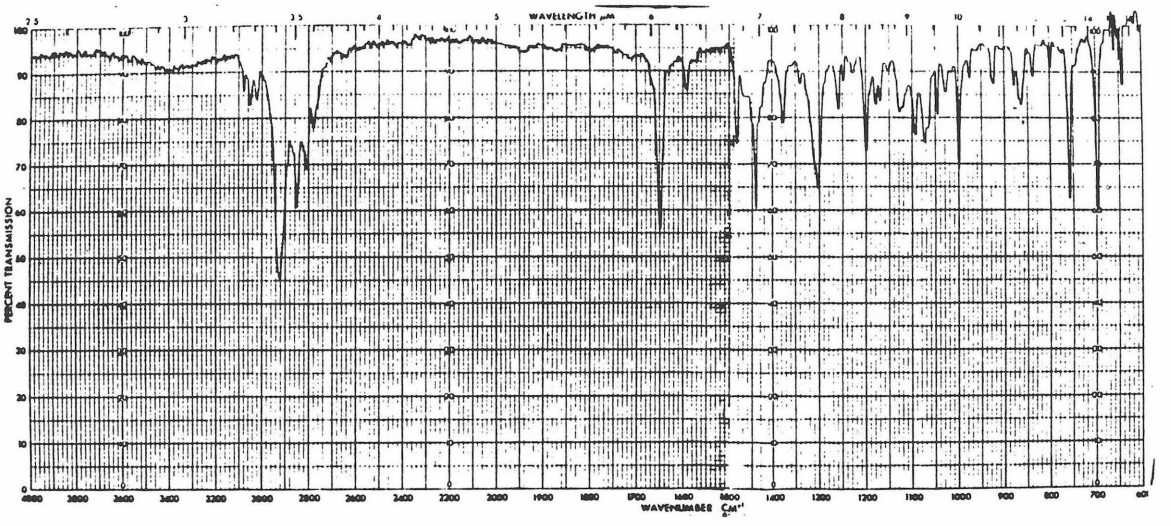

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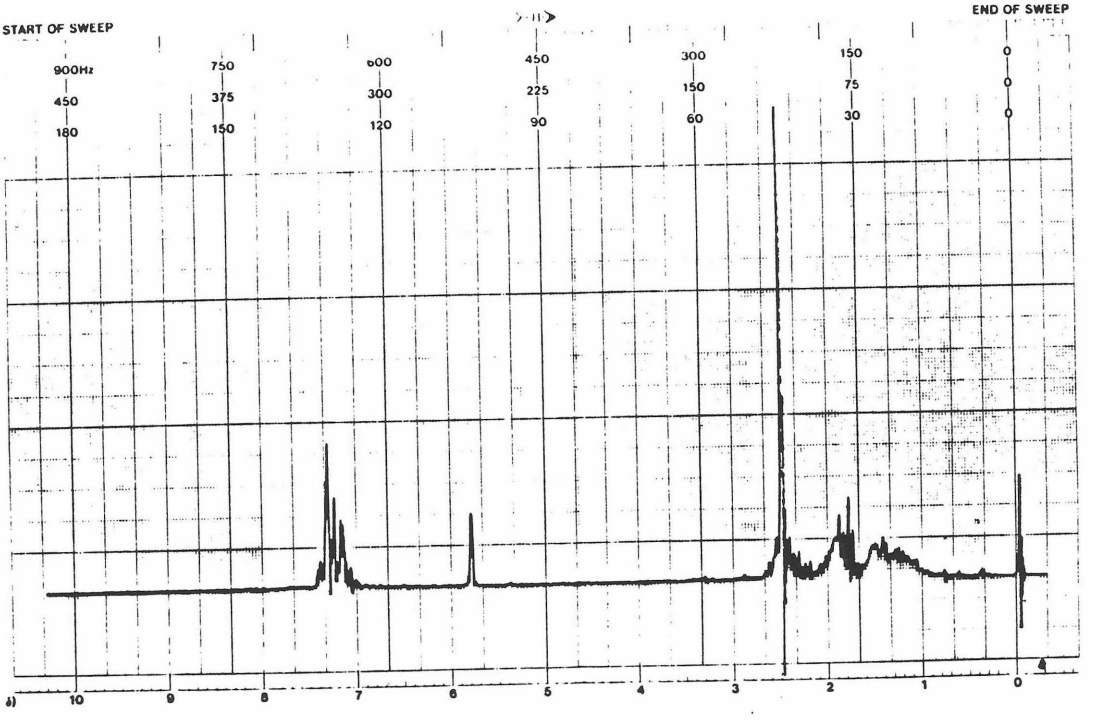

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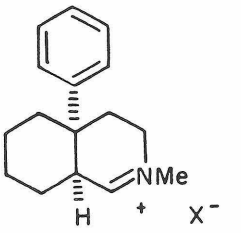

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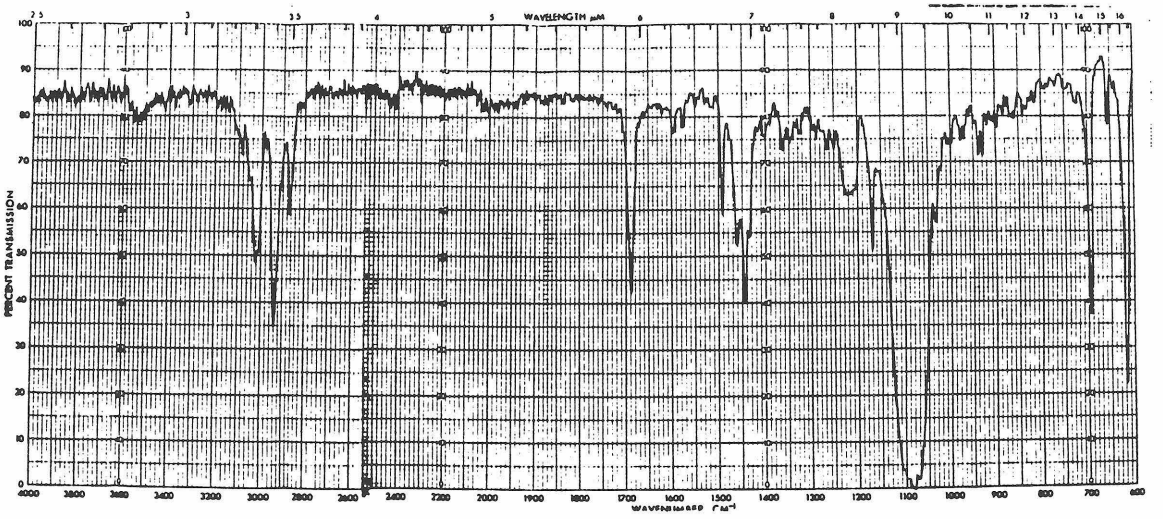

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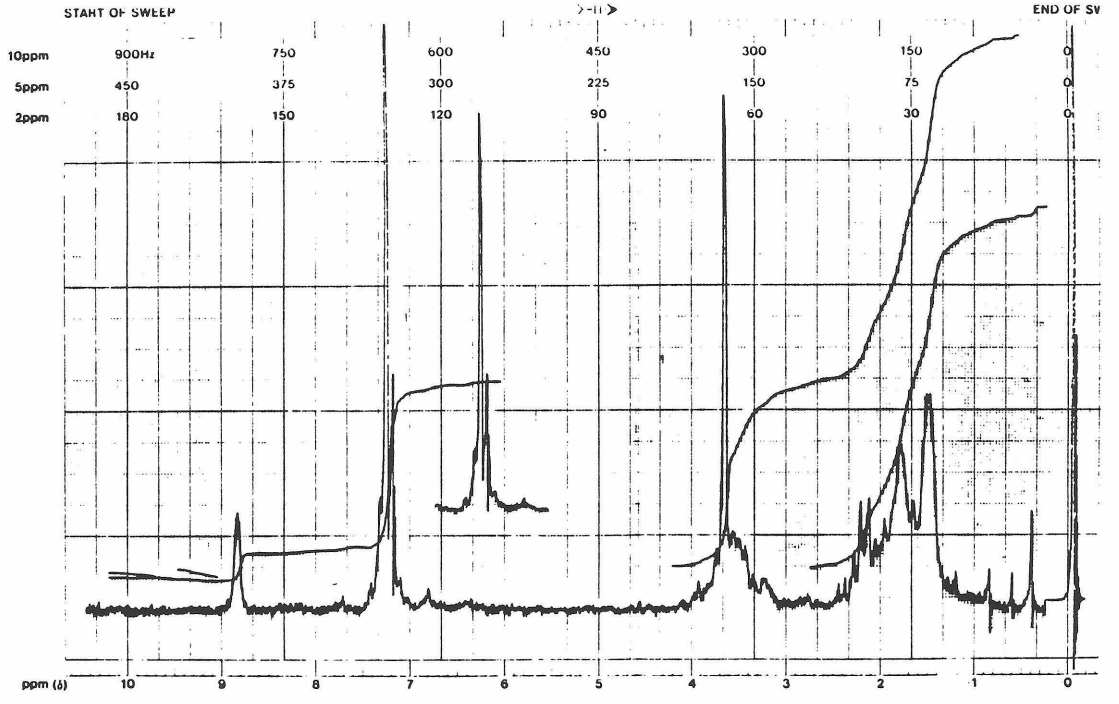

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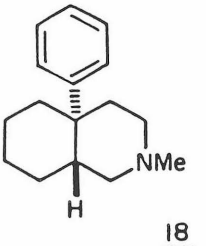

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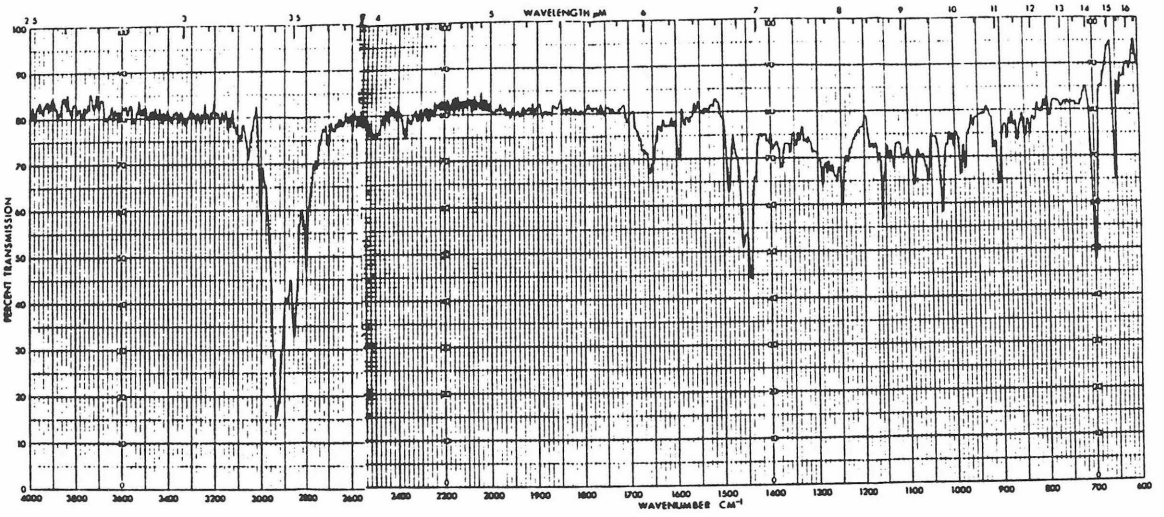

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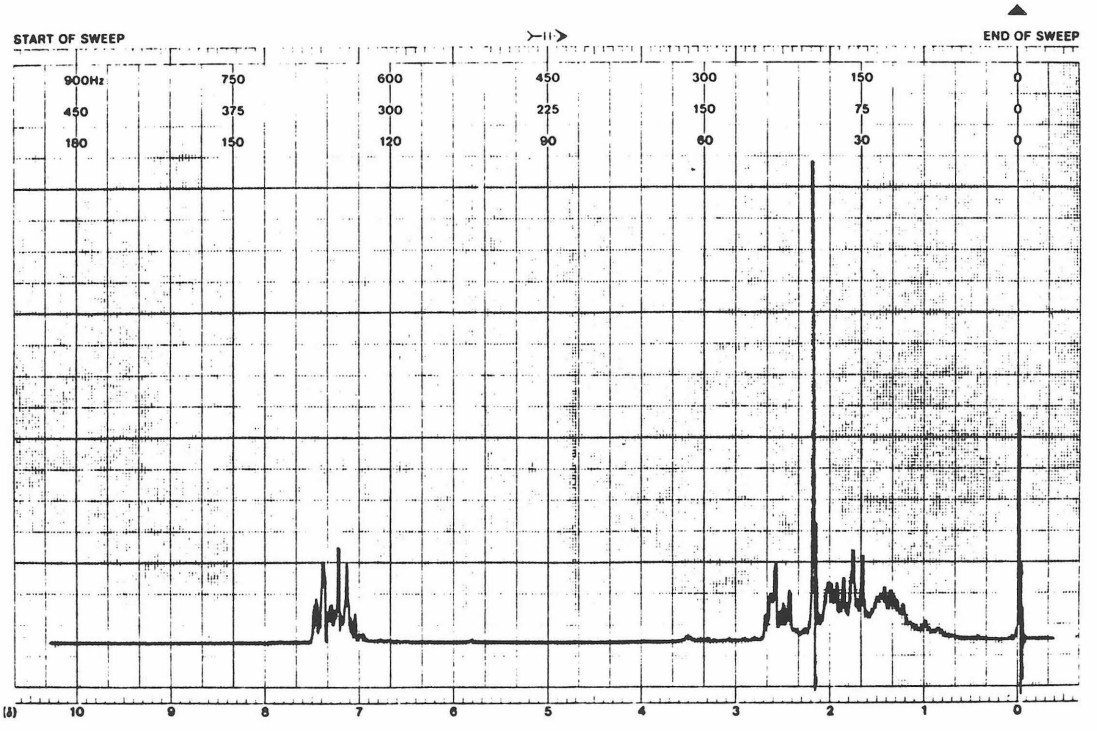

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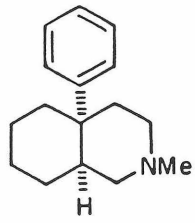

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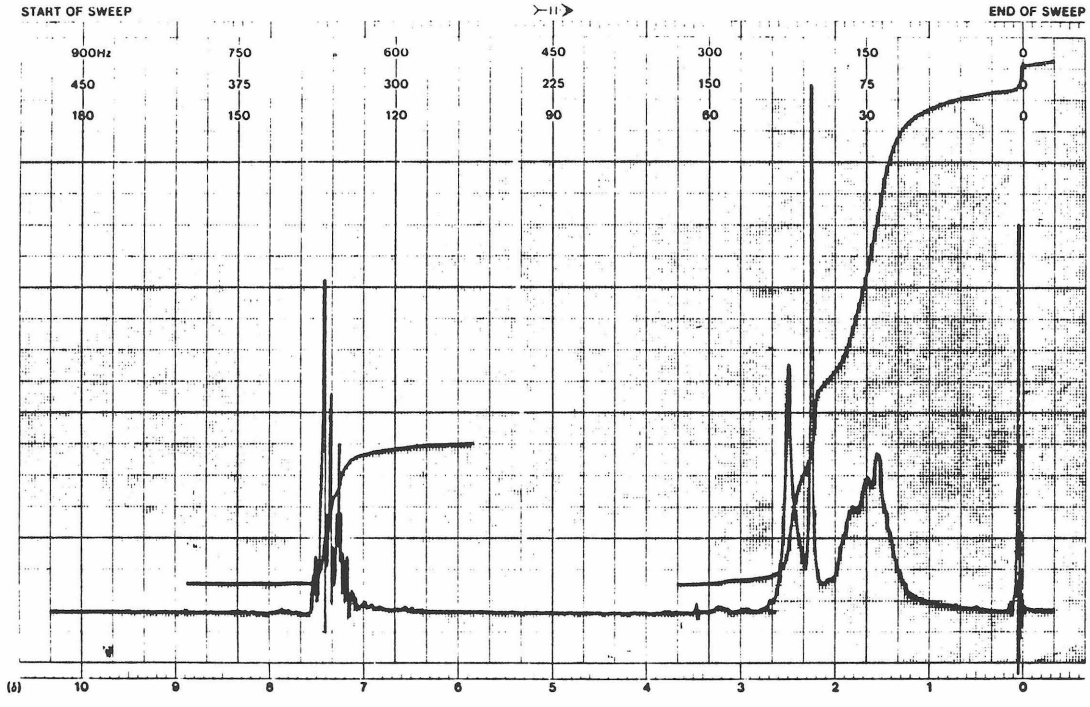

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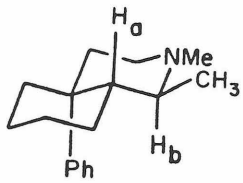

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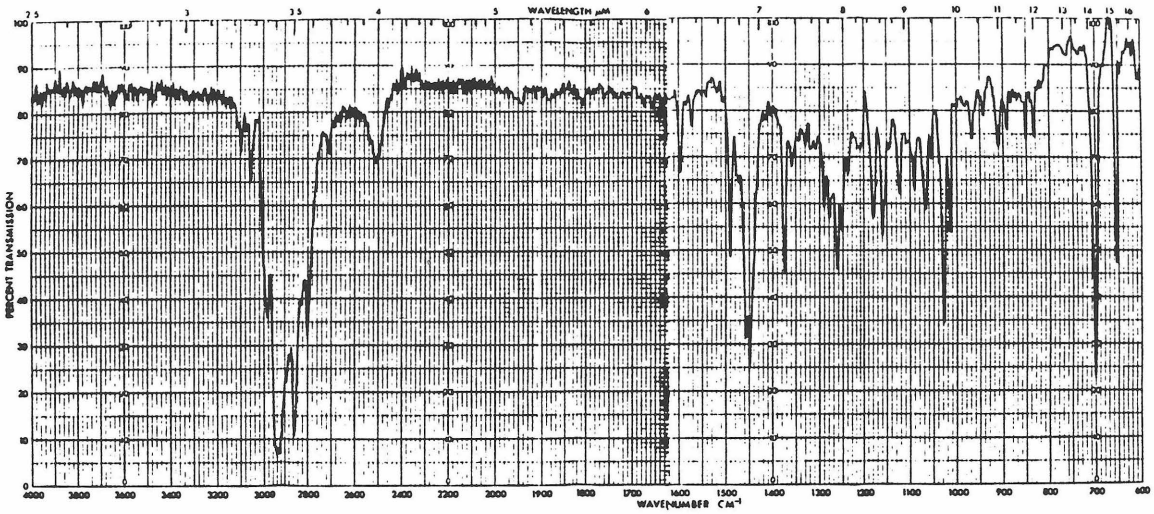

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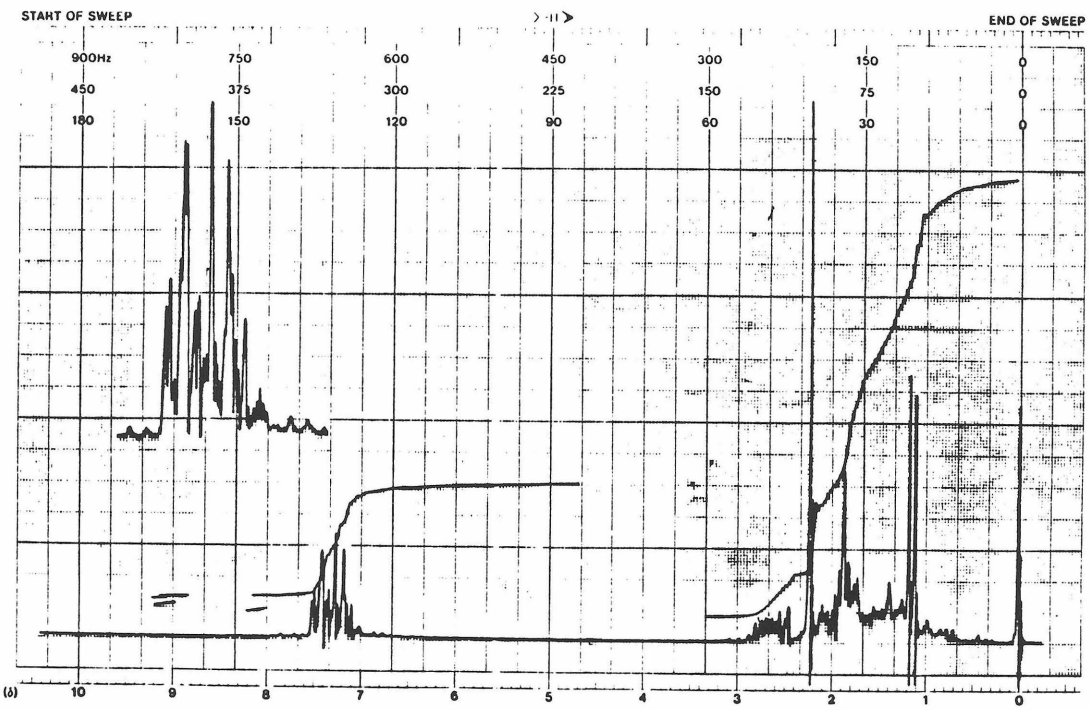

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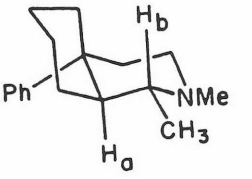

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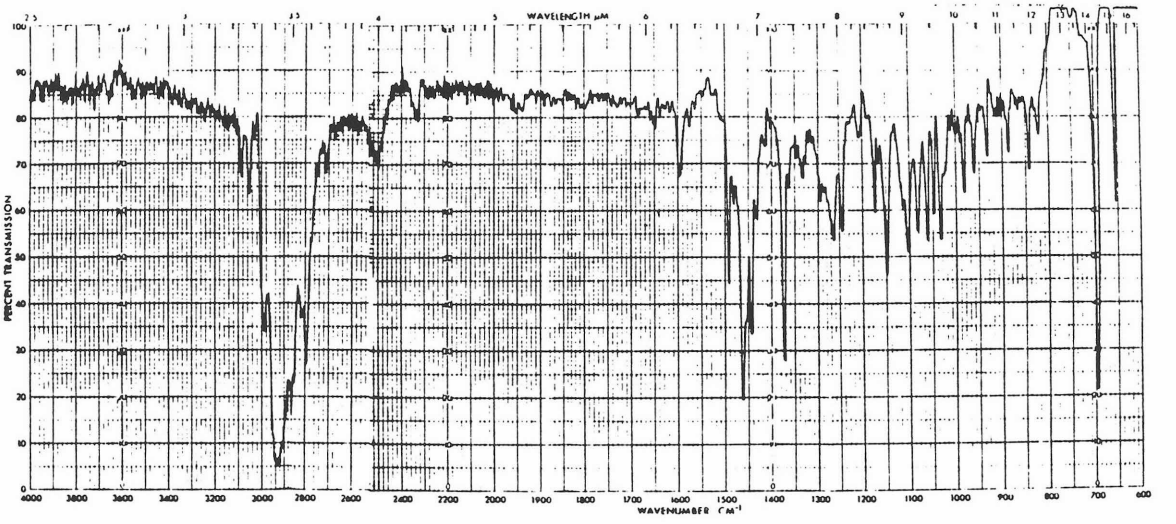

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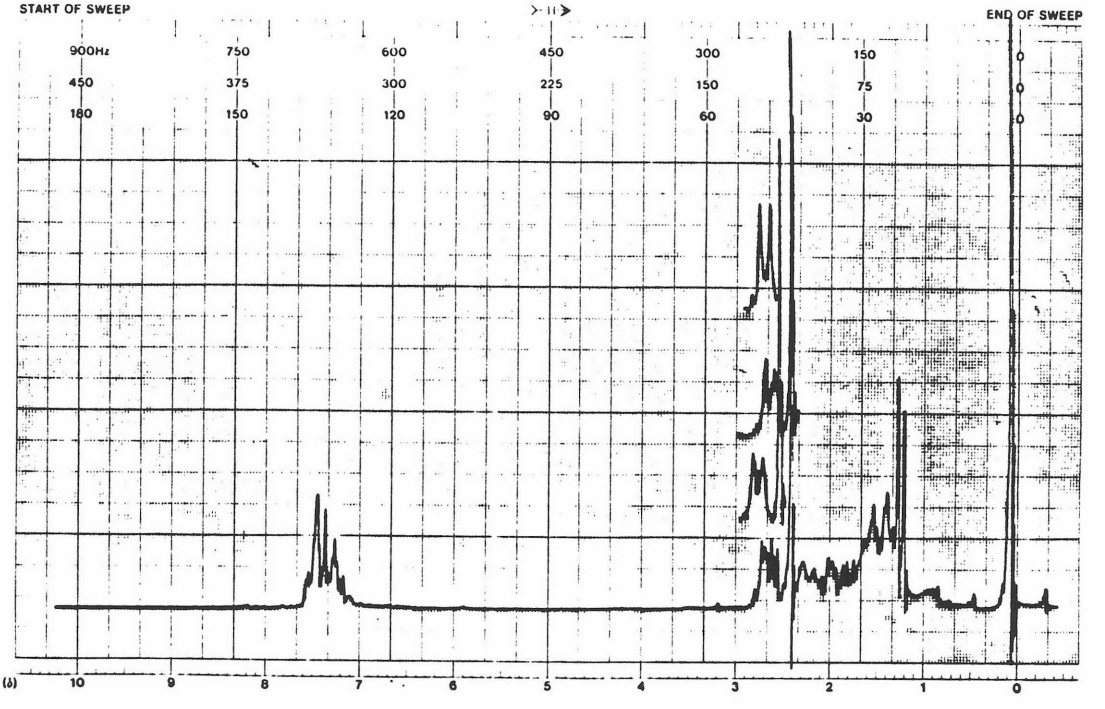

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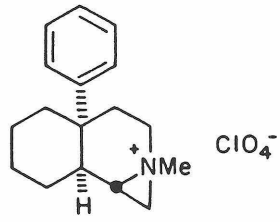

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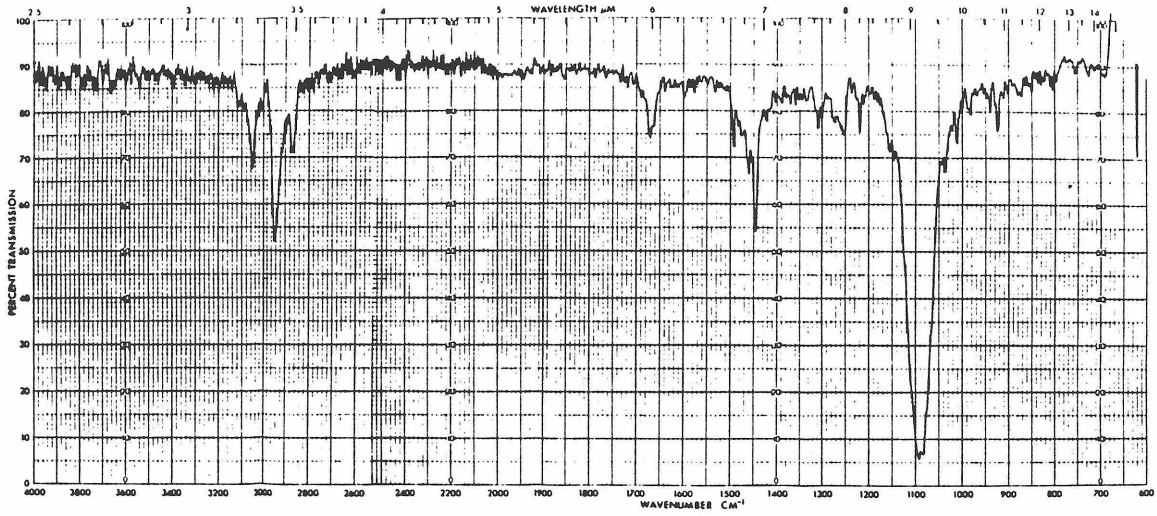

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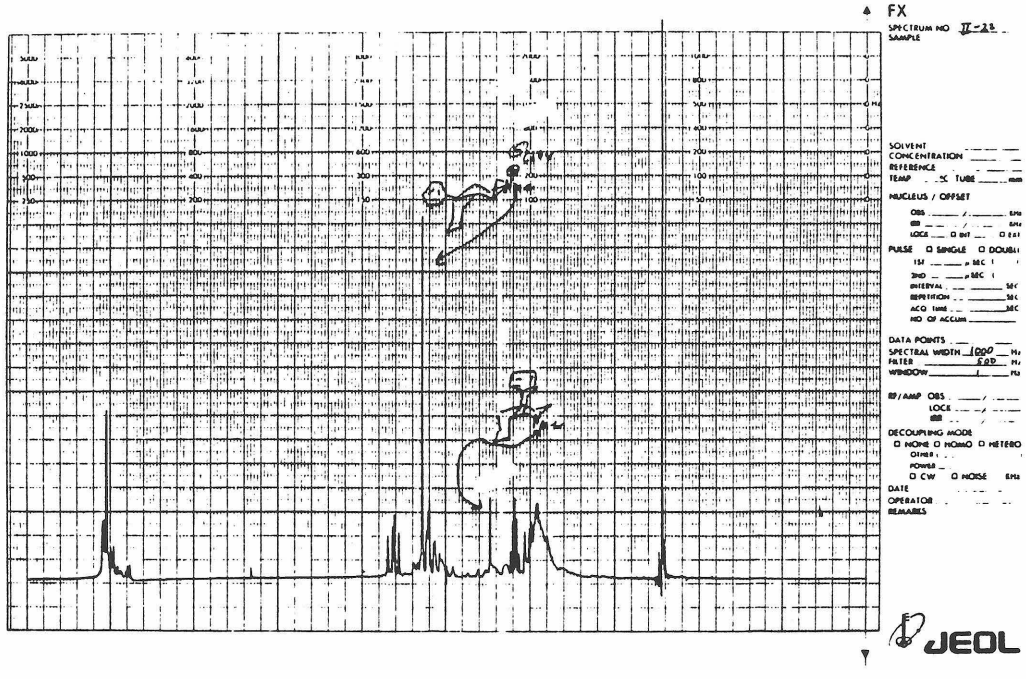
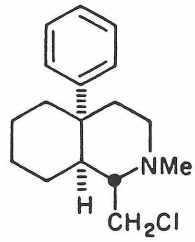


Page 49



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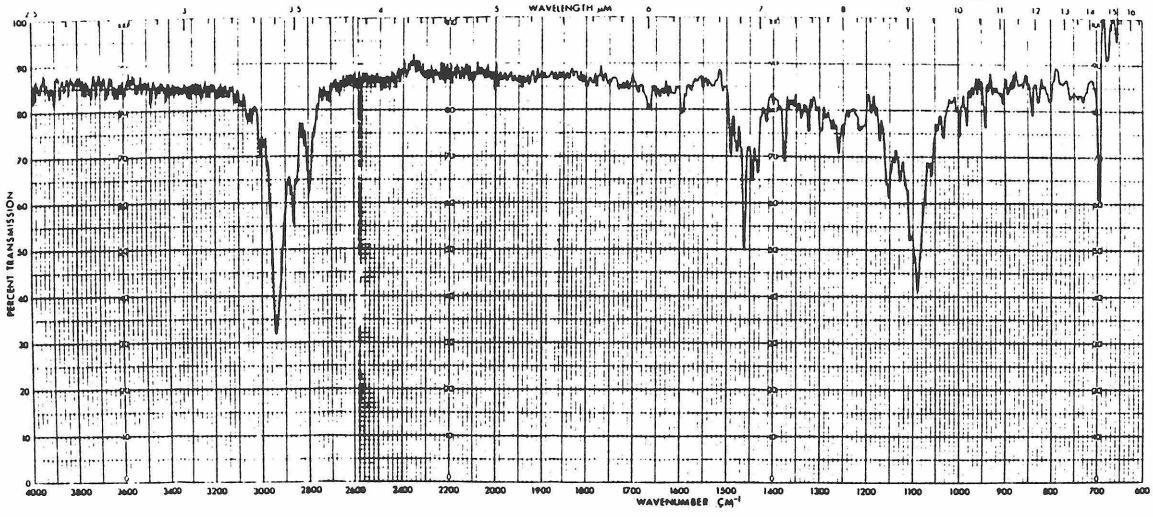
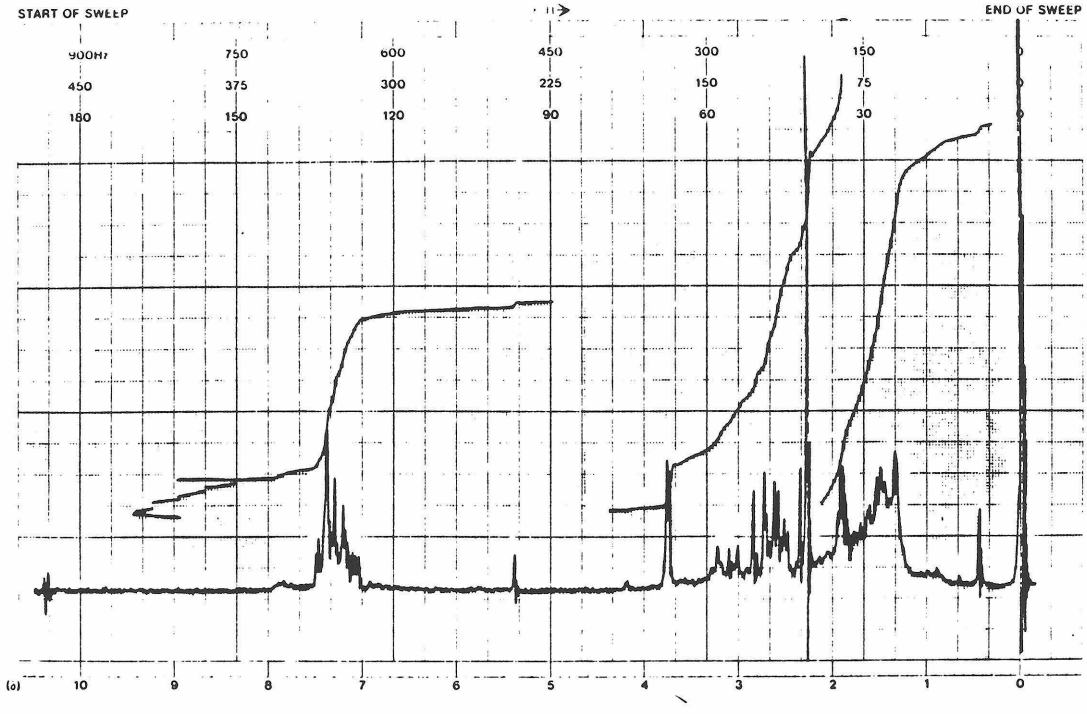
26



CD_3CN



Page 50

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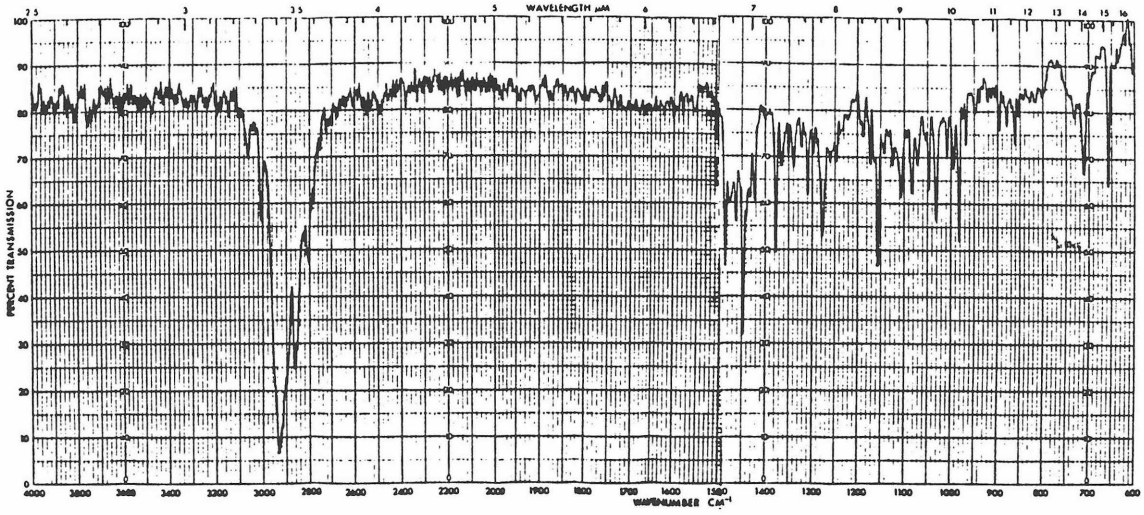
27



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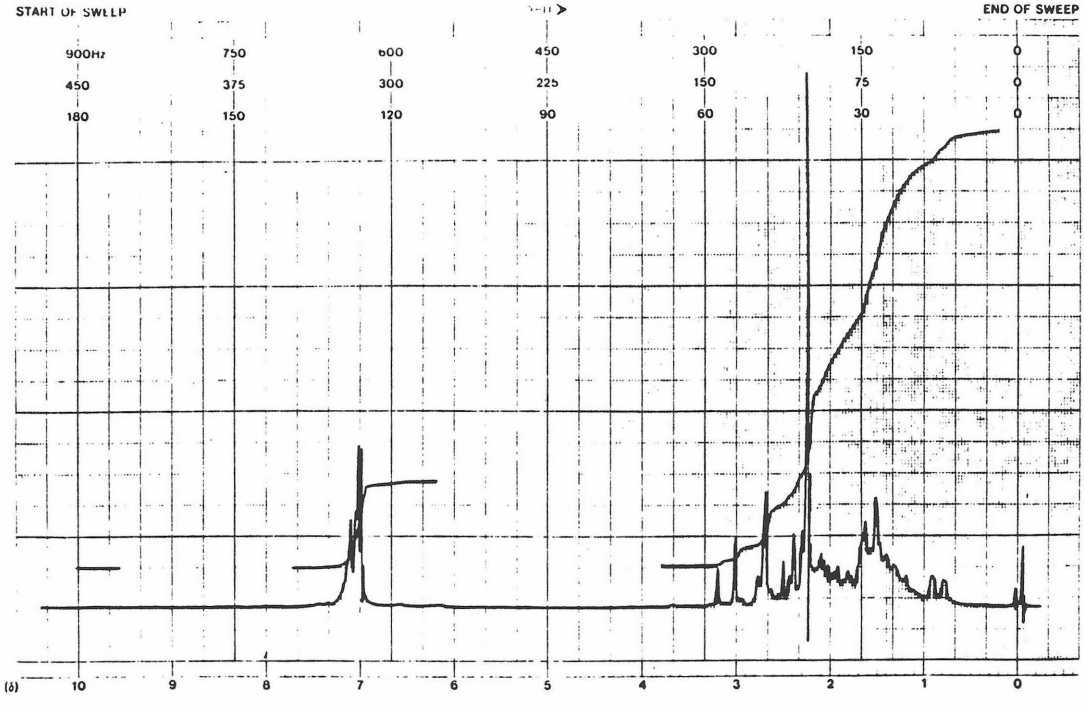
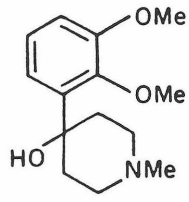


Page 51



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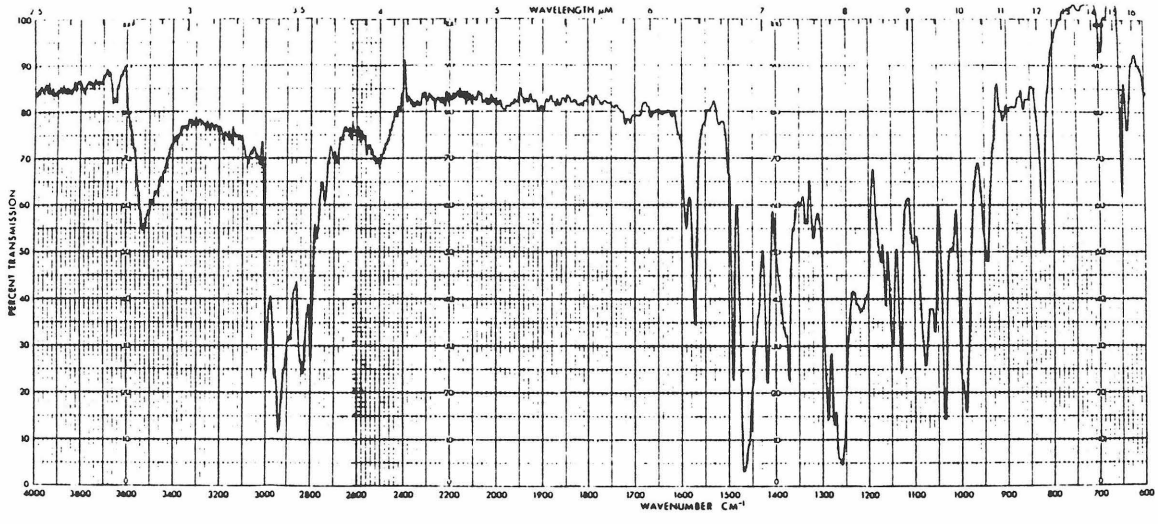

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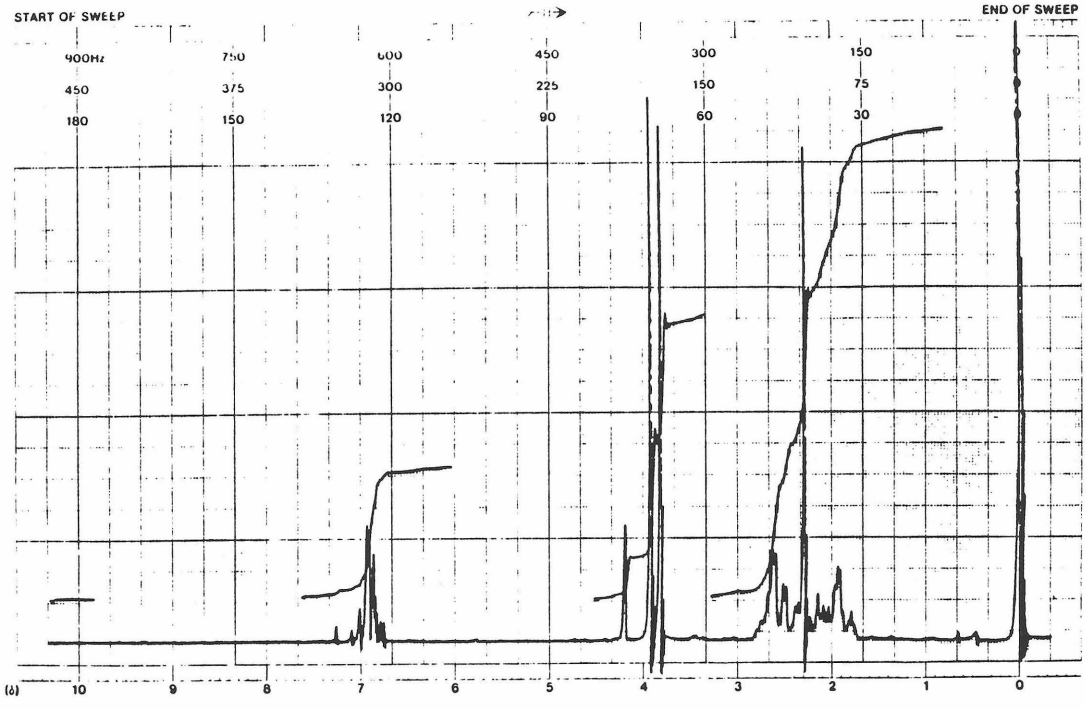
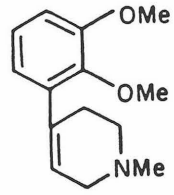


Page 52



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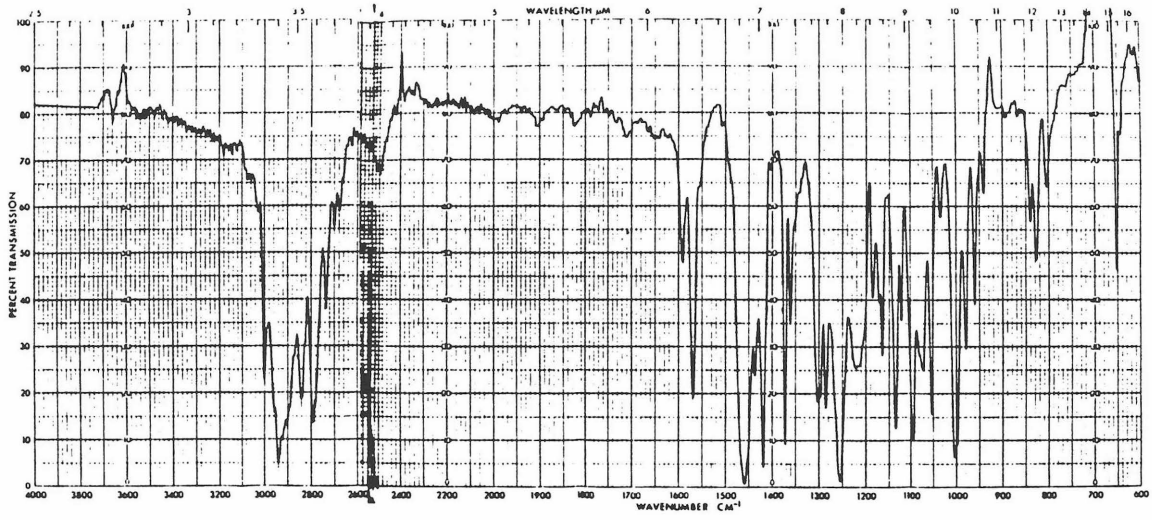

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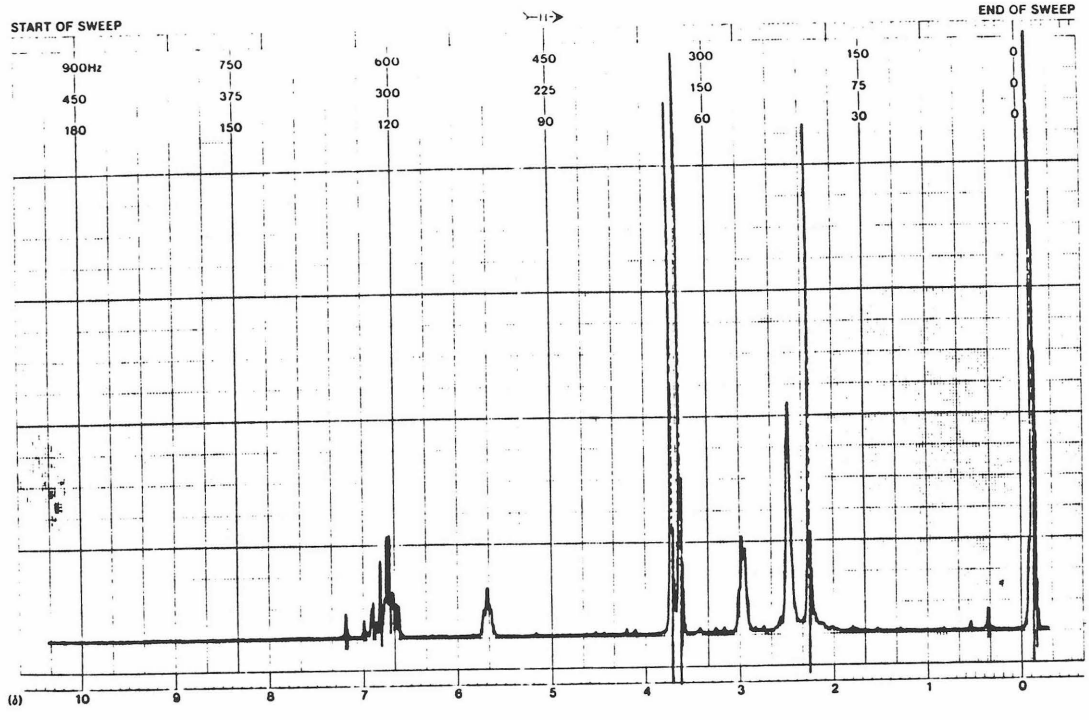

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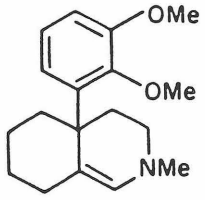

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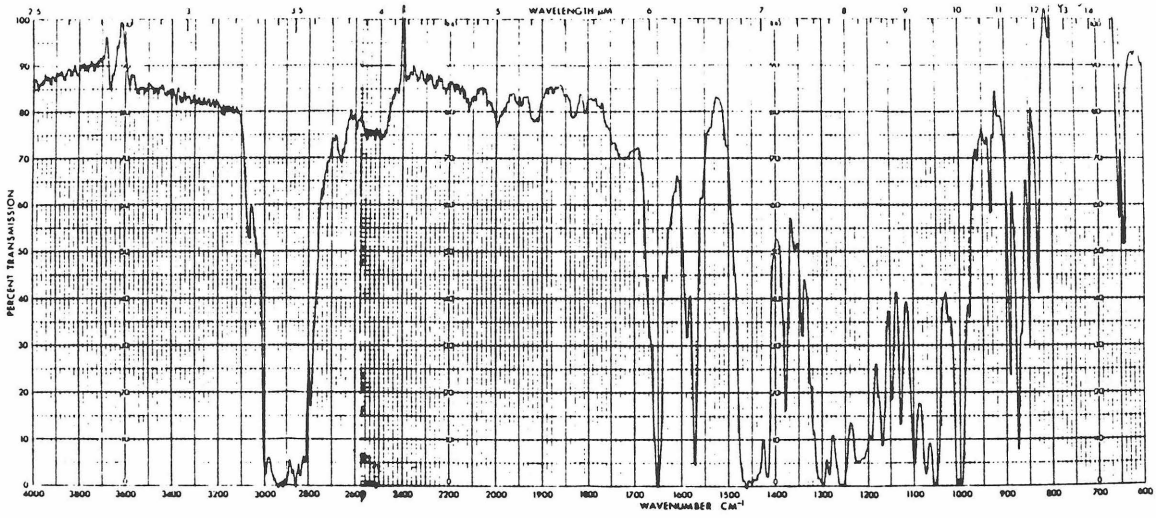

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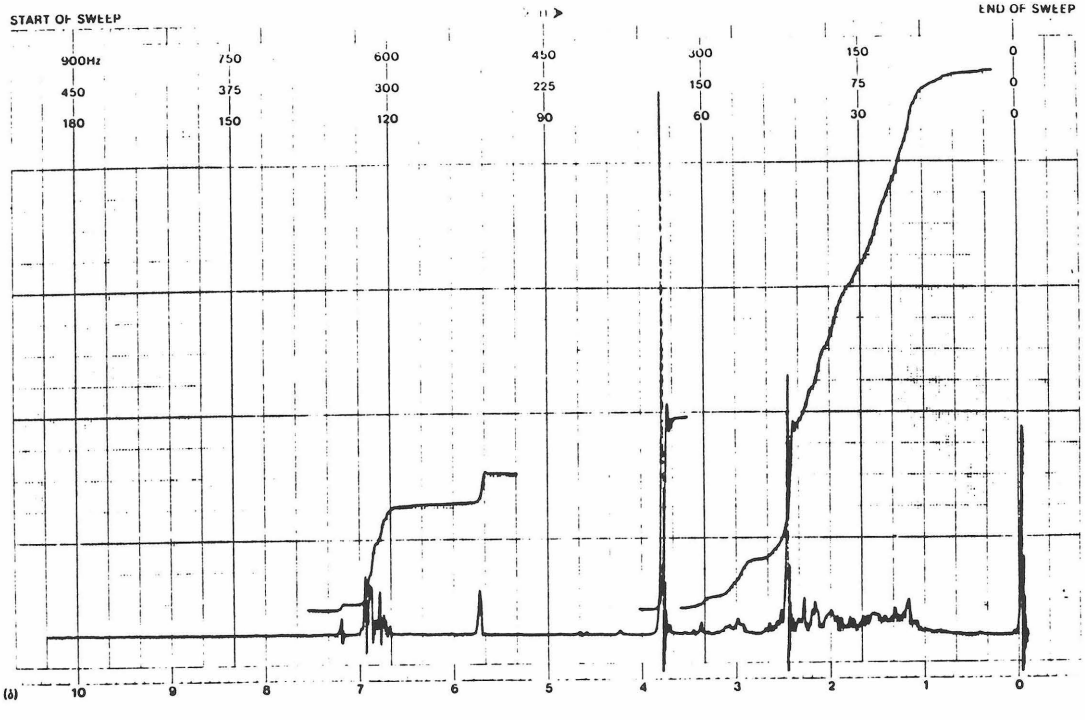

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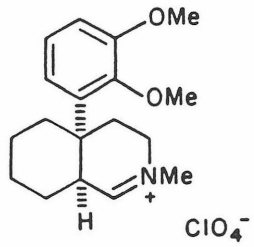

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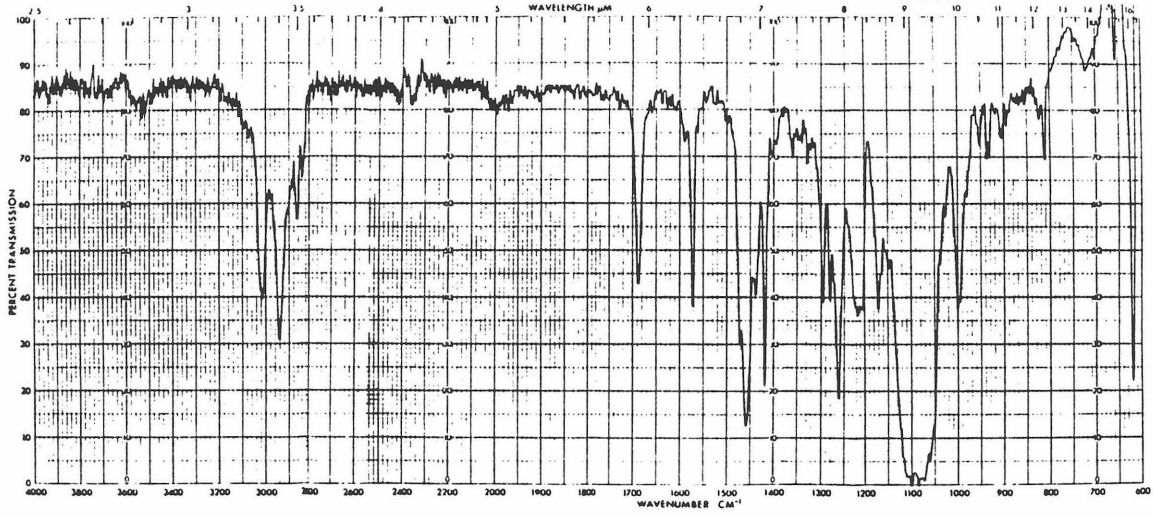

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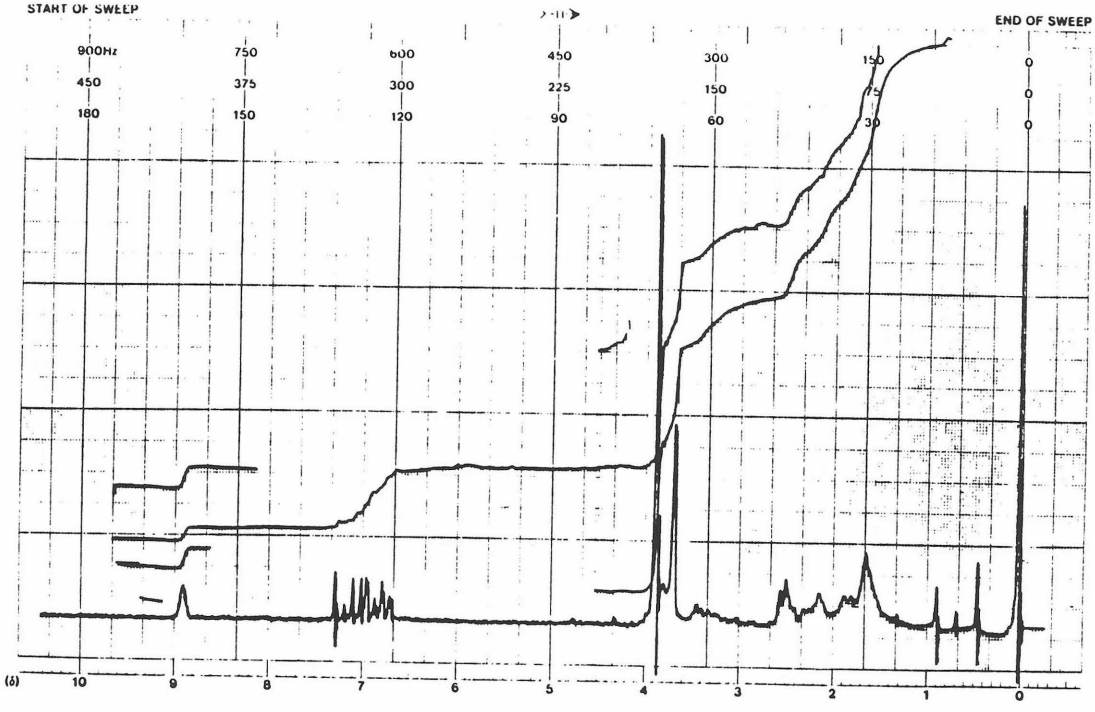
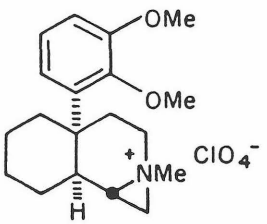
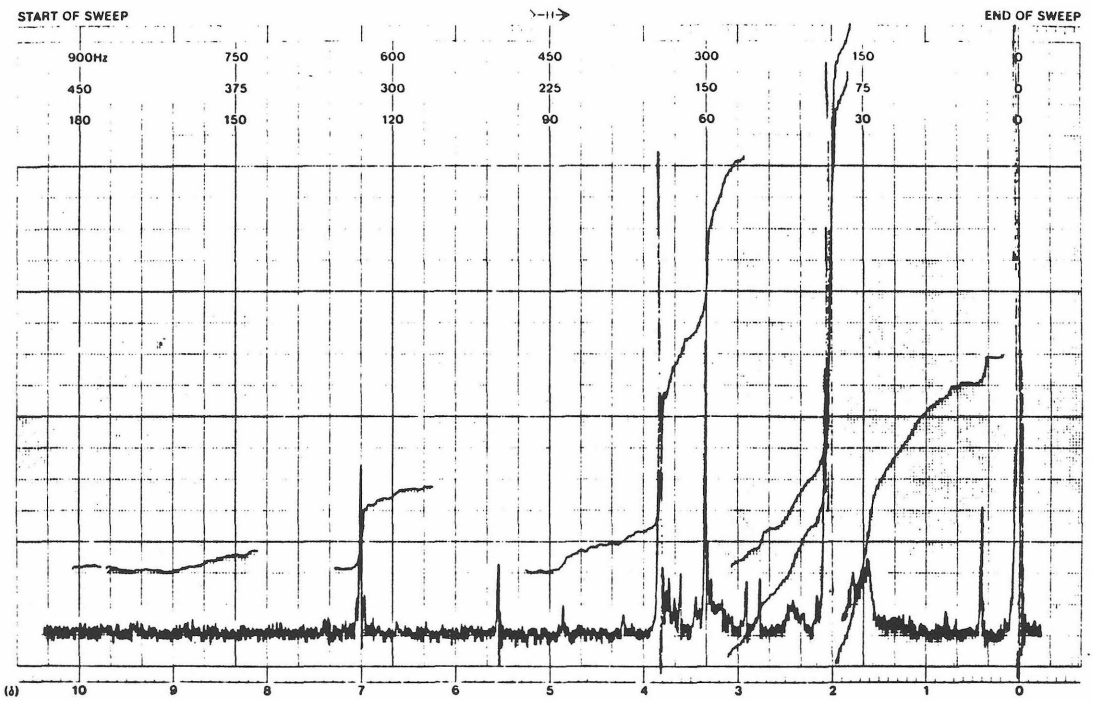


Page 54



36

CD_3CN/CD_3COCD_3



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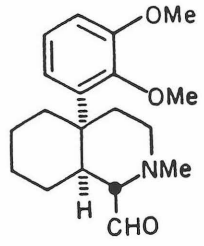

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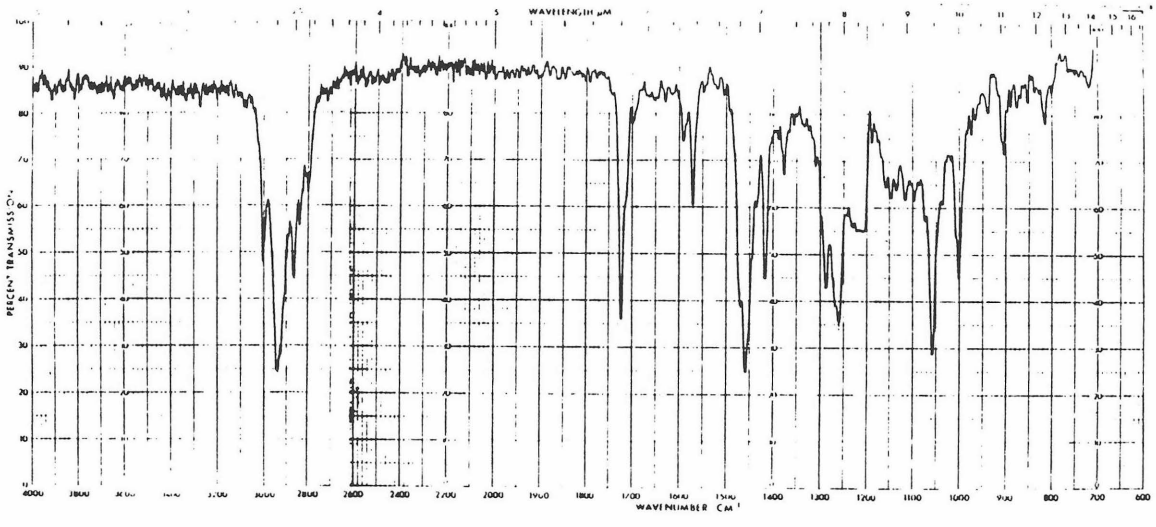
37



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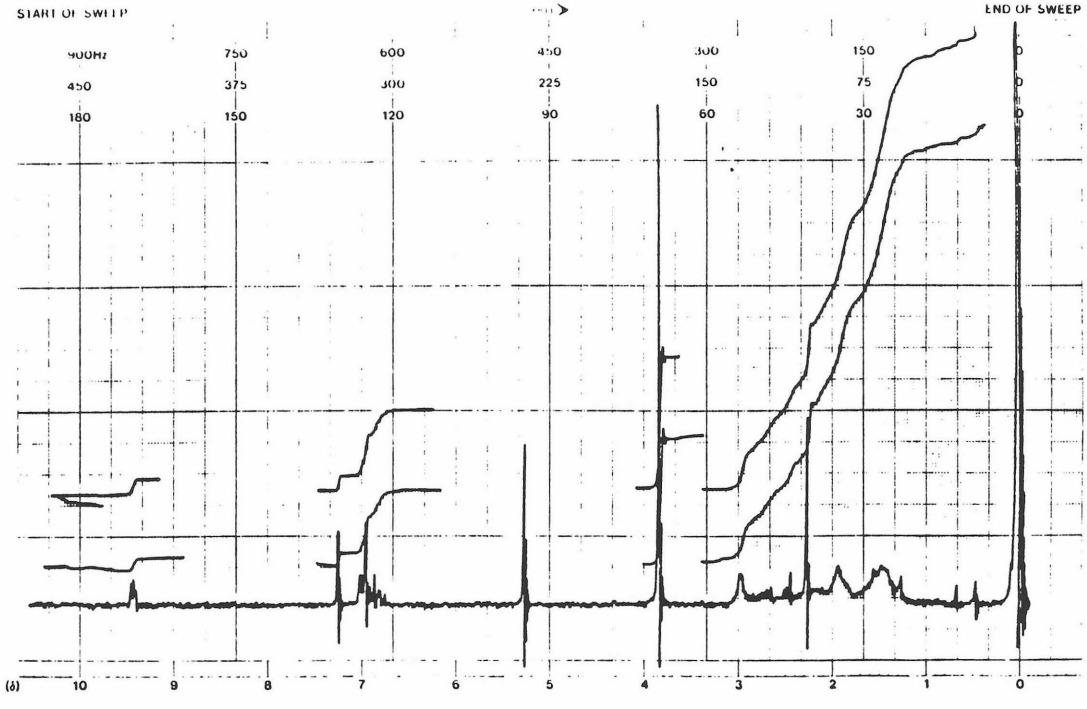
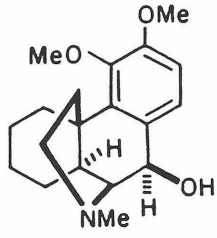


Page 55



38

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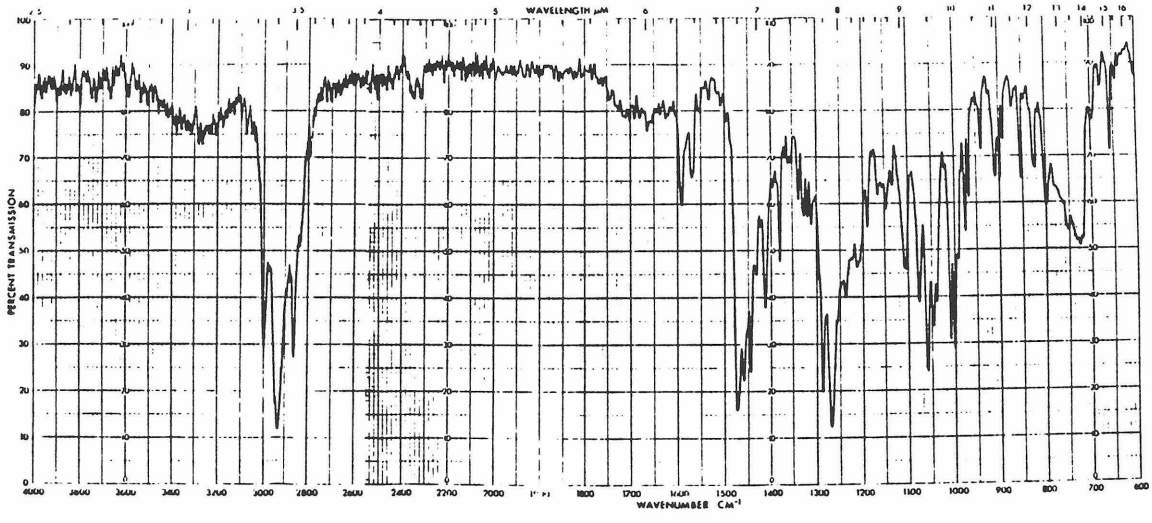

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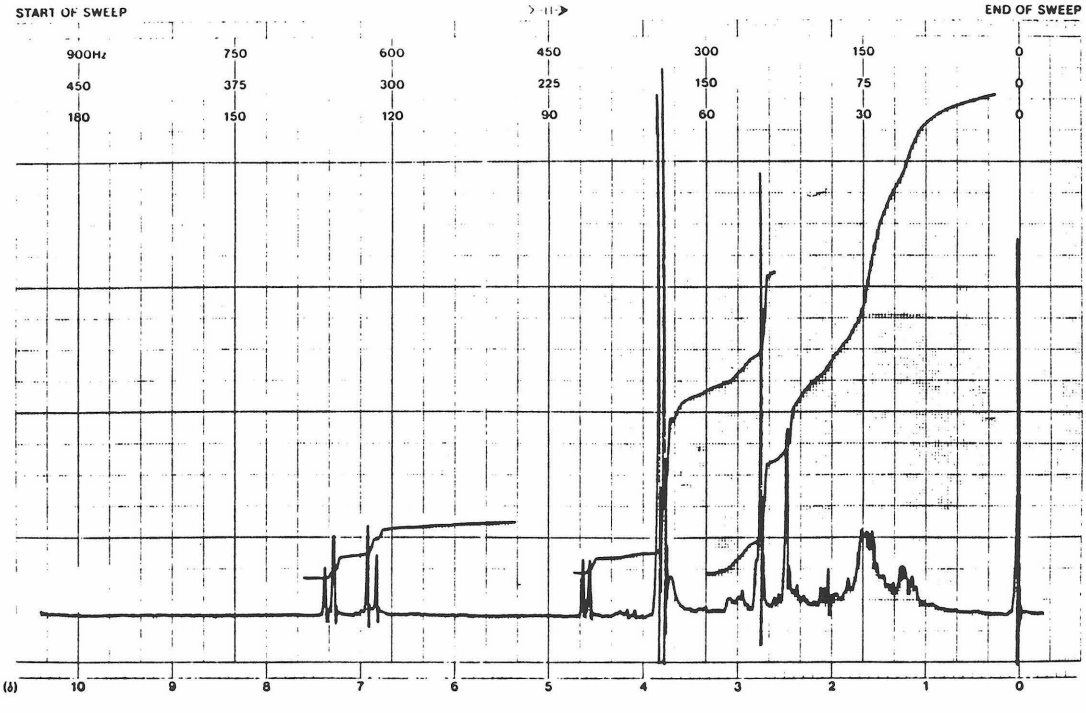
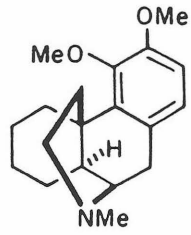


Page 56



39

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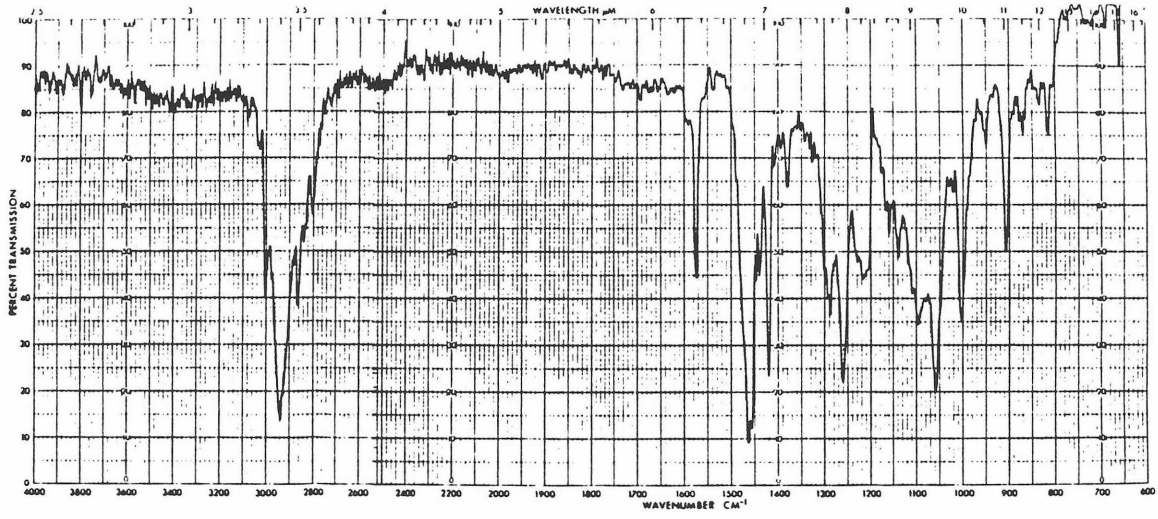
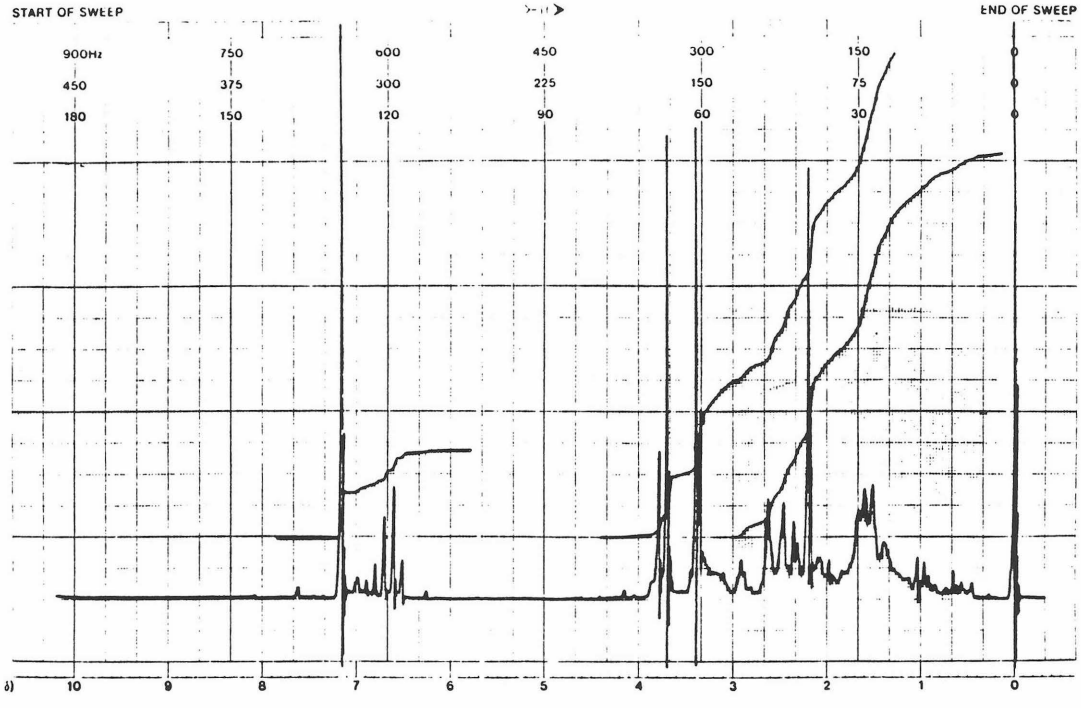
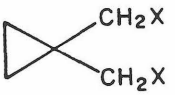


C_6D_6

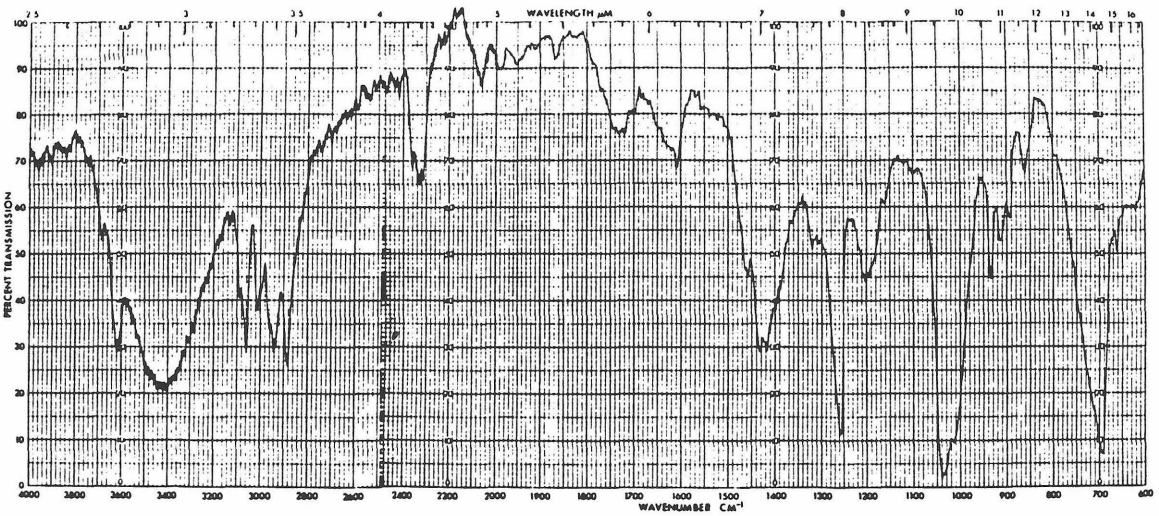


Page 57



41, X = OH

CH_2Cl_2



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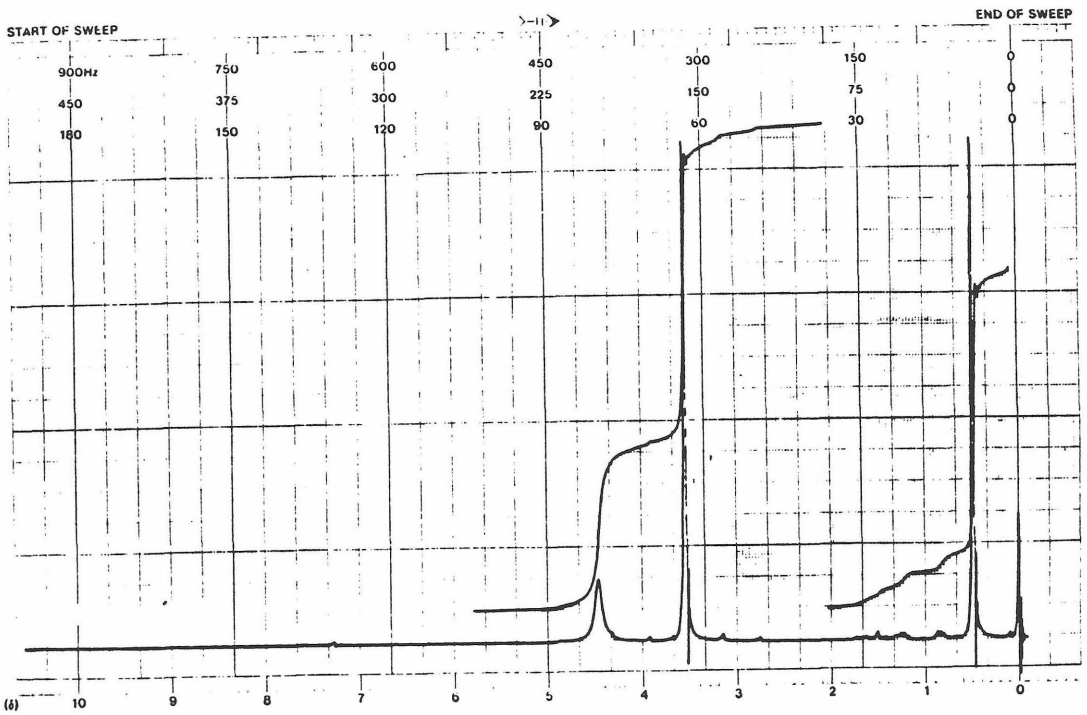
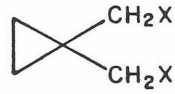
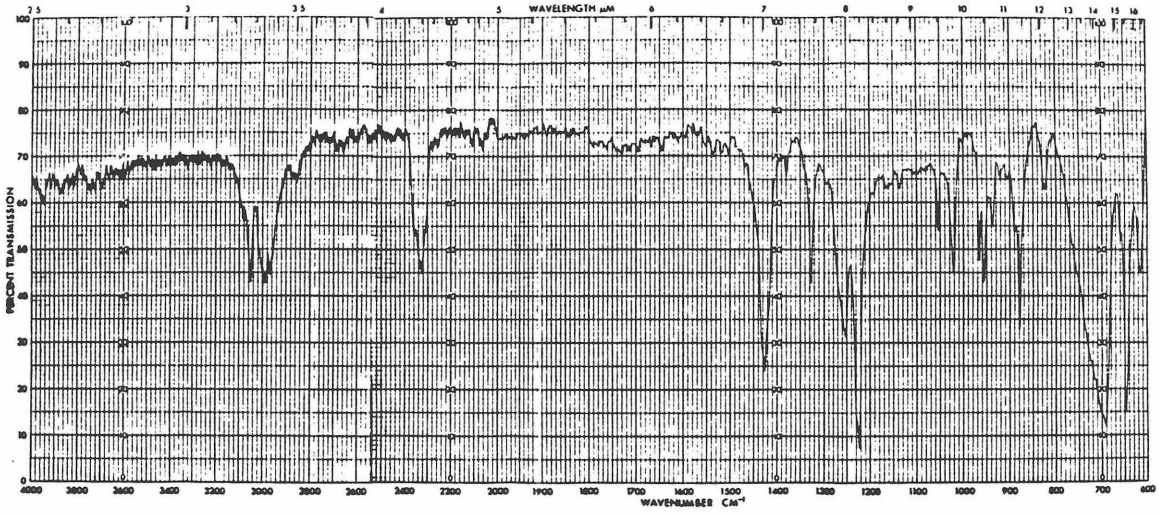


Page 57



42, X = Br

CH_2Cl_2



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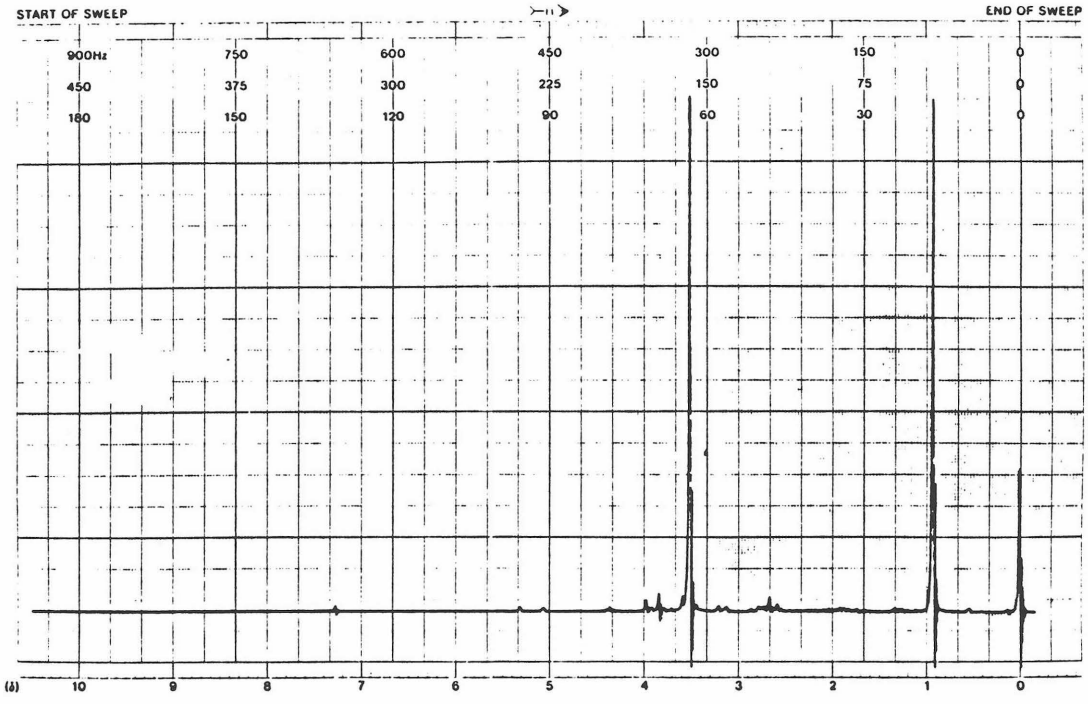
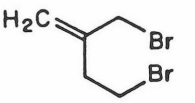
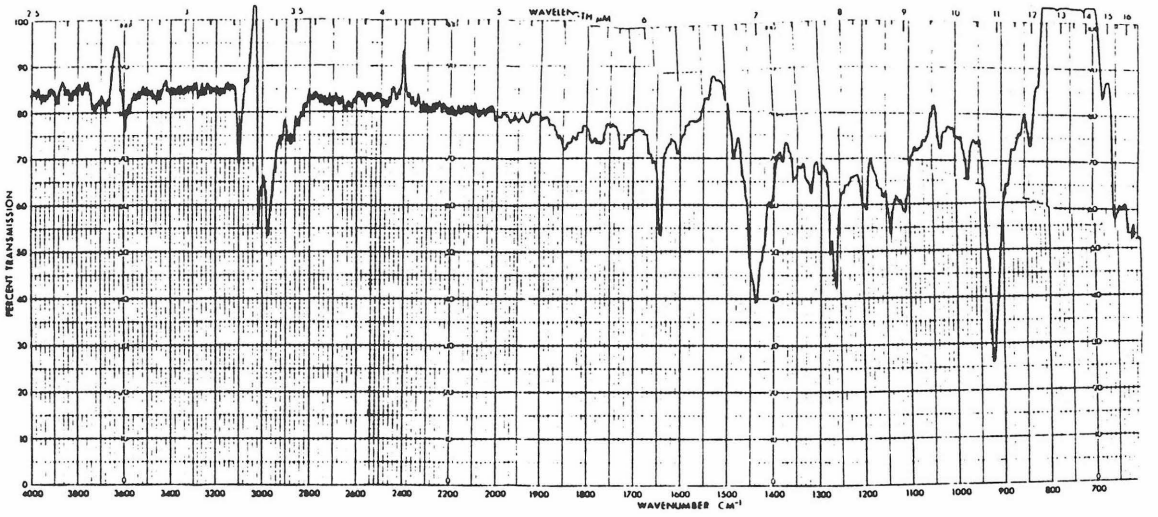


Page 58



8

CH_2Cl_2



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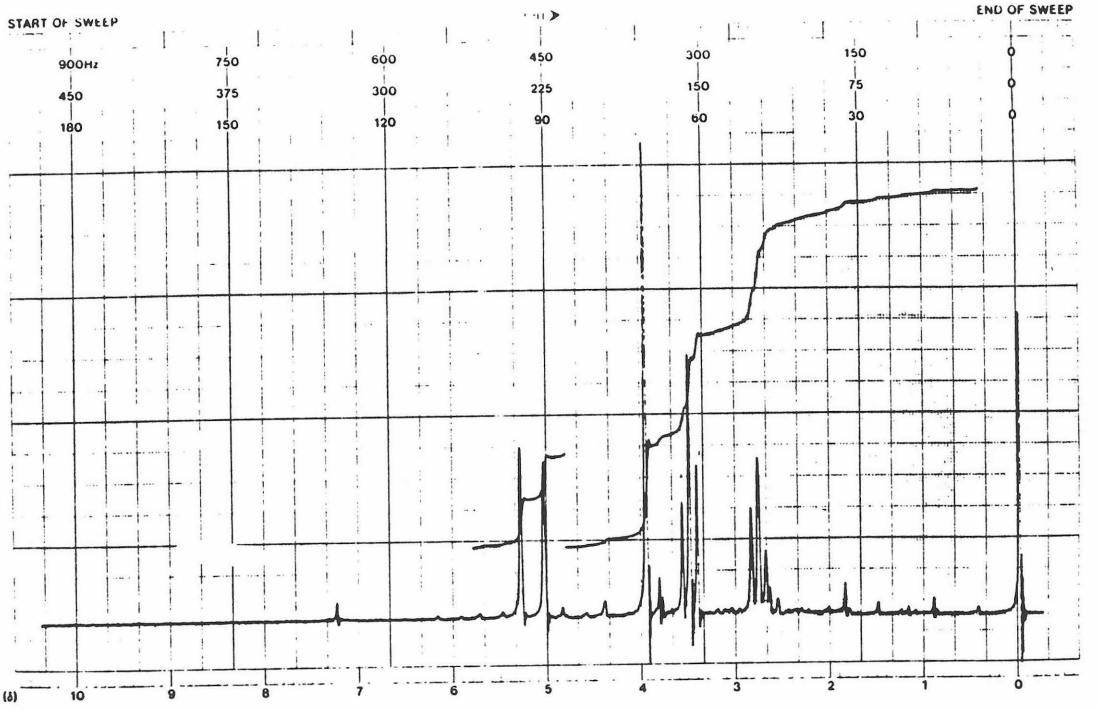
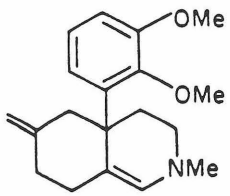


Page 60



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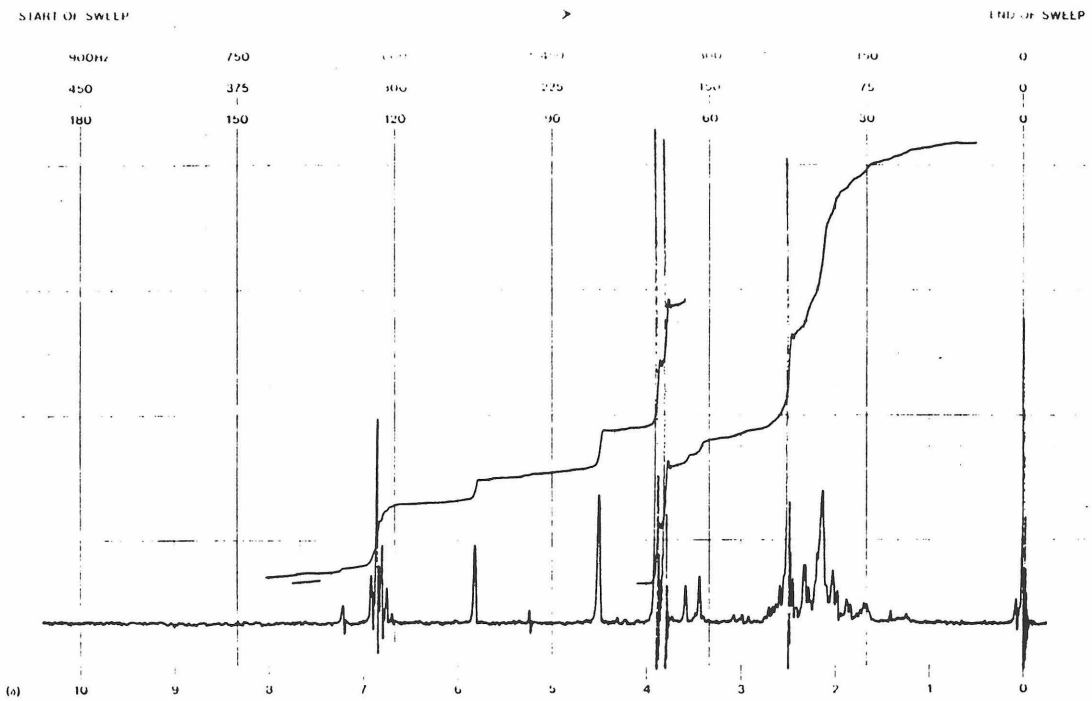
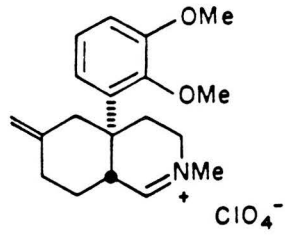
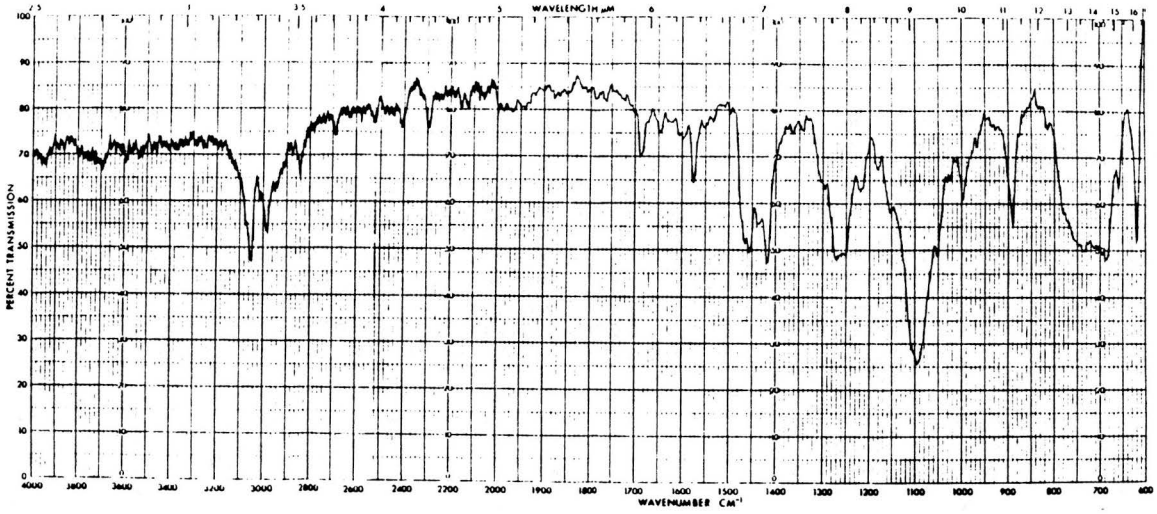


Page 61

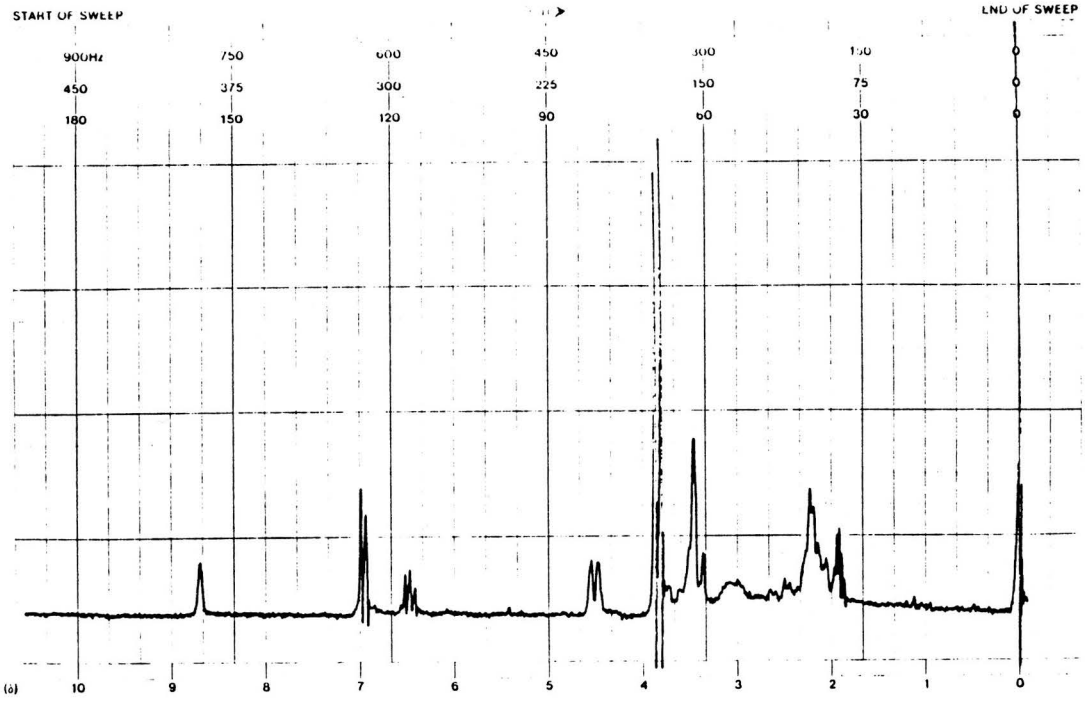


46a

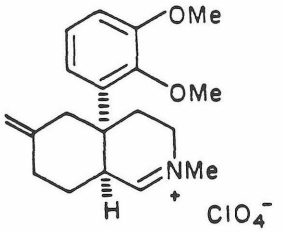
CH_2Cl_2



CD_3CN

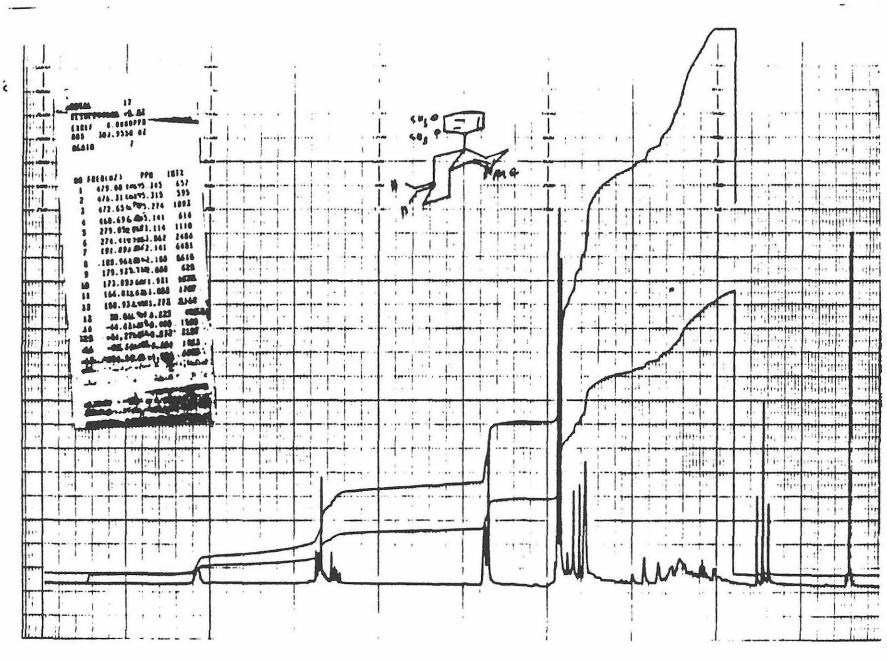


Page 61



46b

CD_3CN



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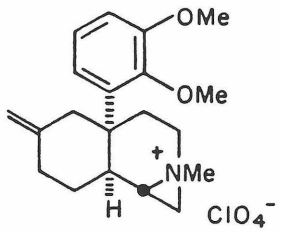
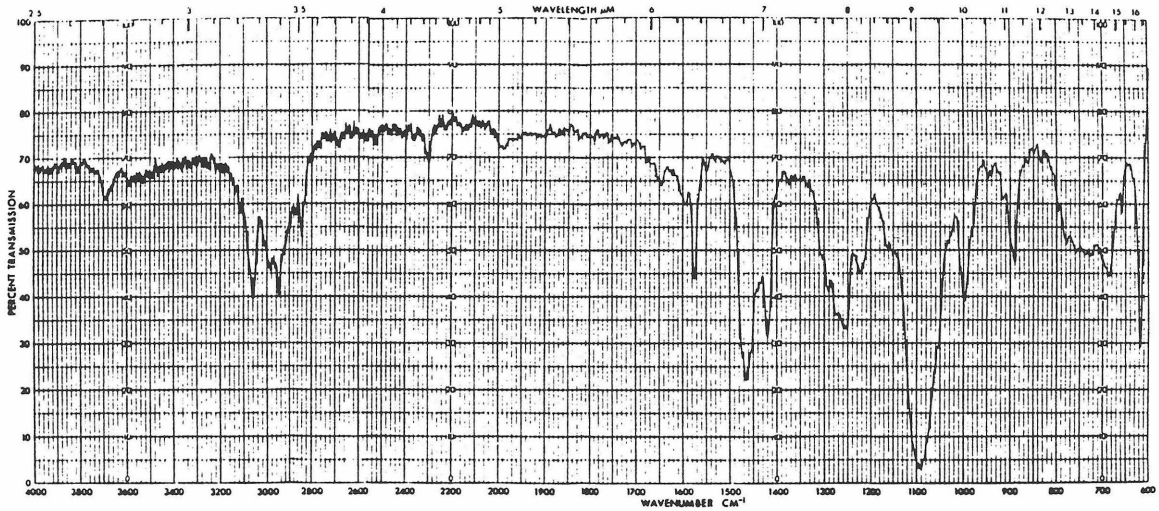
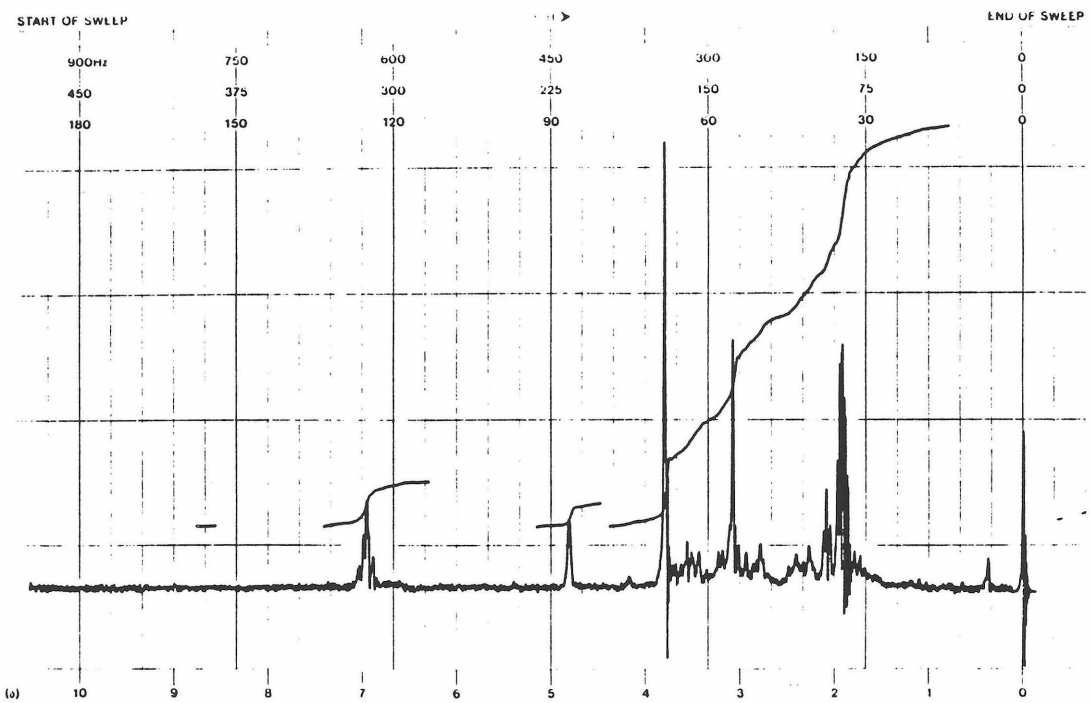


47

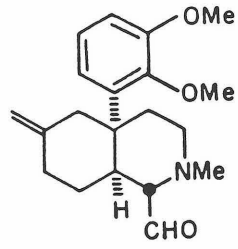
CH_2Cl_2



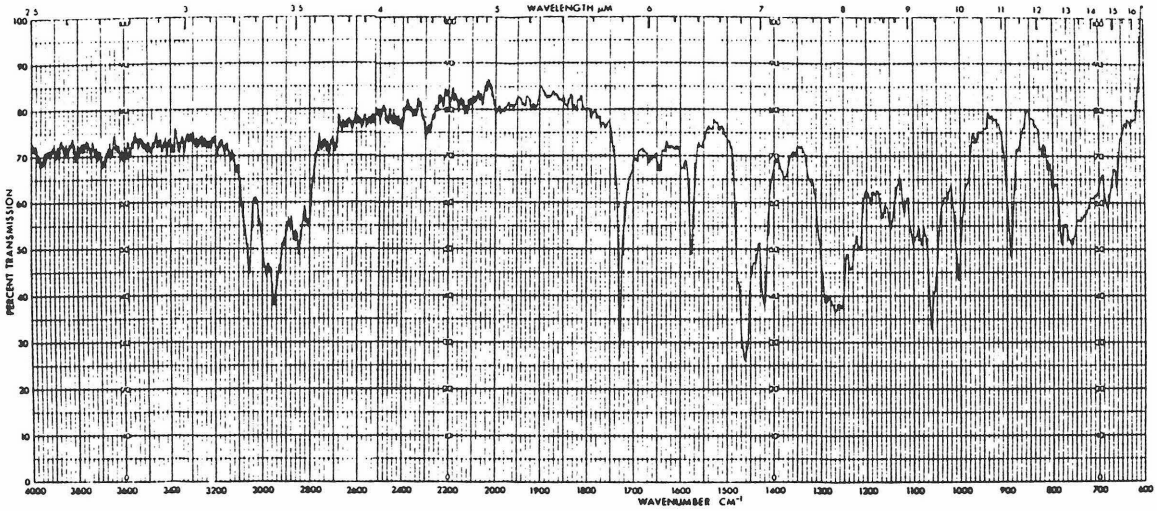
CD_3CN



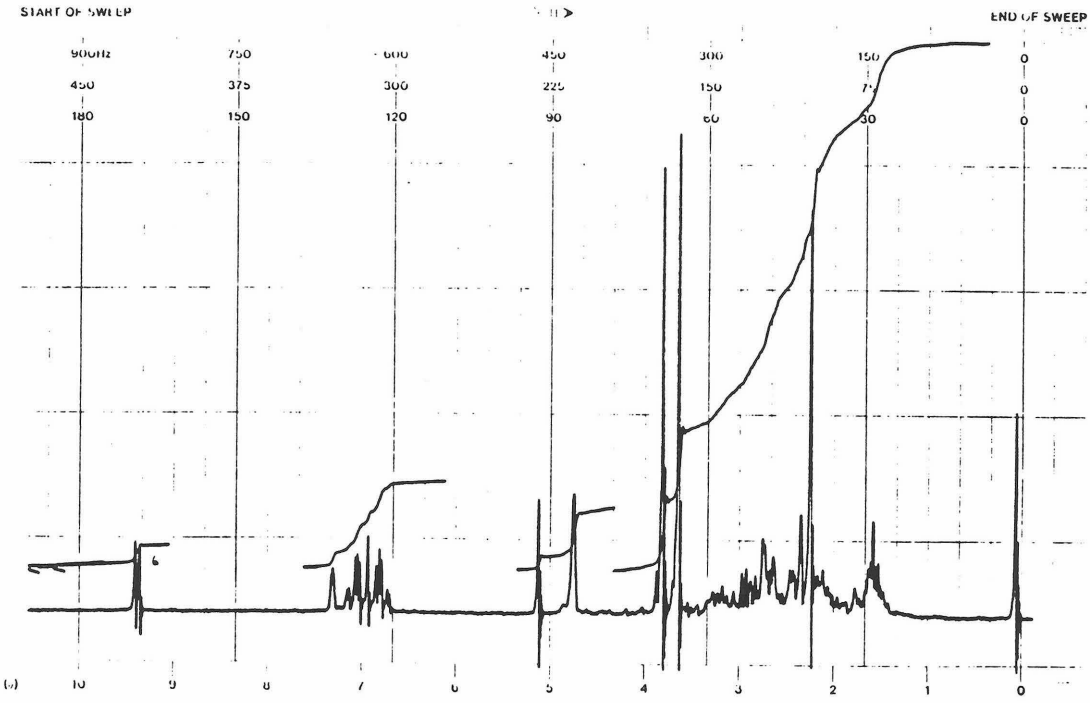
Page 62



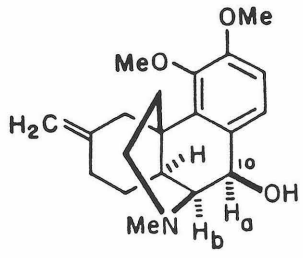
CH_2Cl_2 48



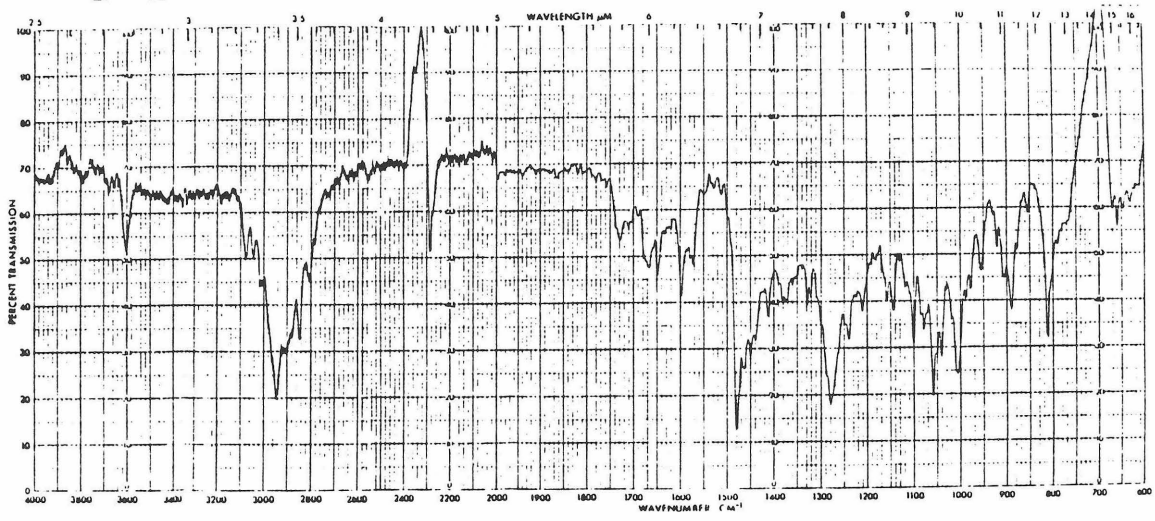
CD_3CN/C_6D_6



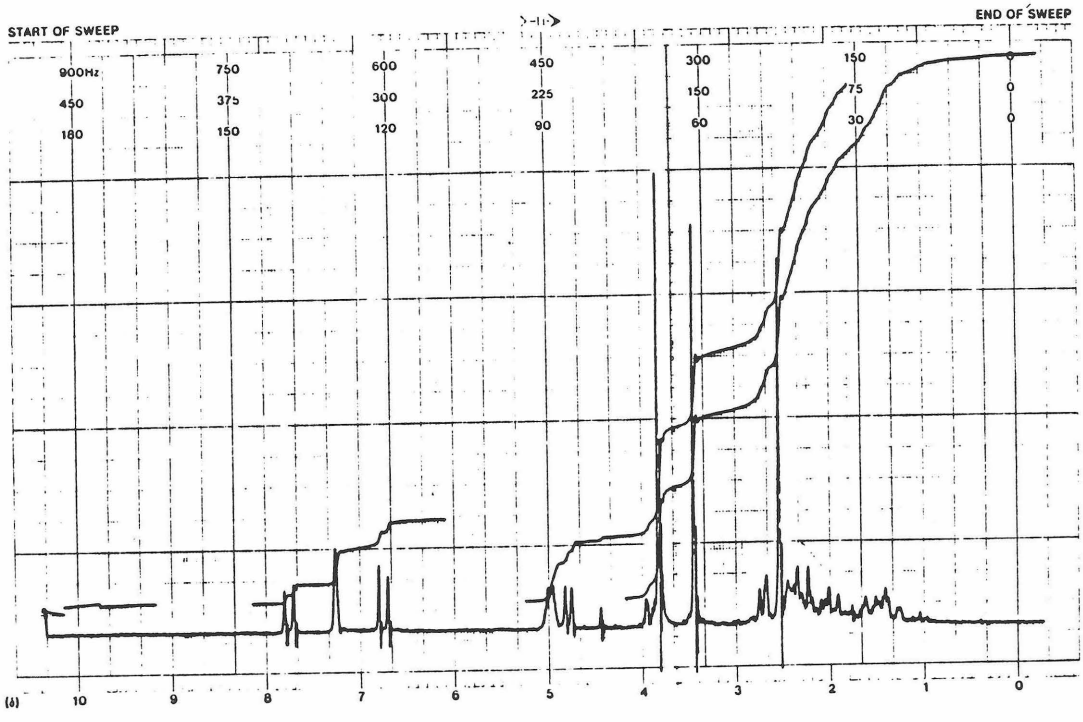
Page 63



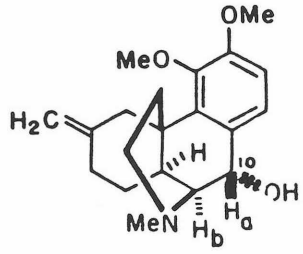
CH_2Cl_2 49



C_6D_6

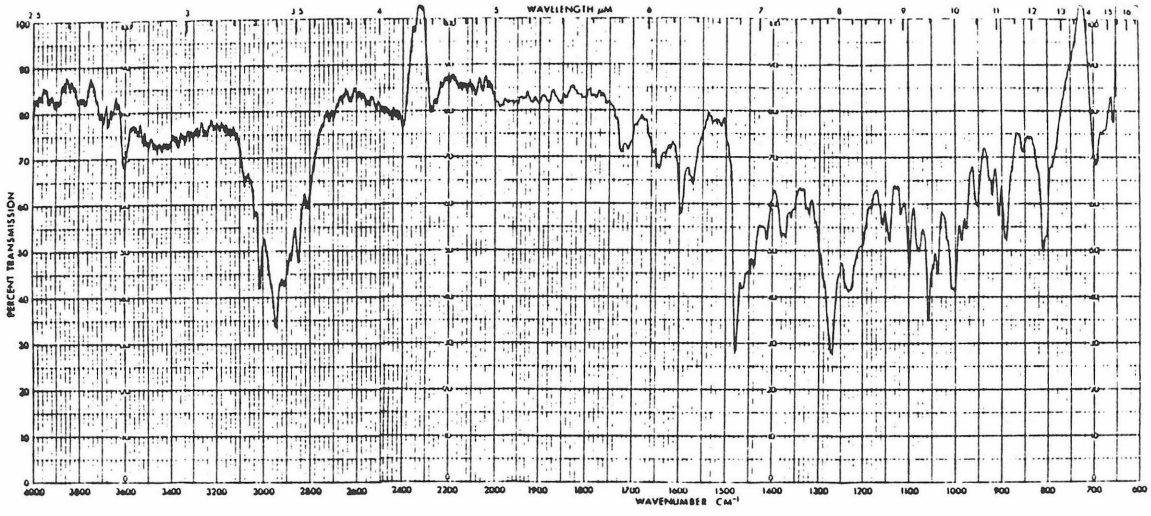


Page 63

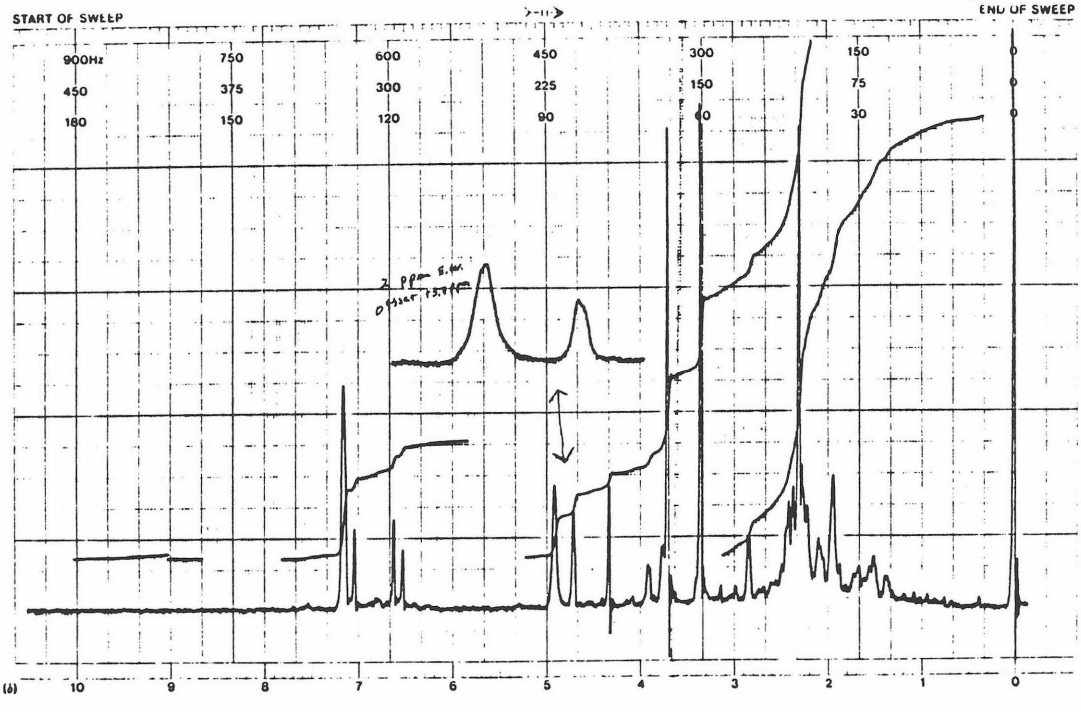


$CHCl_3$

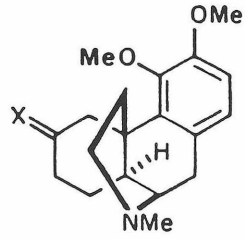
49a, 10α OH



C_6D_6

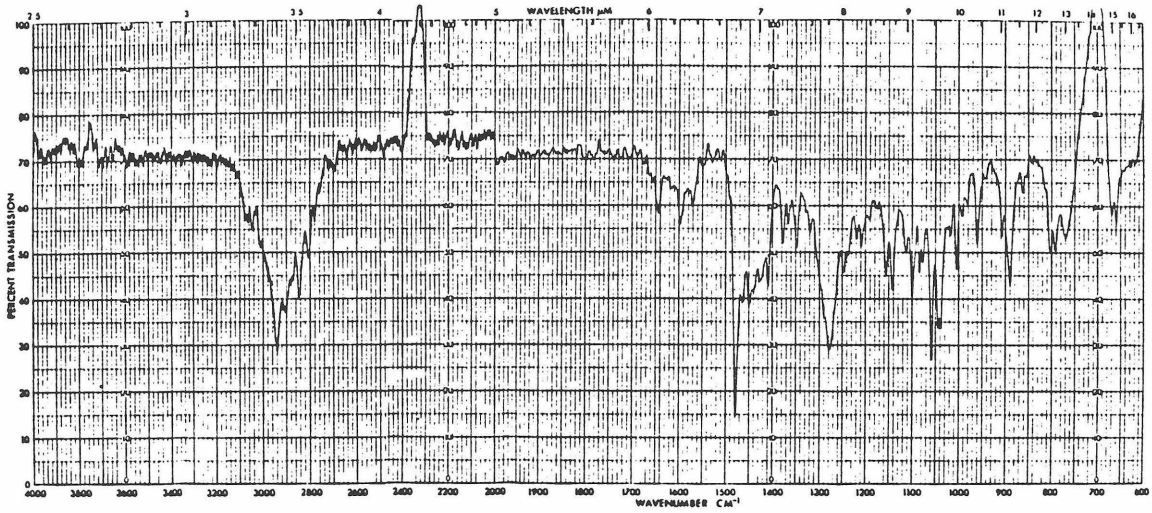


Page 64

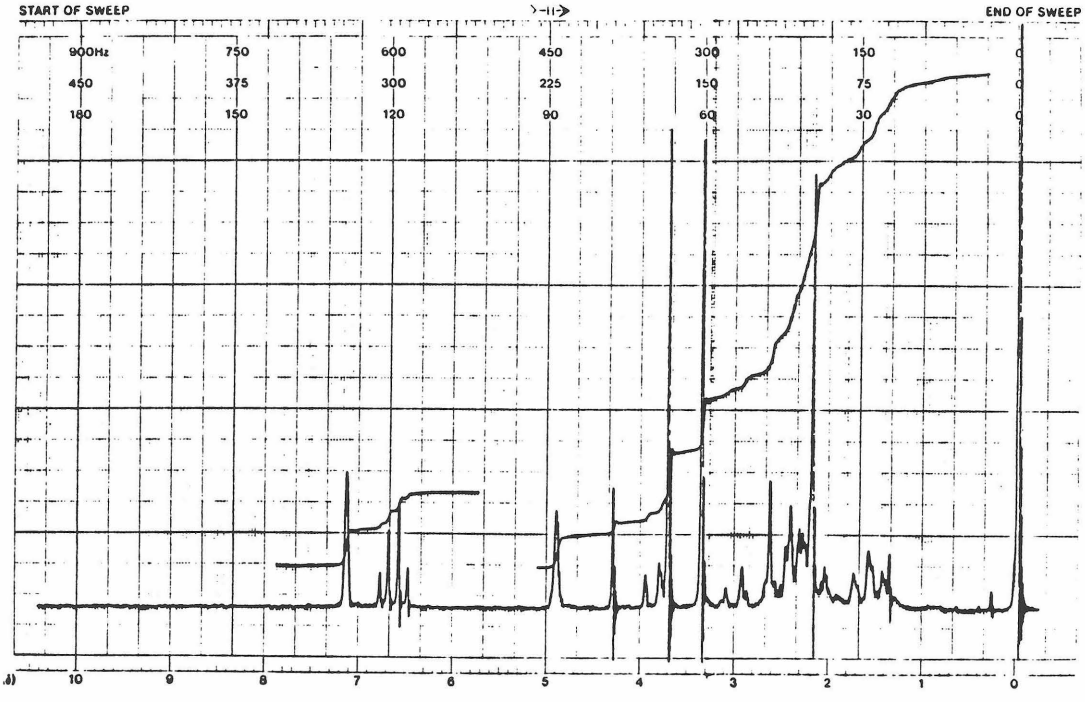


CH_2Cl_2

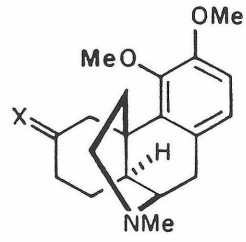
50, X = CH_2



C_6D_6

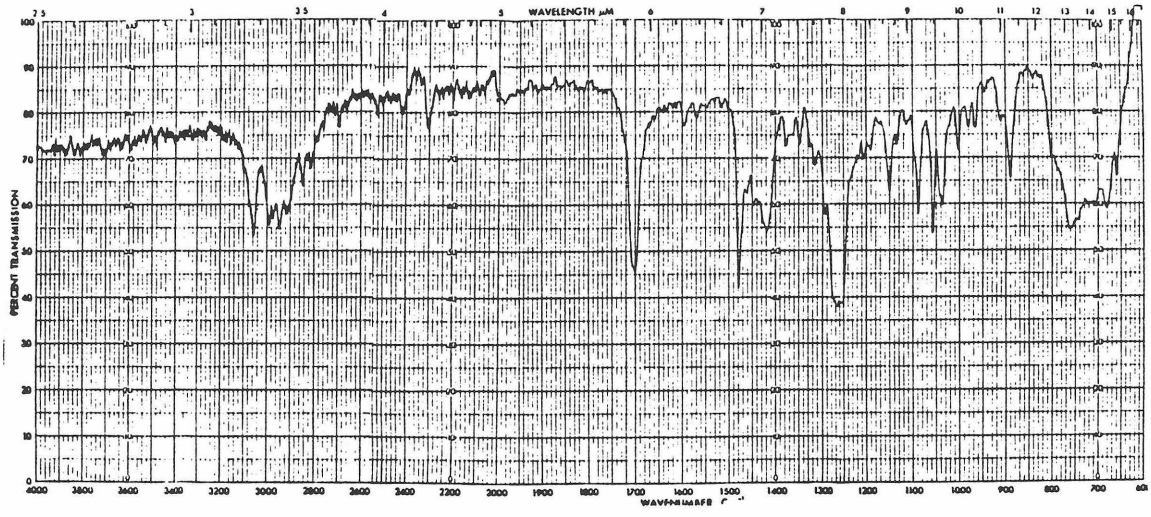


Page 66



CH_2Cl_2

51, X = O



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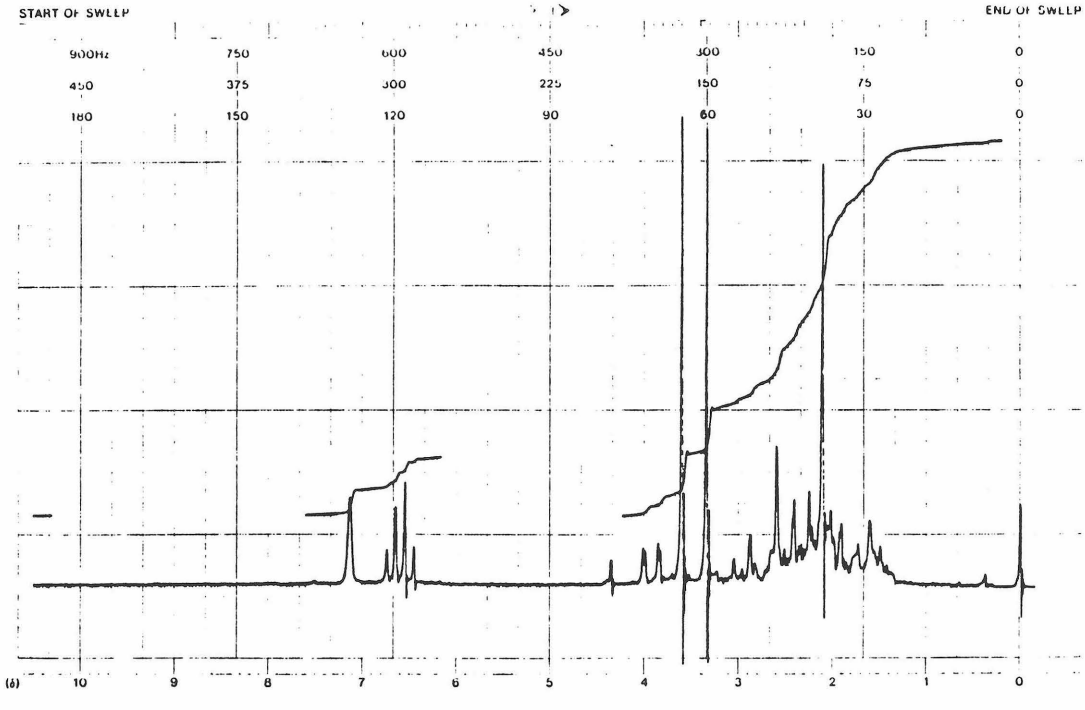
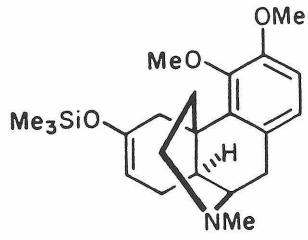
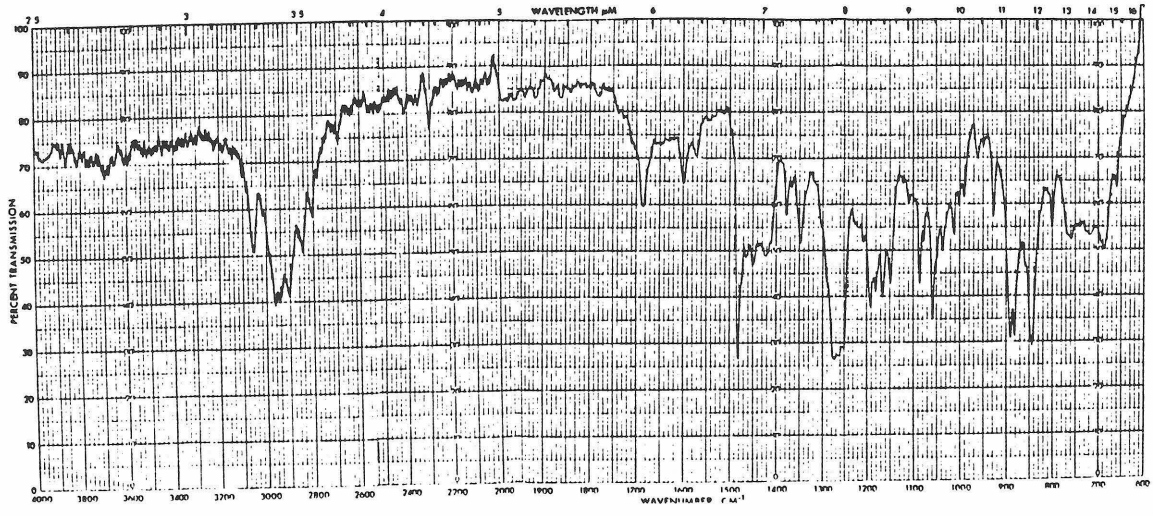


Page 67



52

CH_2Cl_2



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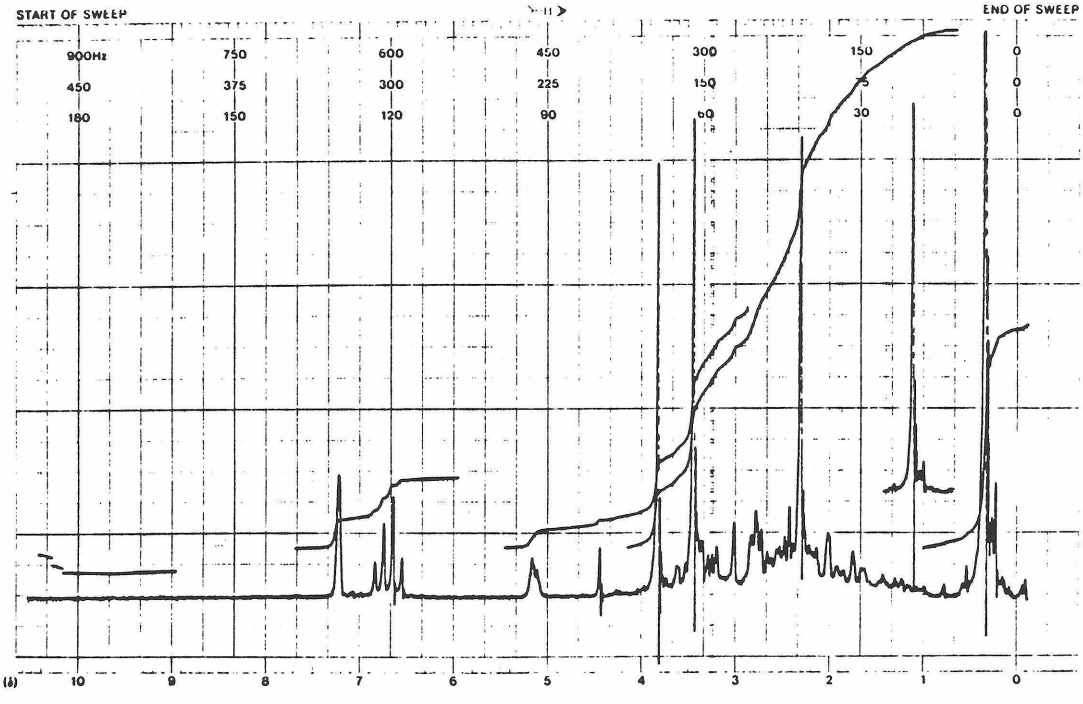
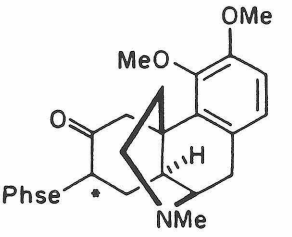
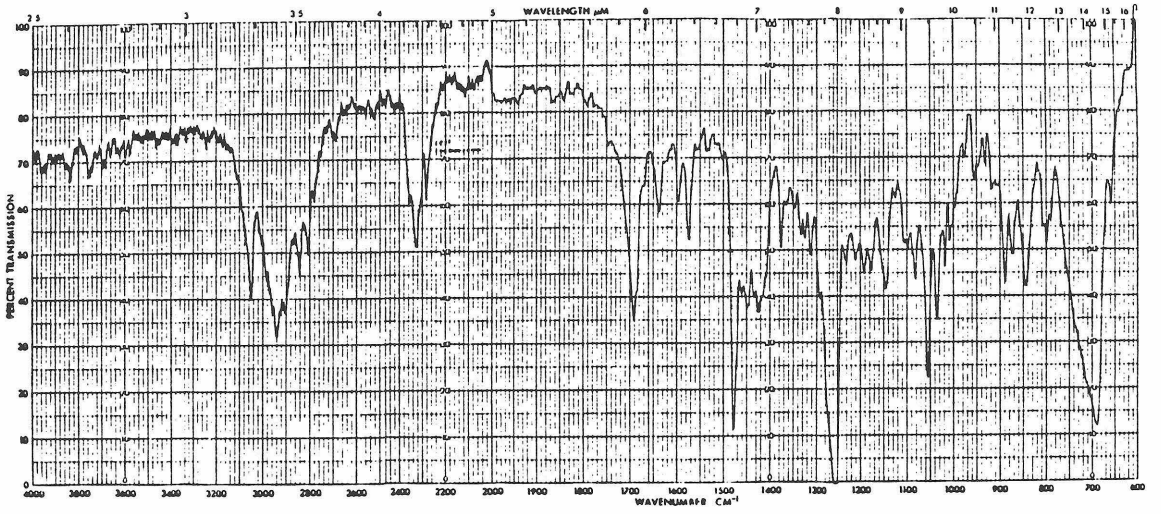


Page 68



53a,b

CH_2Cl_2



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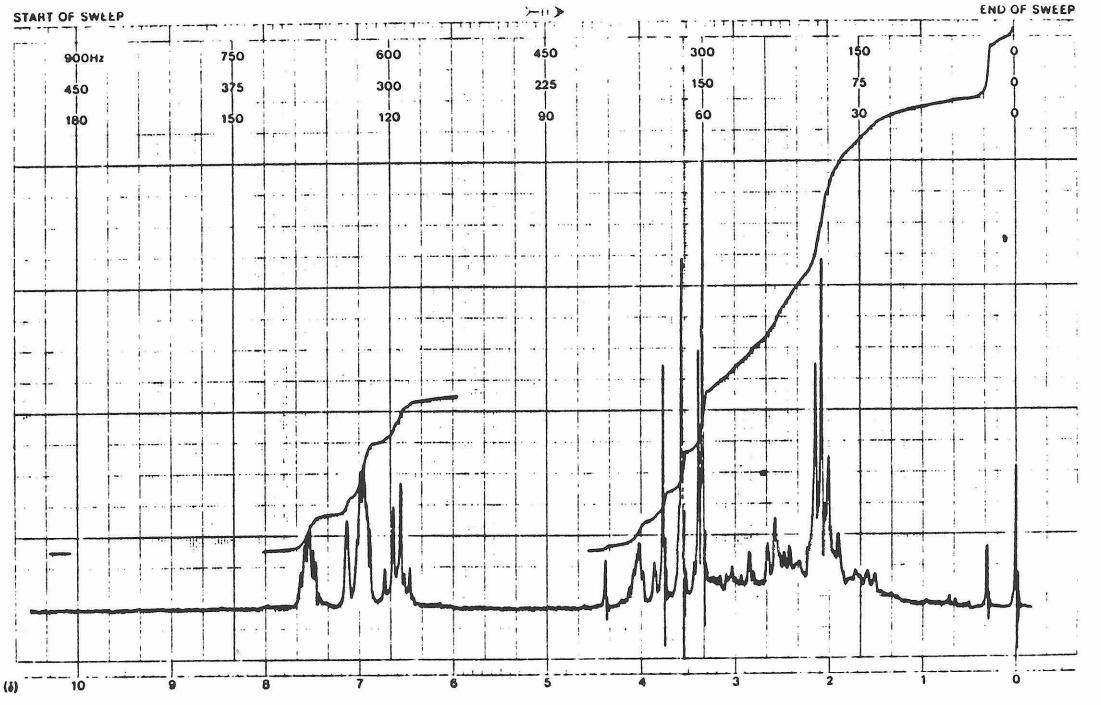
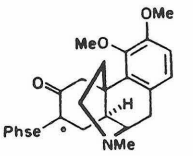
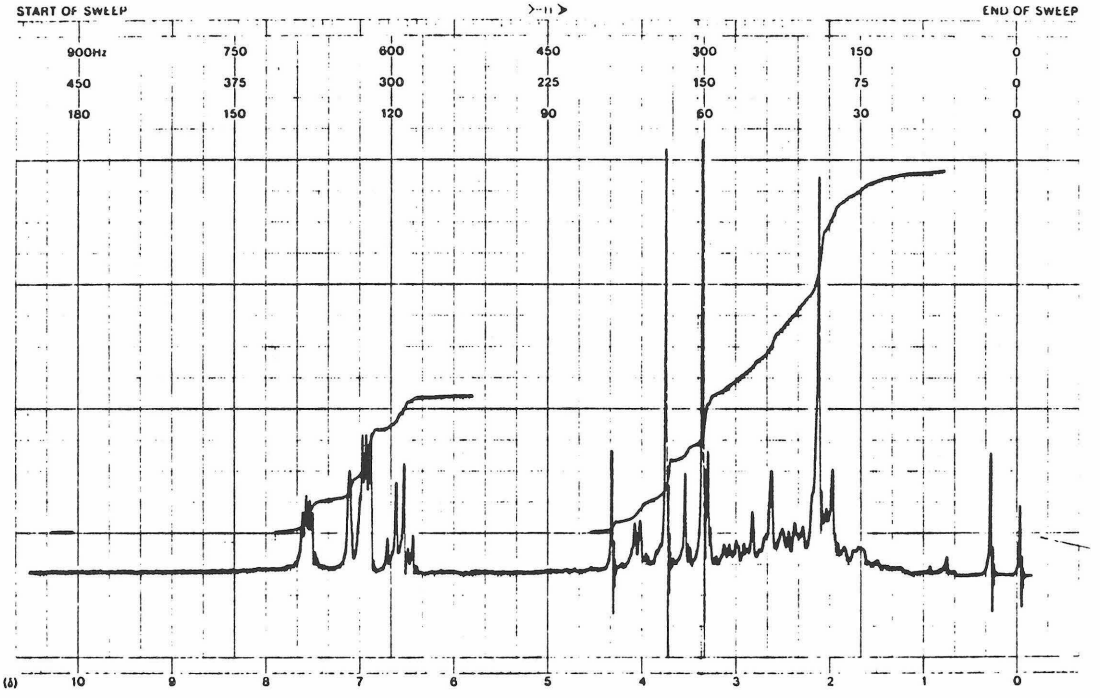


Page 68

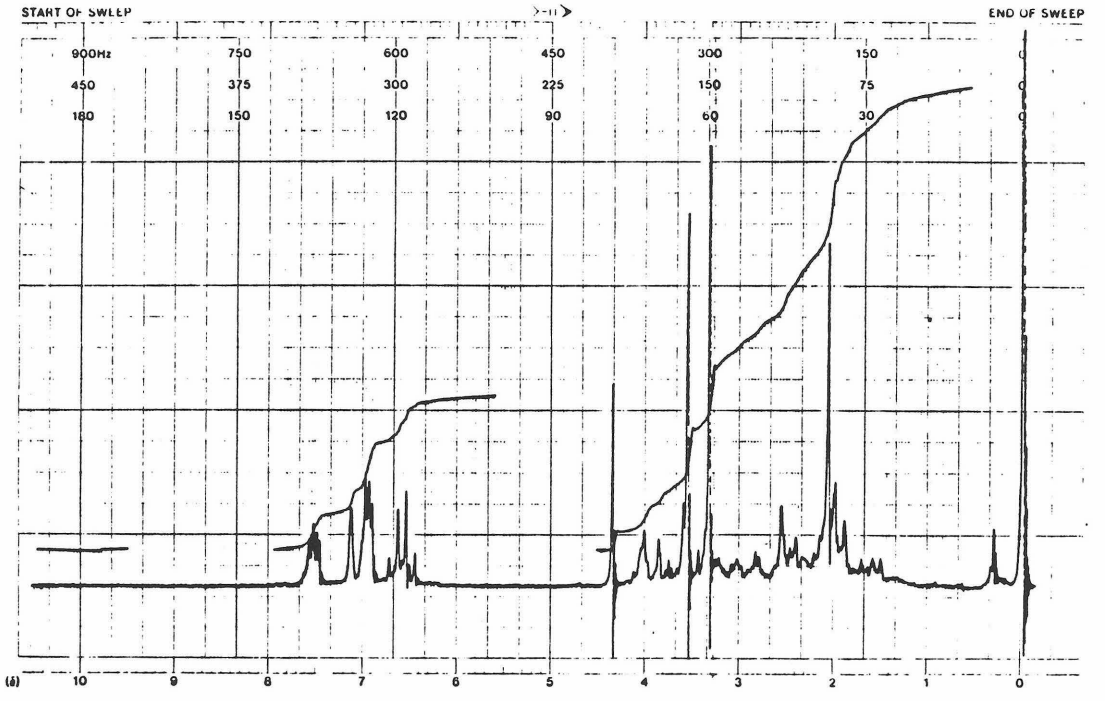


53a,b

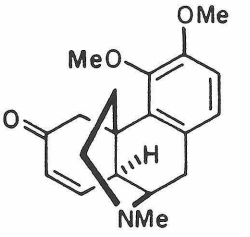
C_6D_6 Epimer A



C_6D_6 Epimer B



Page 69



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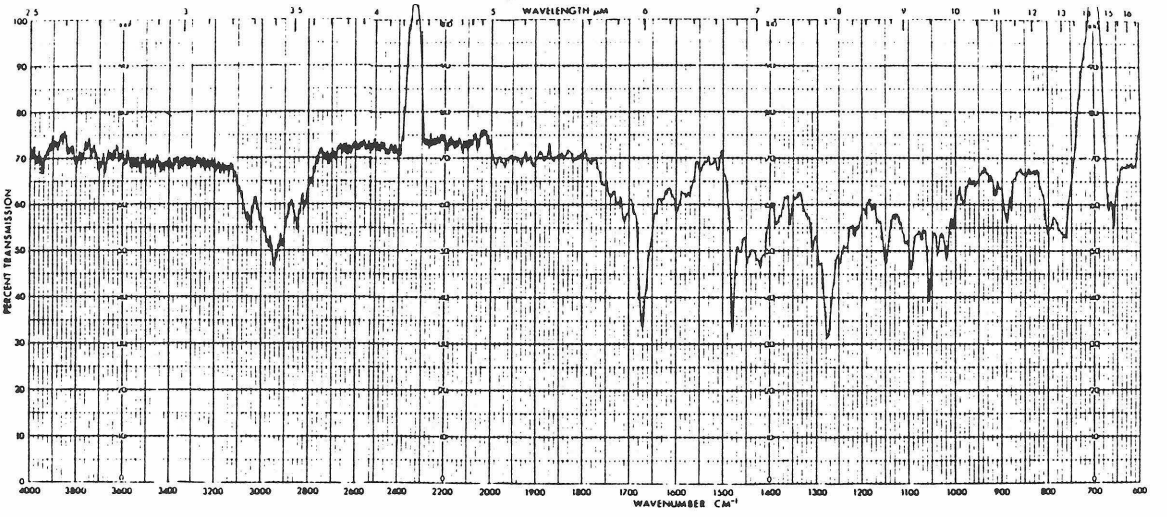
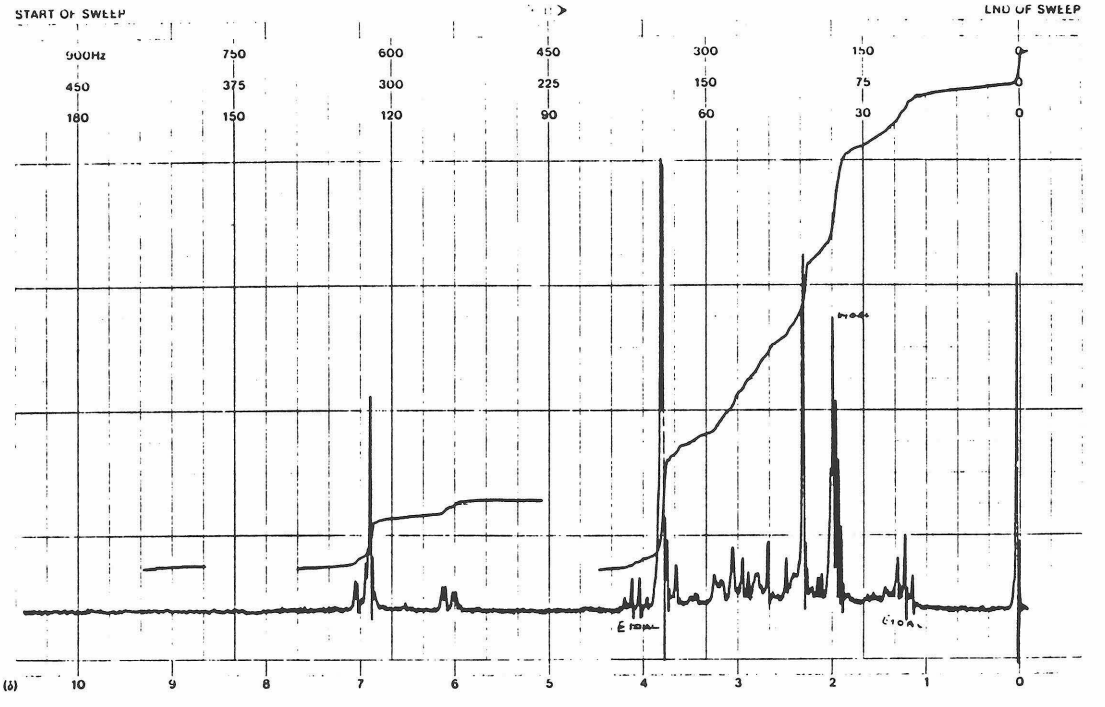
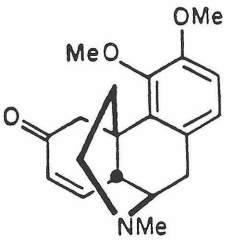
CH_2Cl_2



CD_3CN



Page 71



CH_2Cl_2

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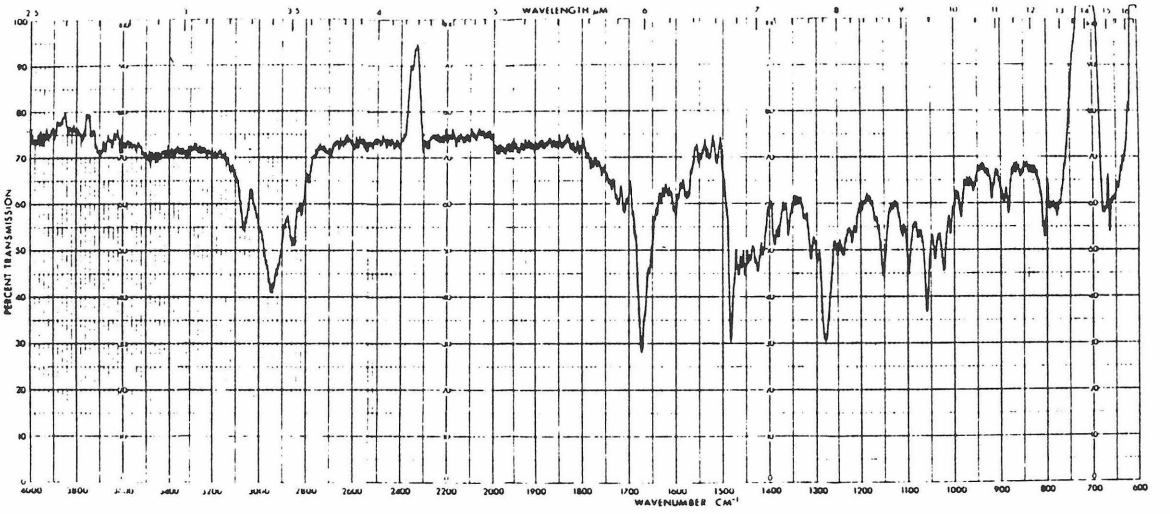

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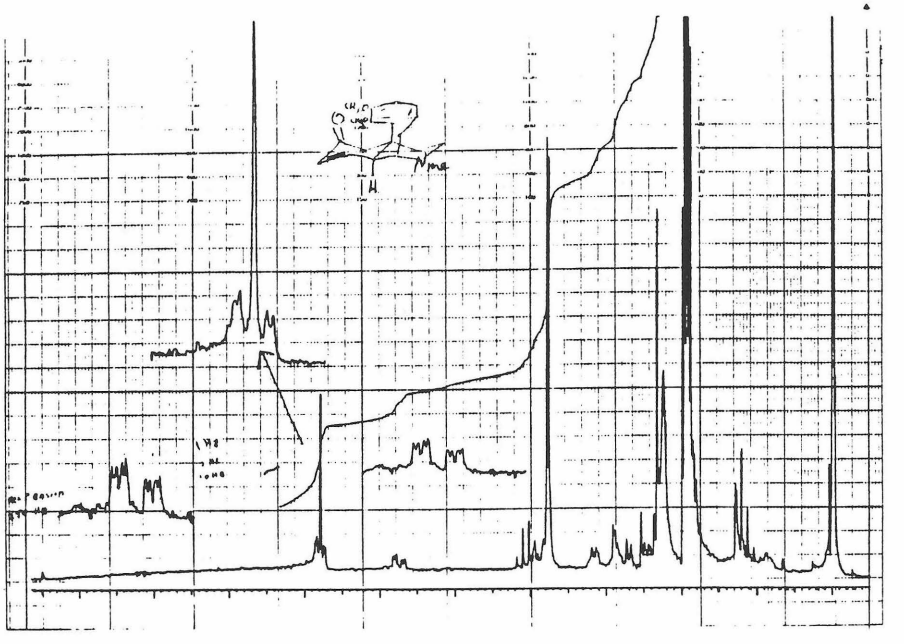
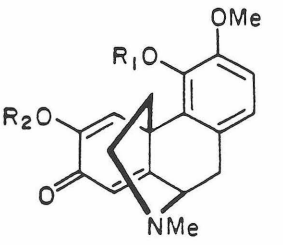
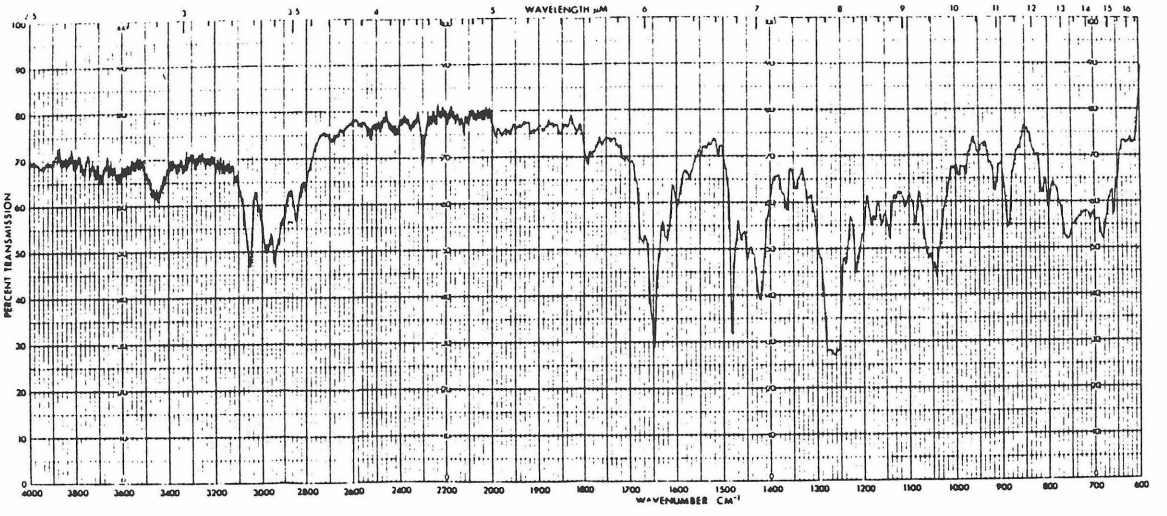


Page 70

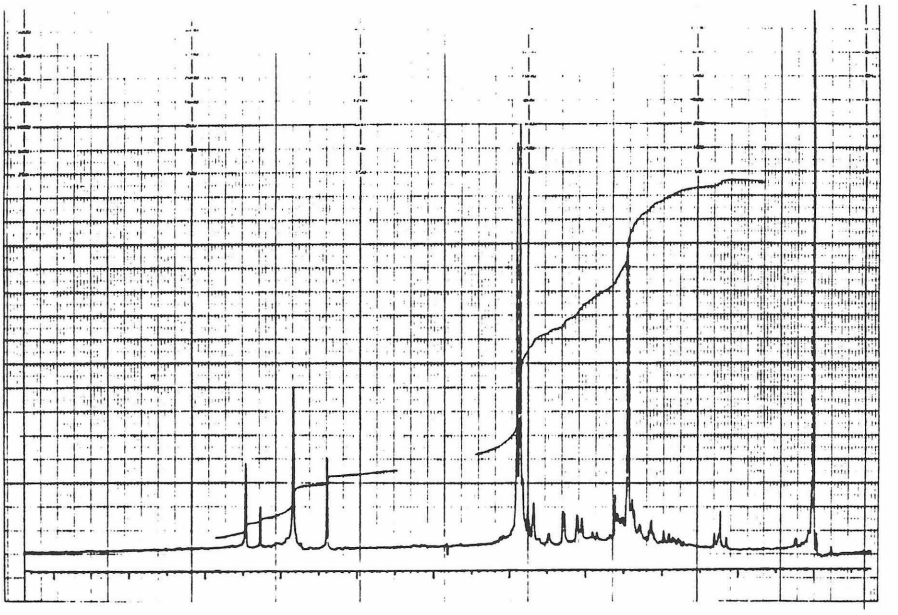


56a, R_1 = Me, R_2 = H

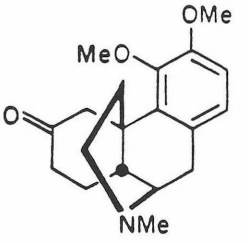
CH_2Cl_2



$CDCl_3$

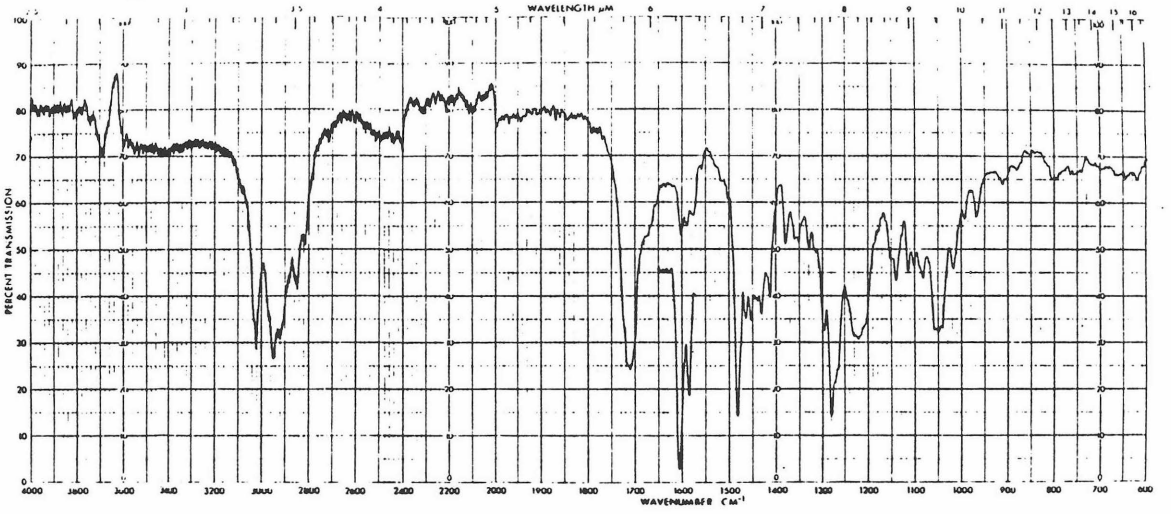


Page 71

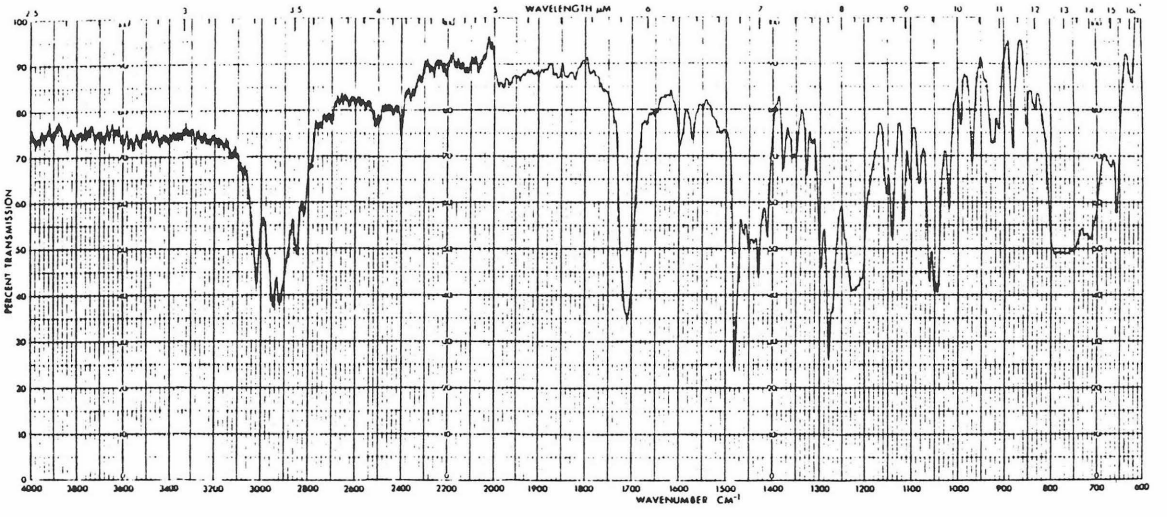


57

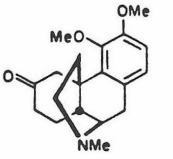
$CHCl_3$ Synthetic



$CHCl_3$ Authentic



Page 71



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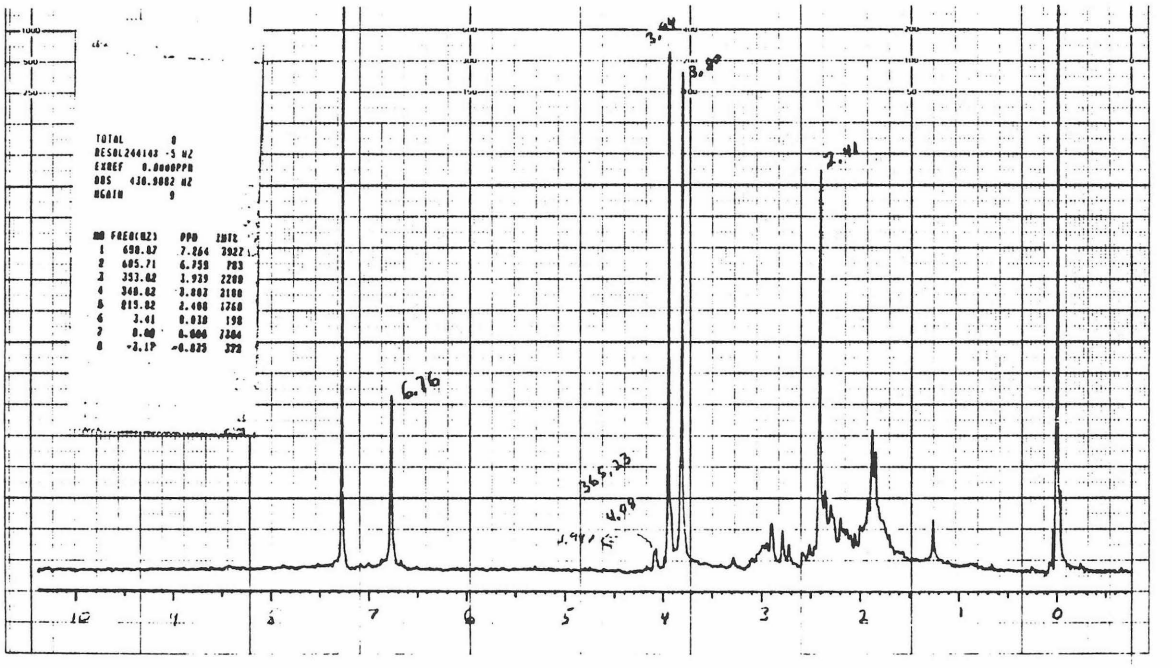
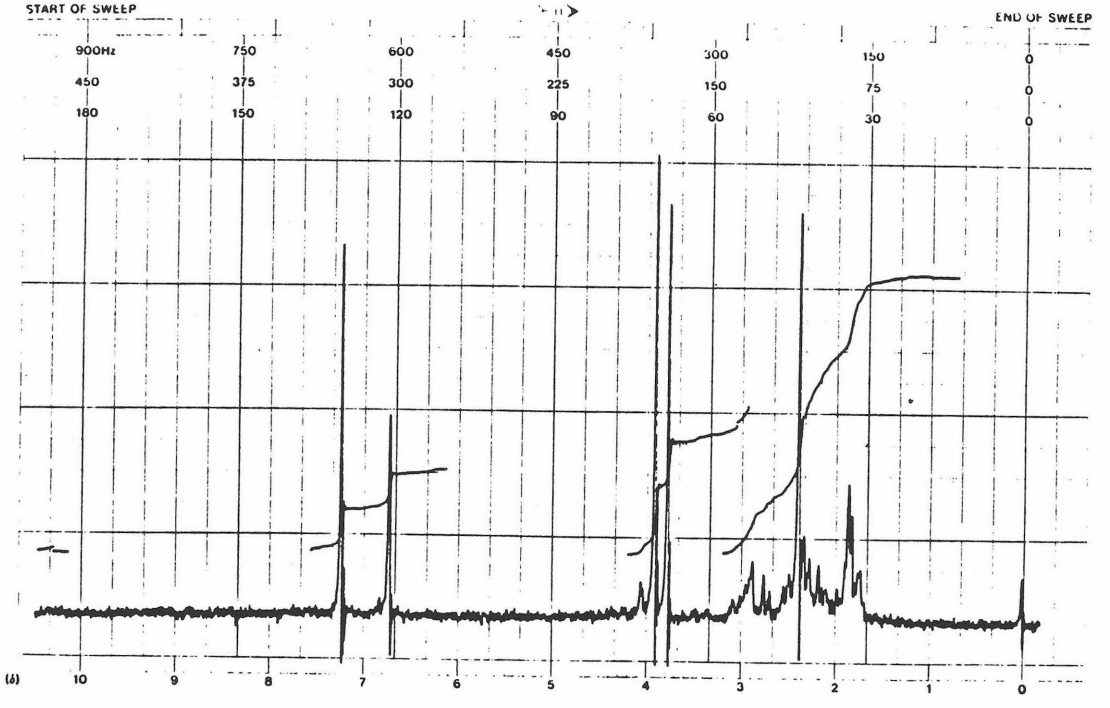
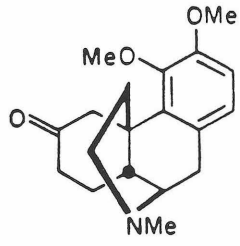
$CDCl_3$ (90 MHz) Synthetic



$CDCl_3$ (90 MHz) Authentic



Page 71



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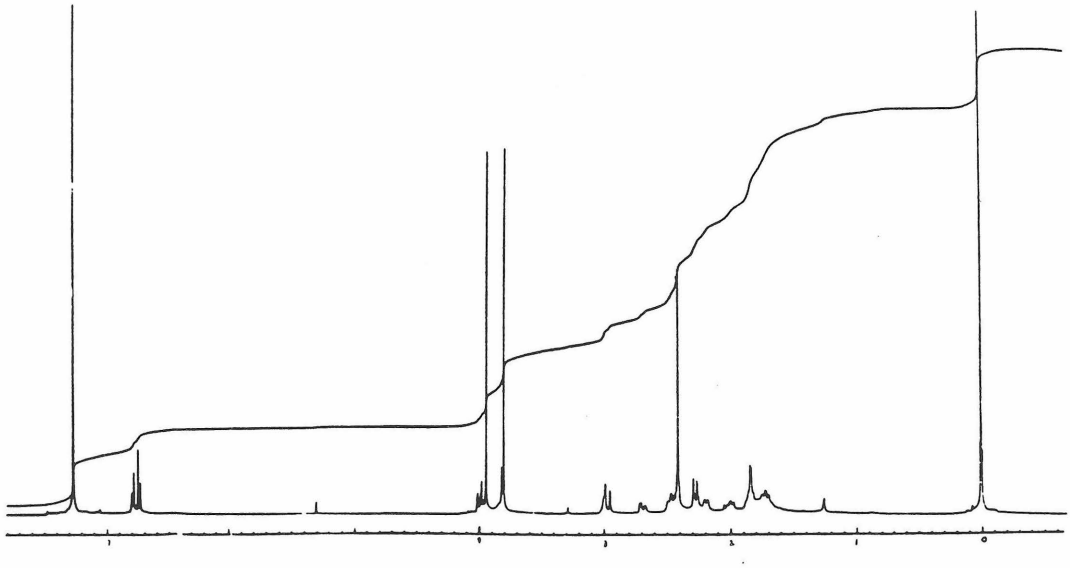
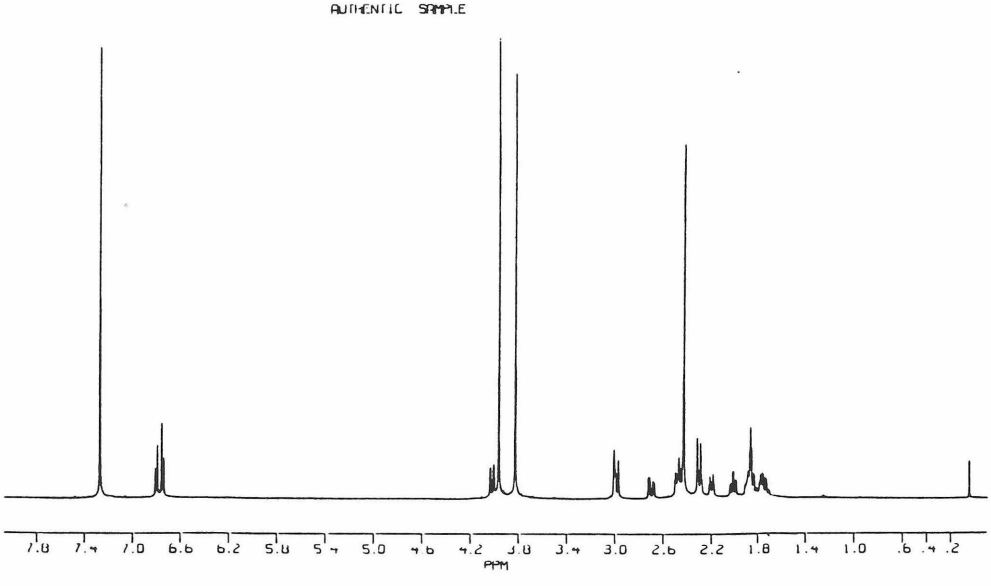
$CDCl_3$ (500 MHz) Synthetic



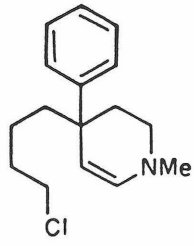
$CDCl_3$ (500 MHz) Authentic



APPENDIX II

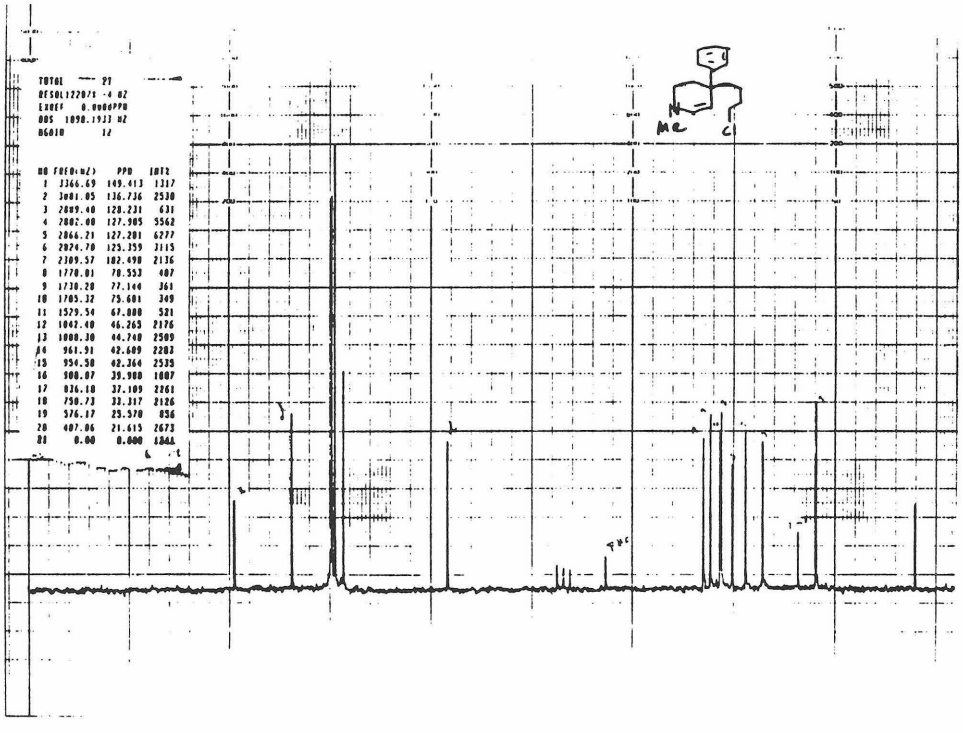
^{13}C NMR Spectral Catalog

Page 41

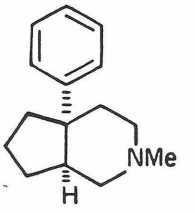


IIc

$CDCl_3$



Page 39



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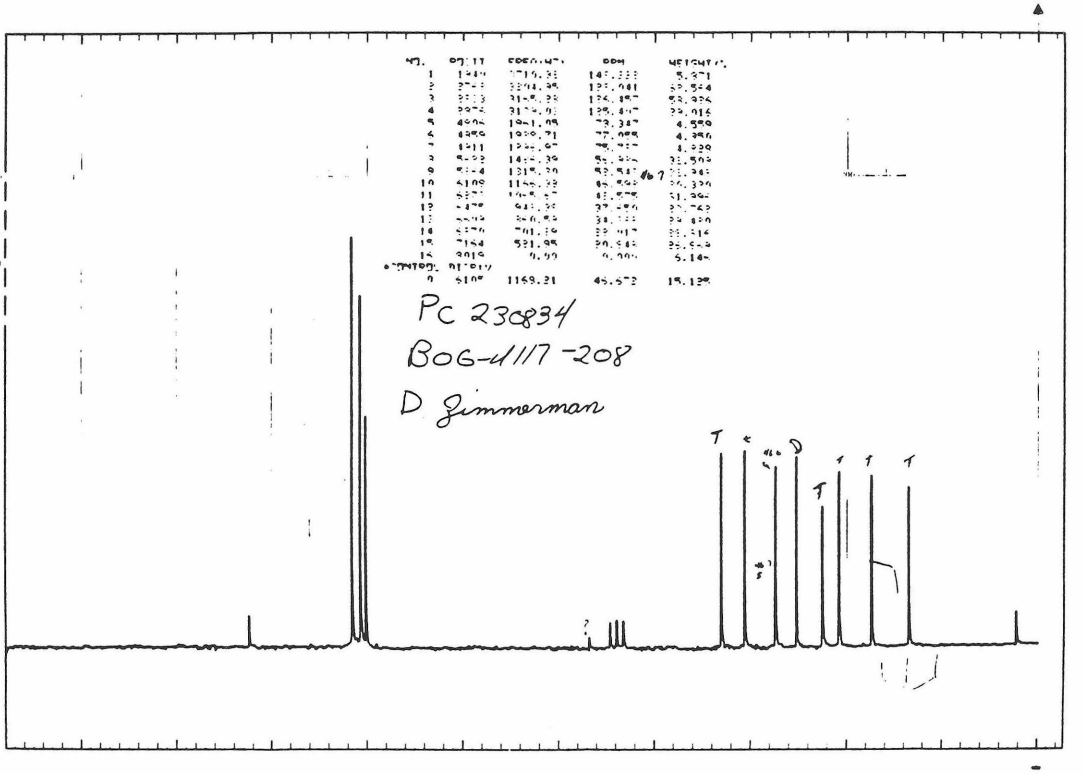
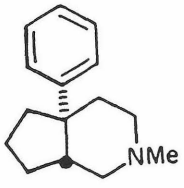


Page 39



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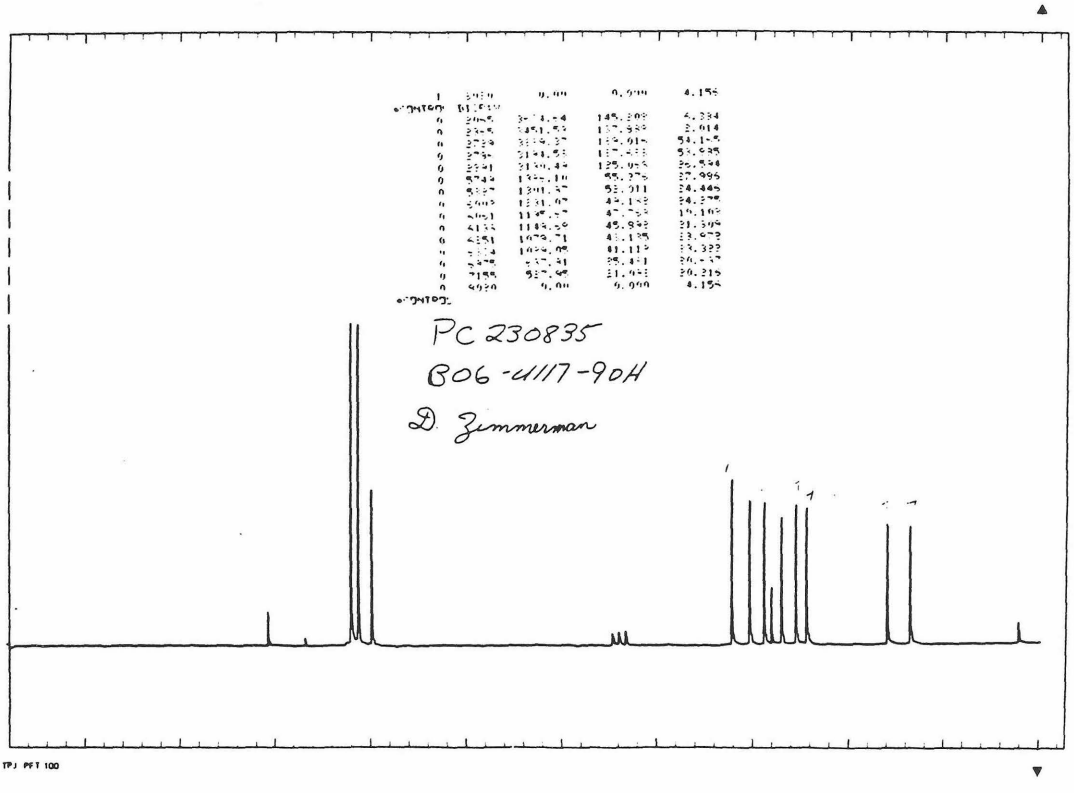

Page 42

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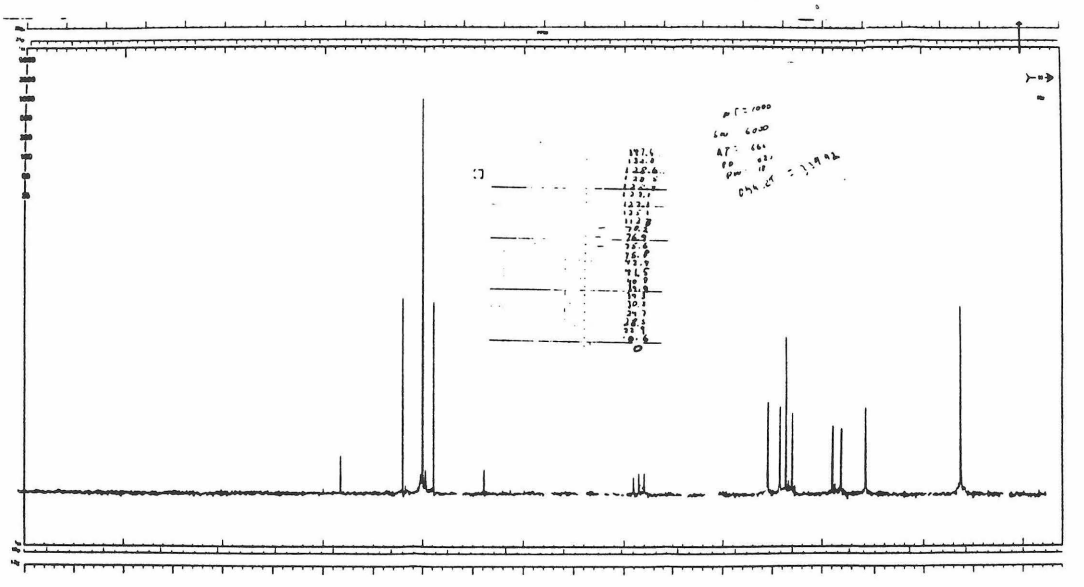
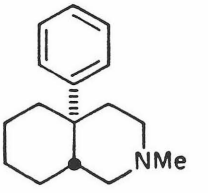


Page 44



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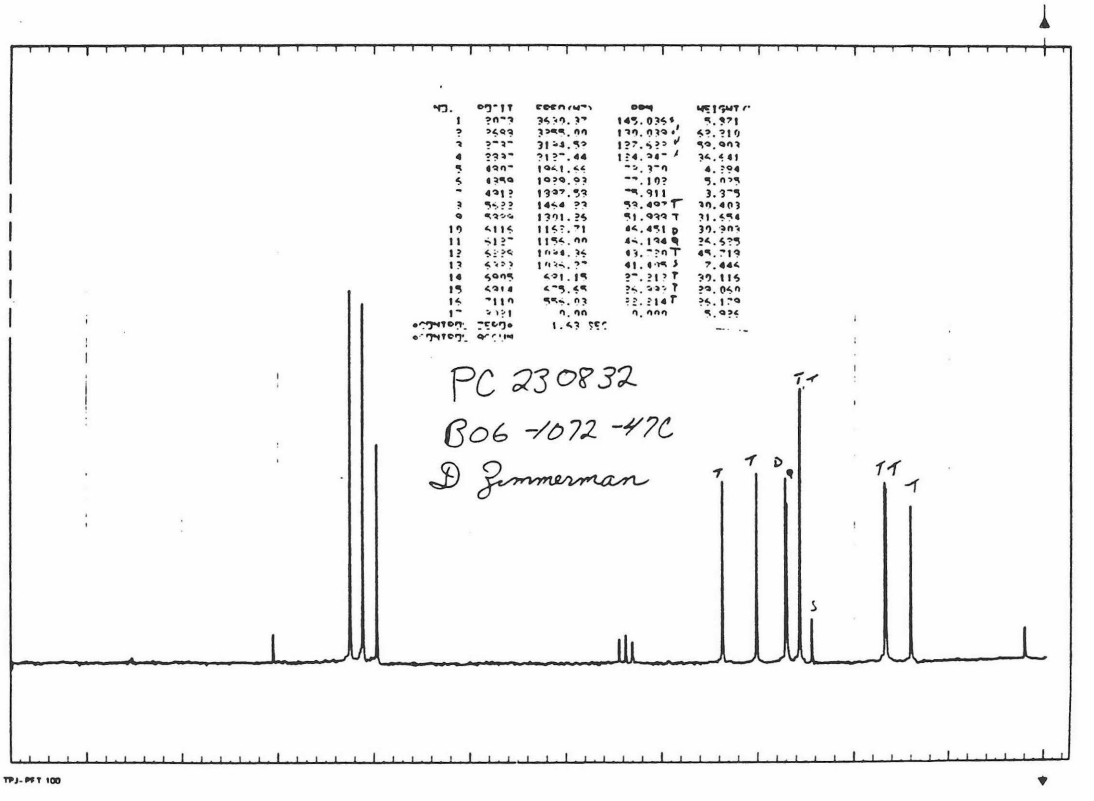
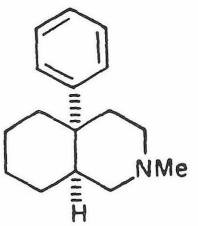


Page 46



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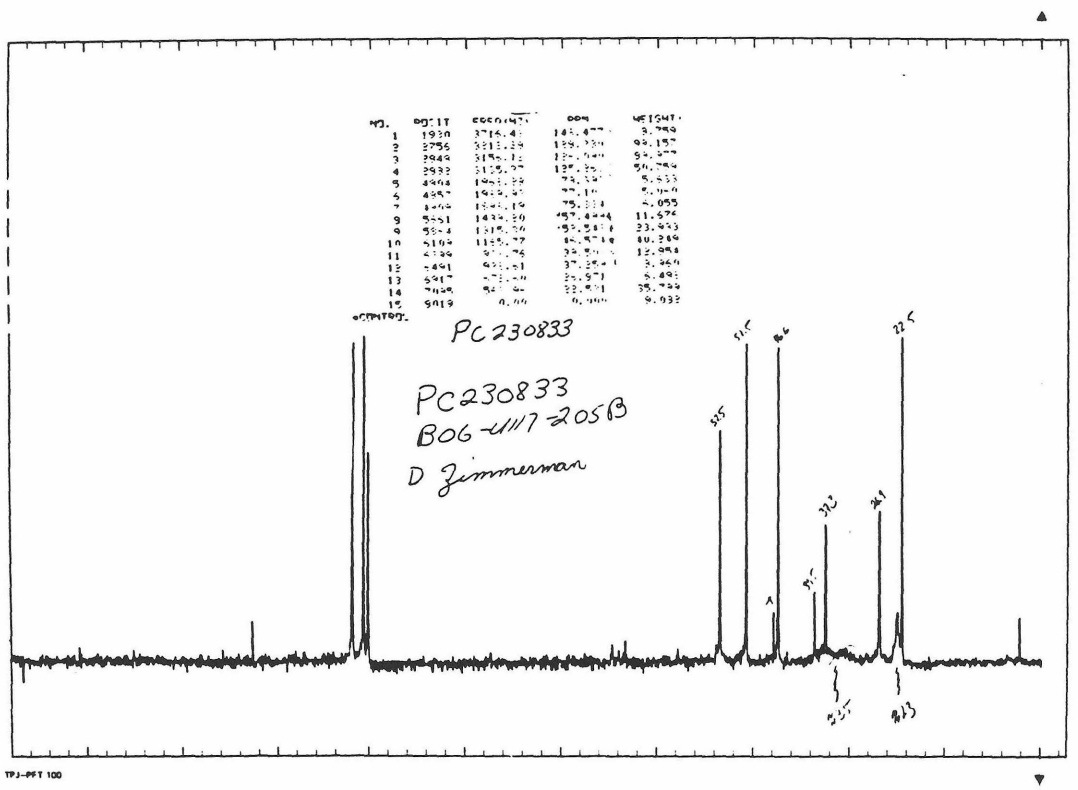
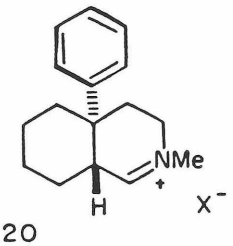


Page 43



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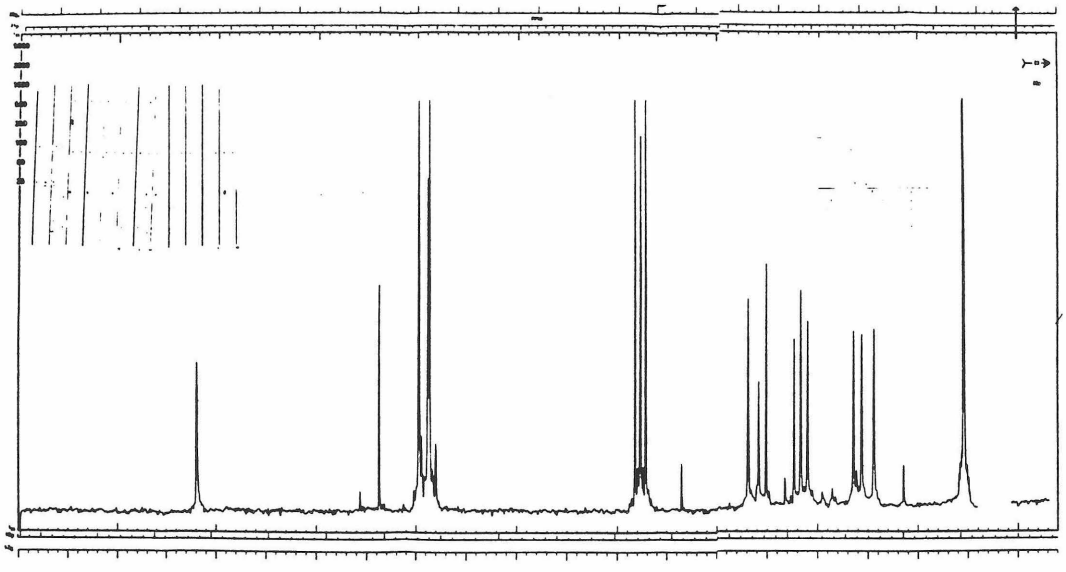

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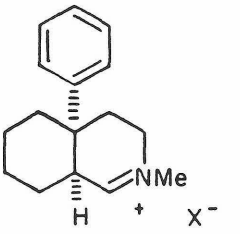

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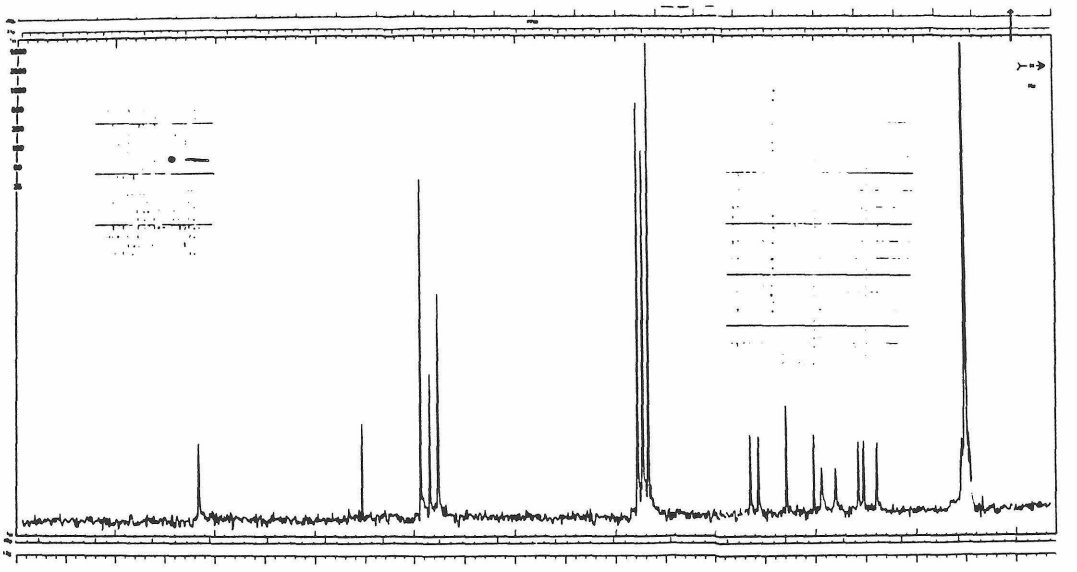
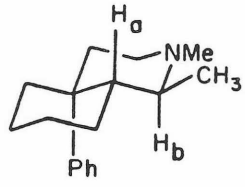


Page 46



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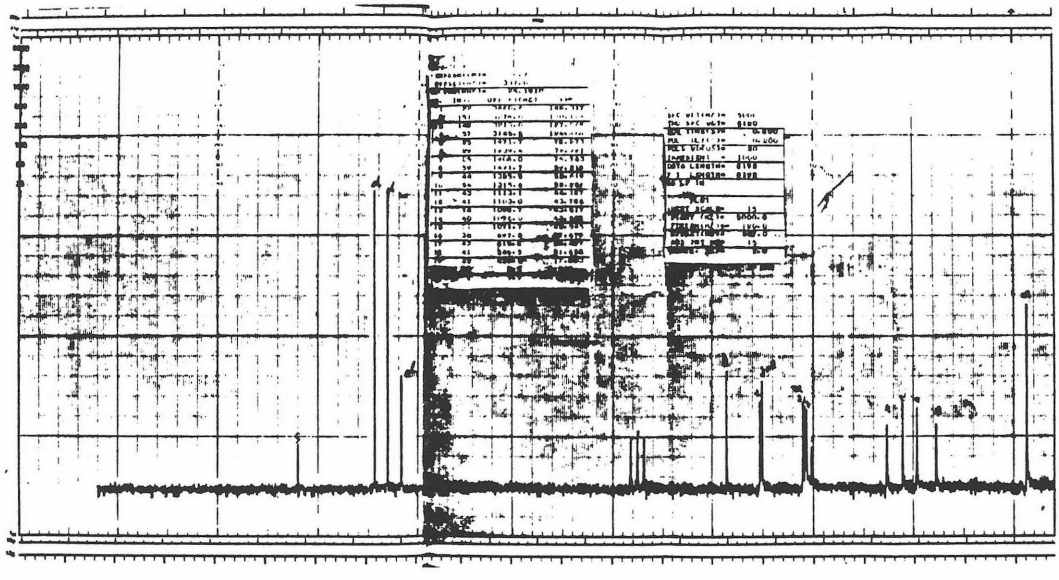
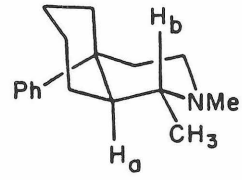


Page 47



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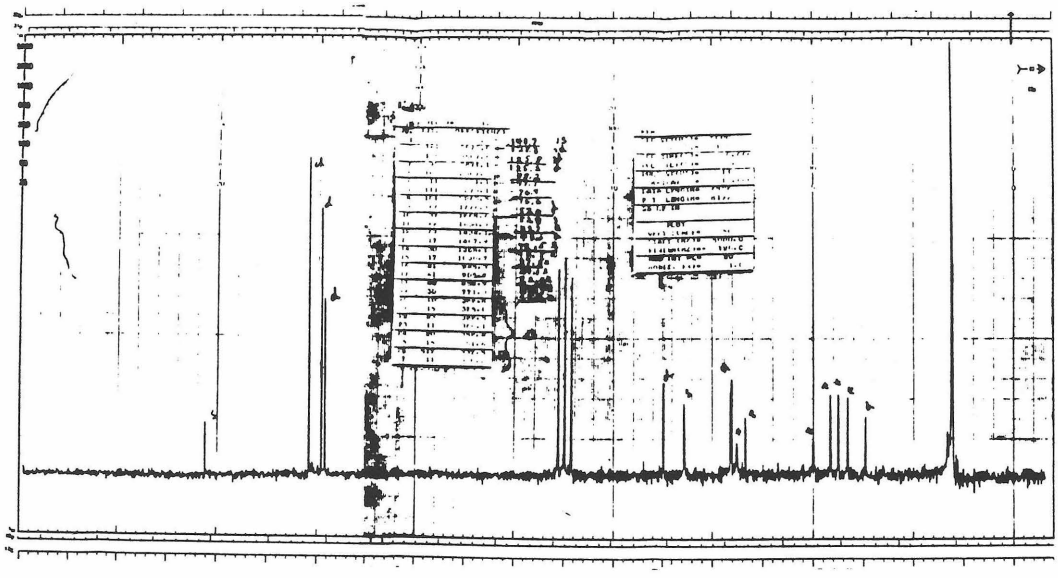
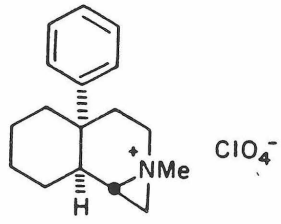


Page 48



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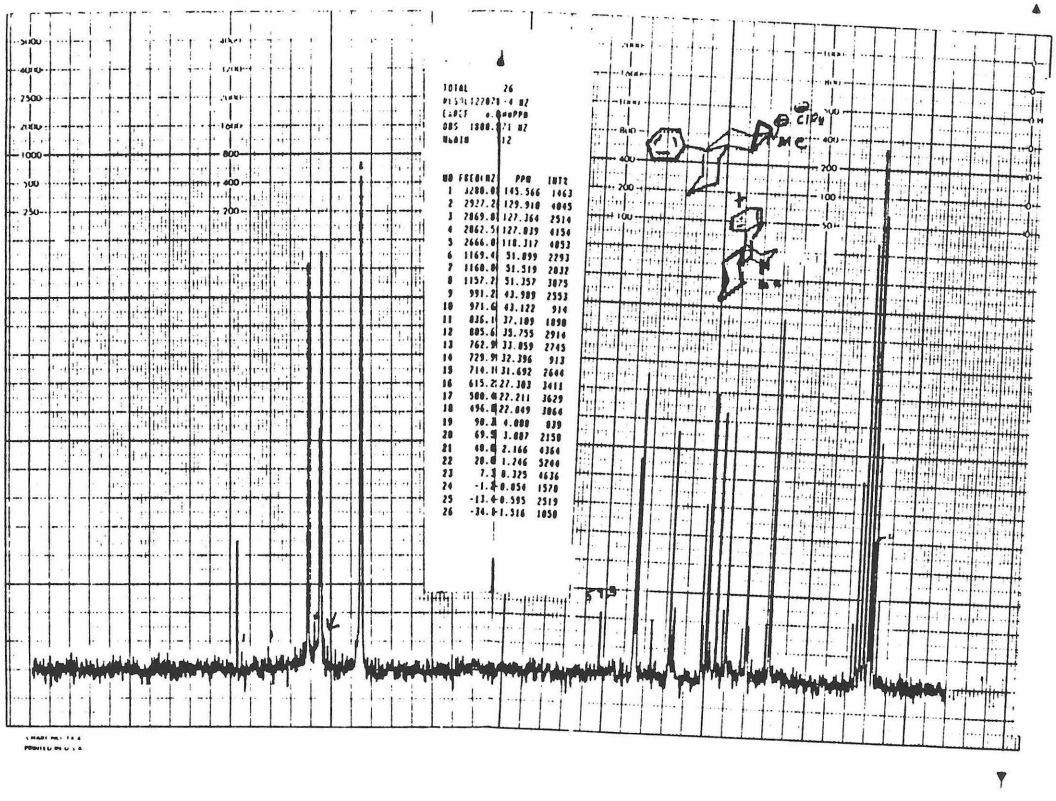
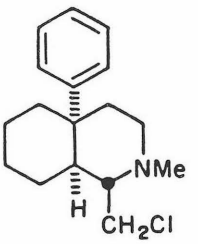


Page 49



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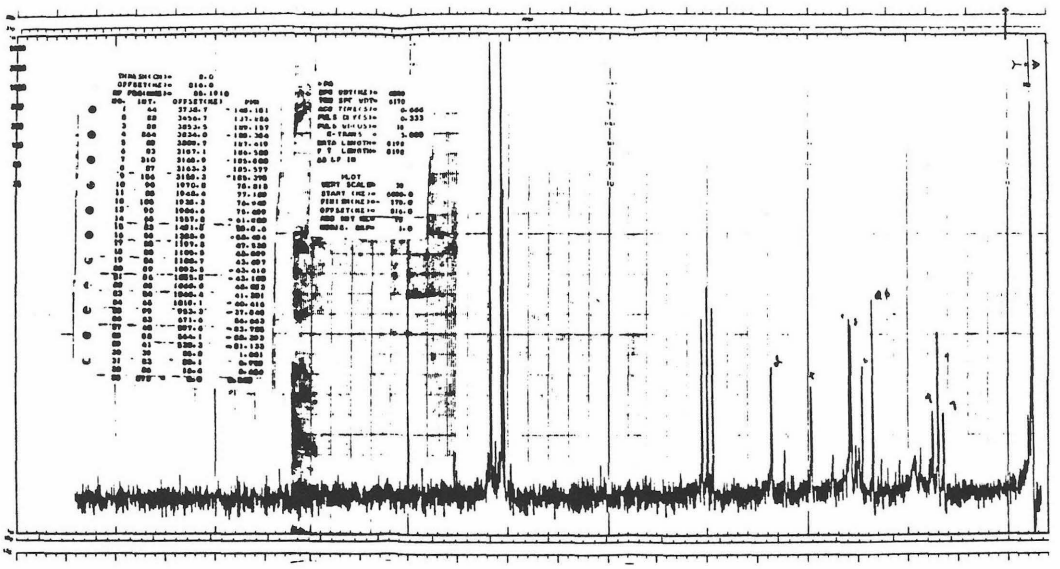

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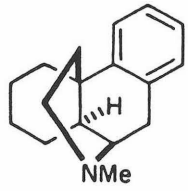

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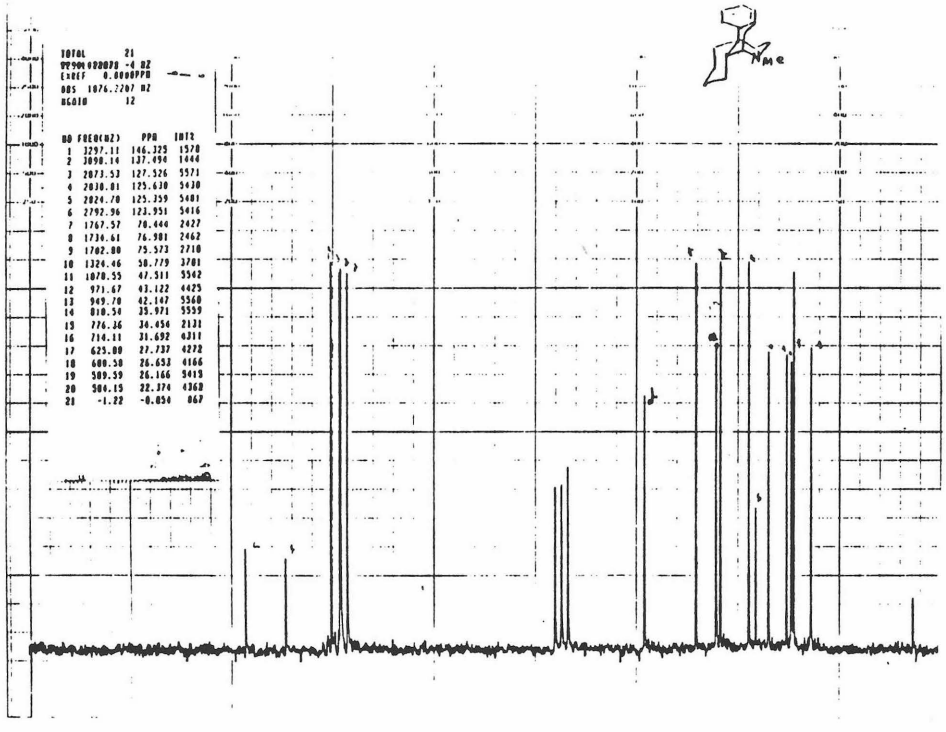
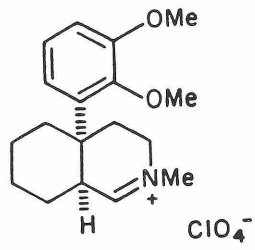
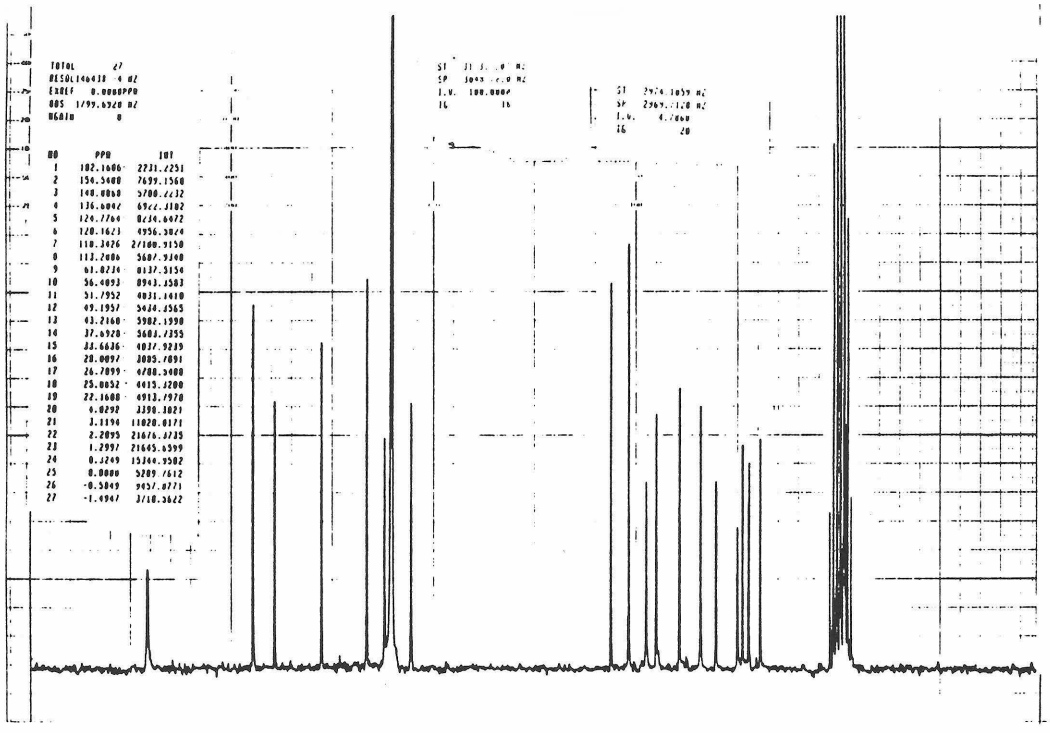


Page 53

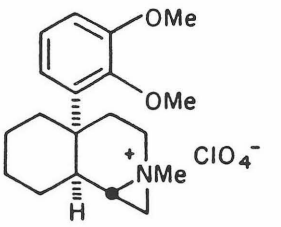


35

$CDCl_3$

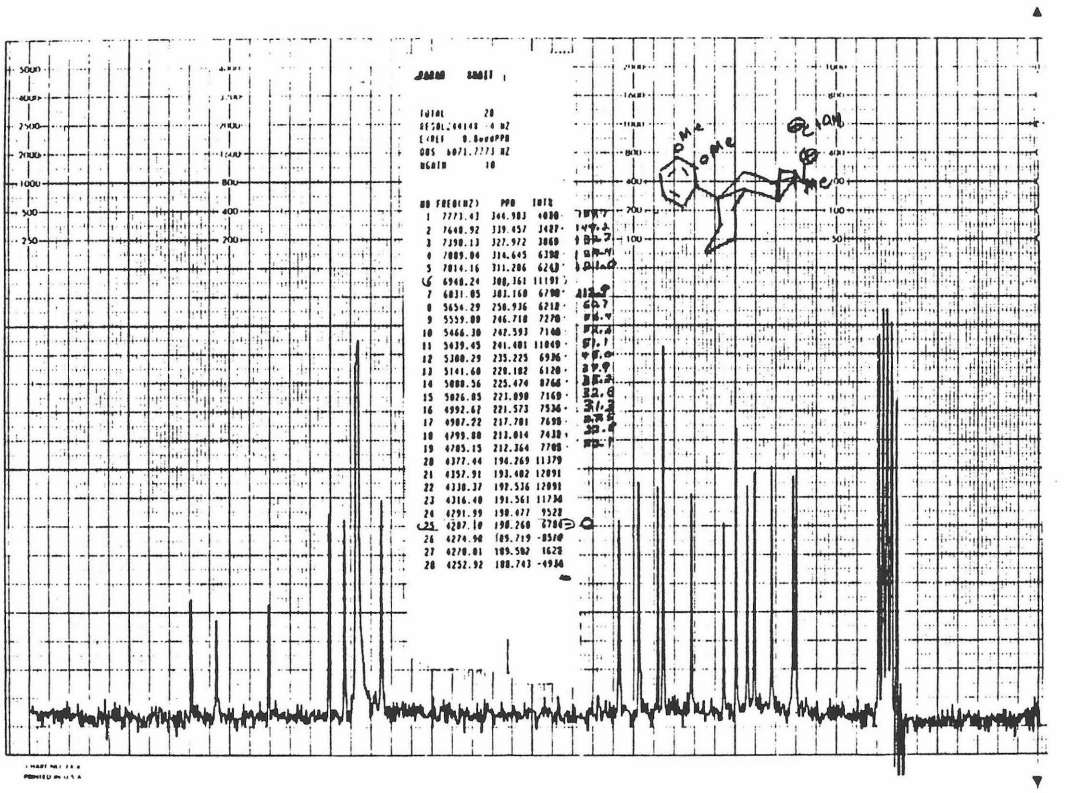


Page 54

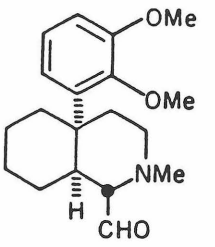


36

CD_3CN

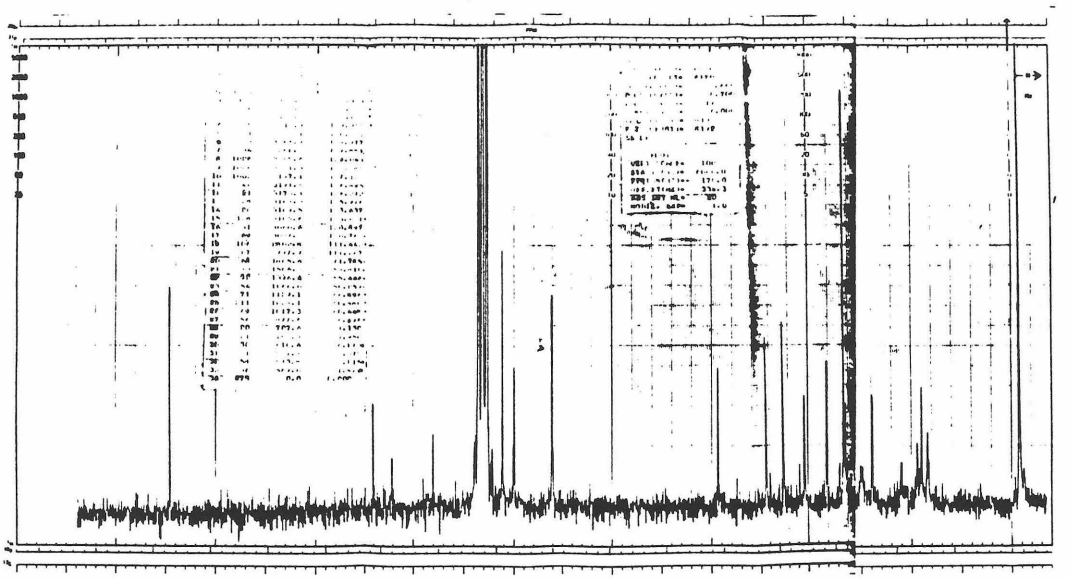


Page 54

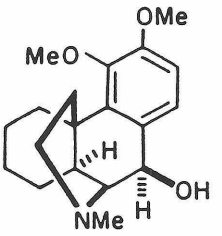


37

C_6D_6

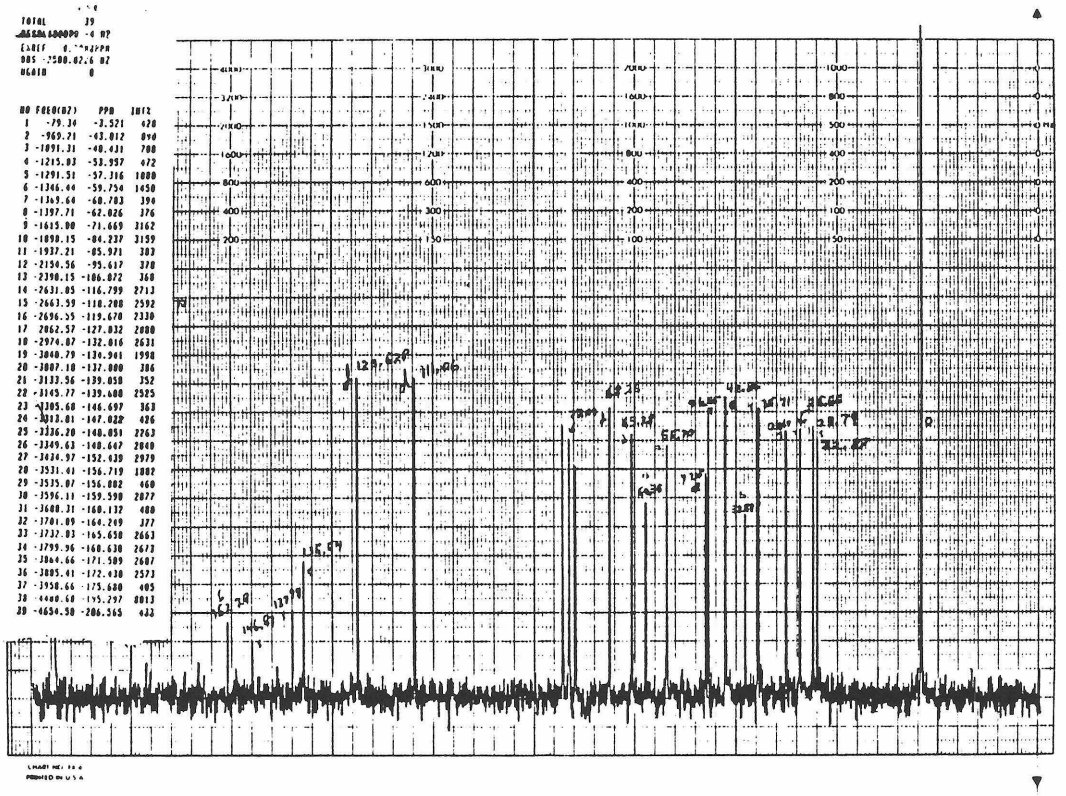


Page 55

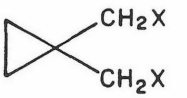


38

$CDCl_3$

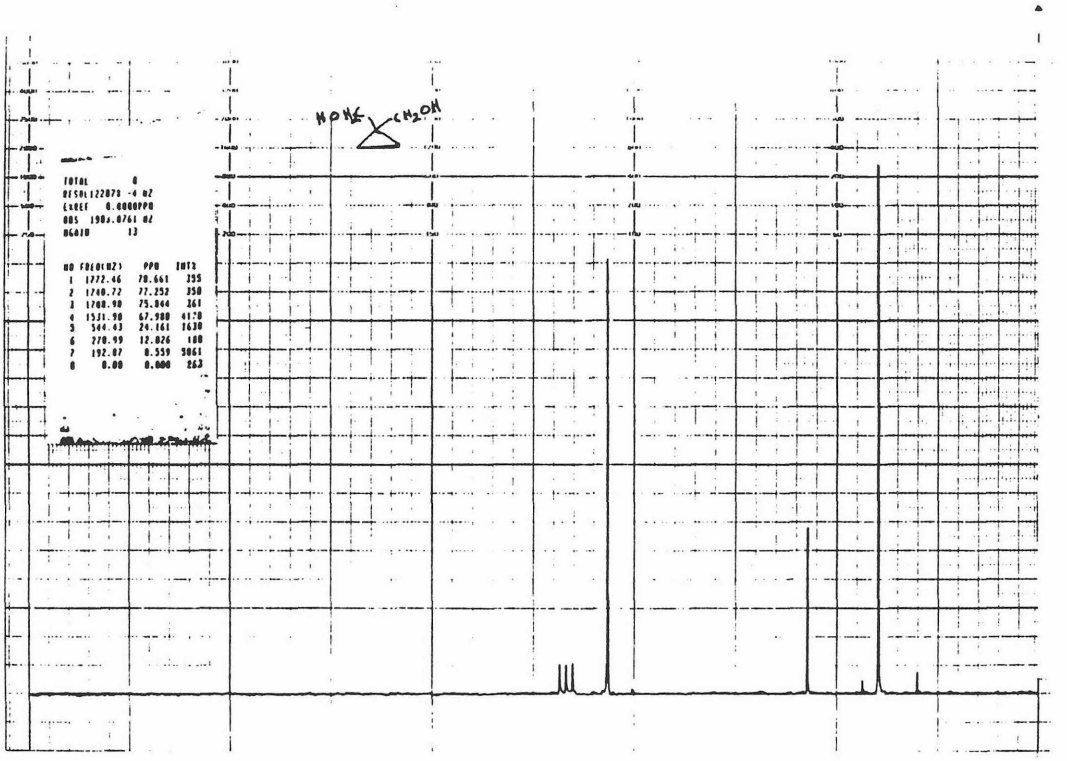


Page 57

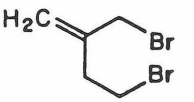


41, X = OH

$CDCl_3$

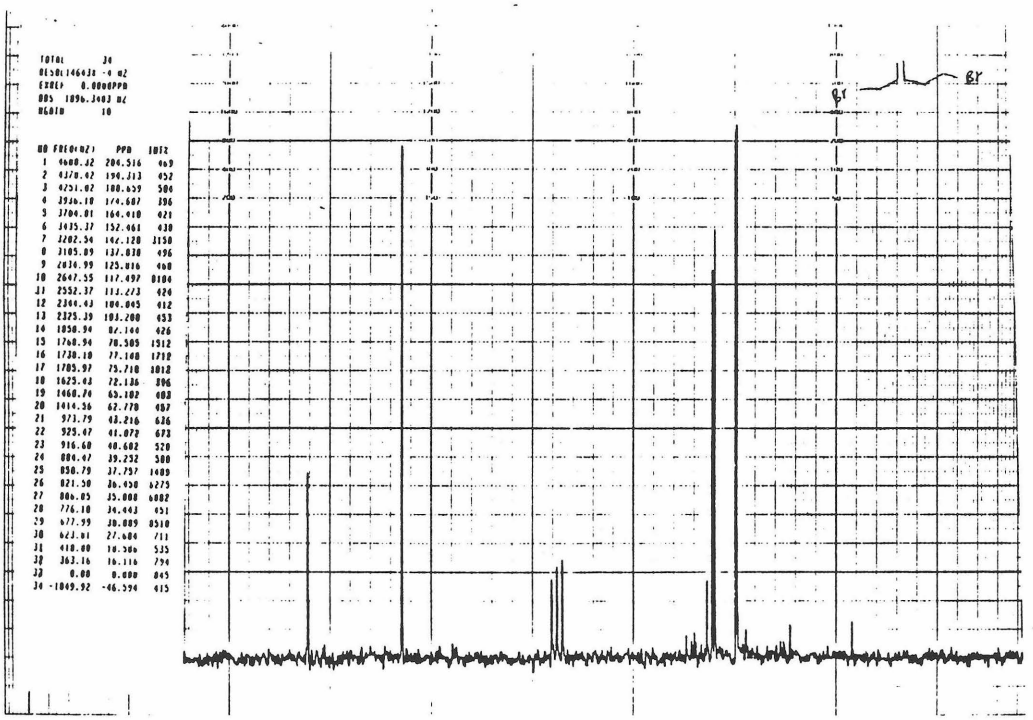


Page 58

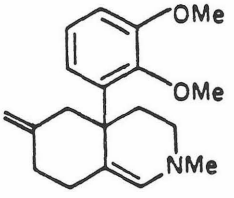


8

$CDCl_3$

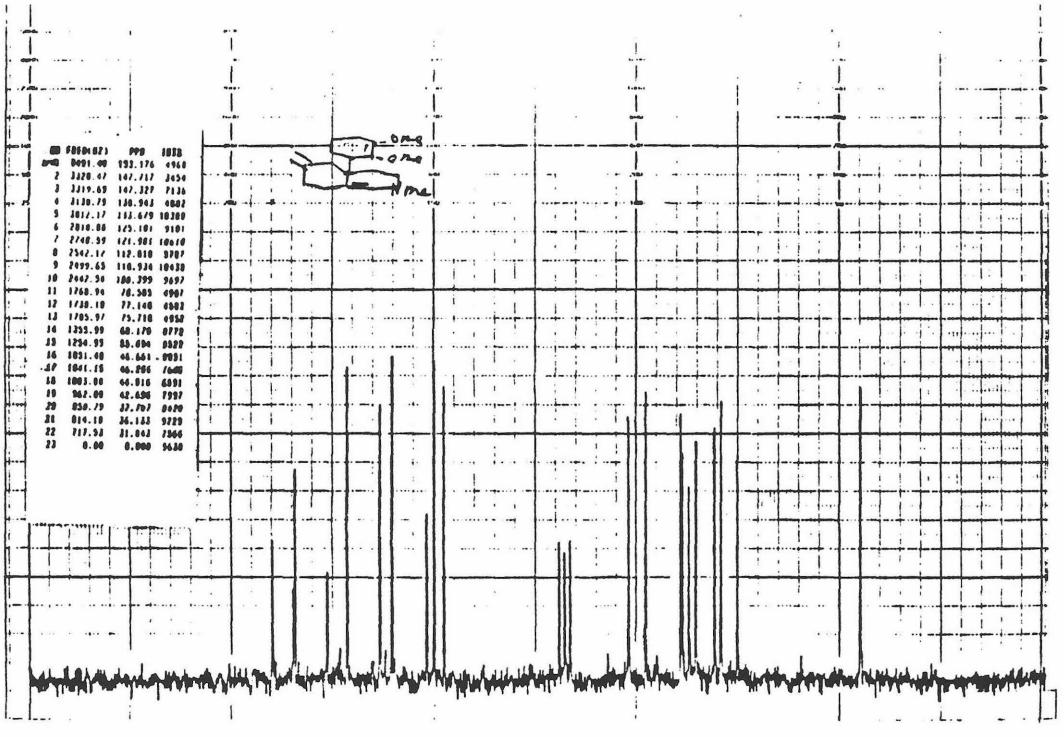


Page 60

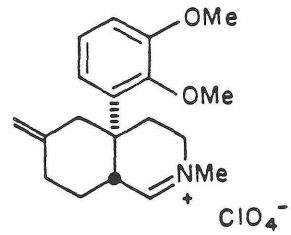


45

$CDCl_3$

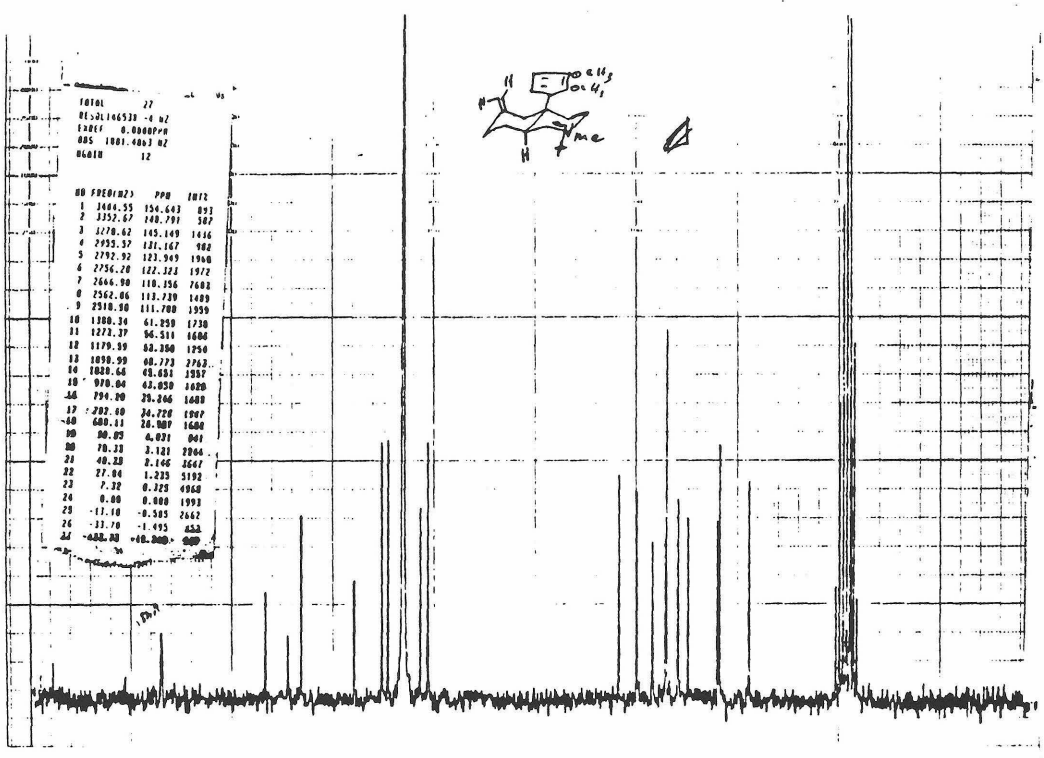


Page 59

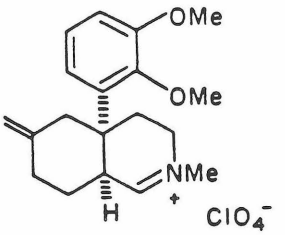


46a

CD_3CN

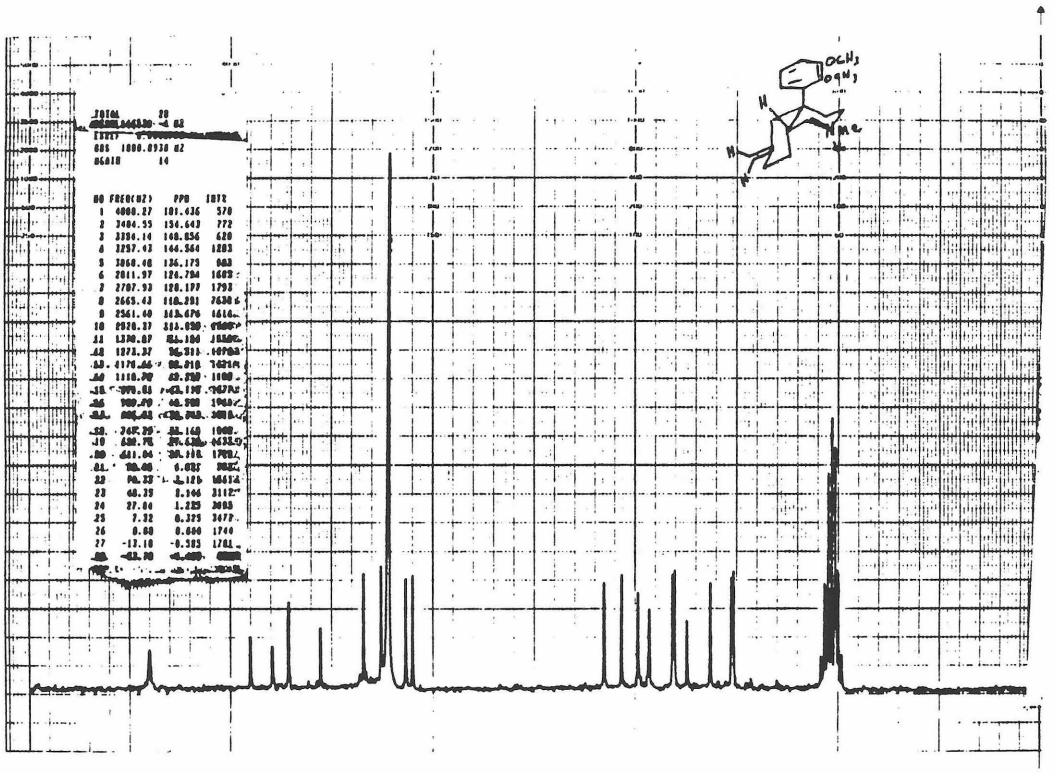


Page 61

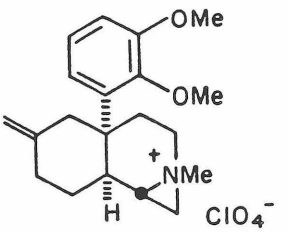


46b

CD_3CN

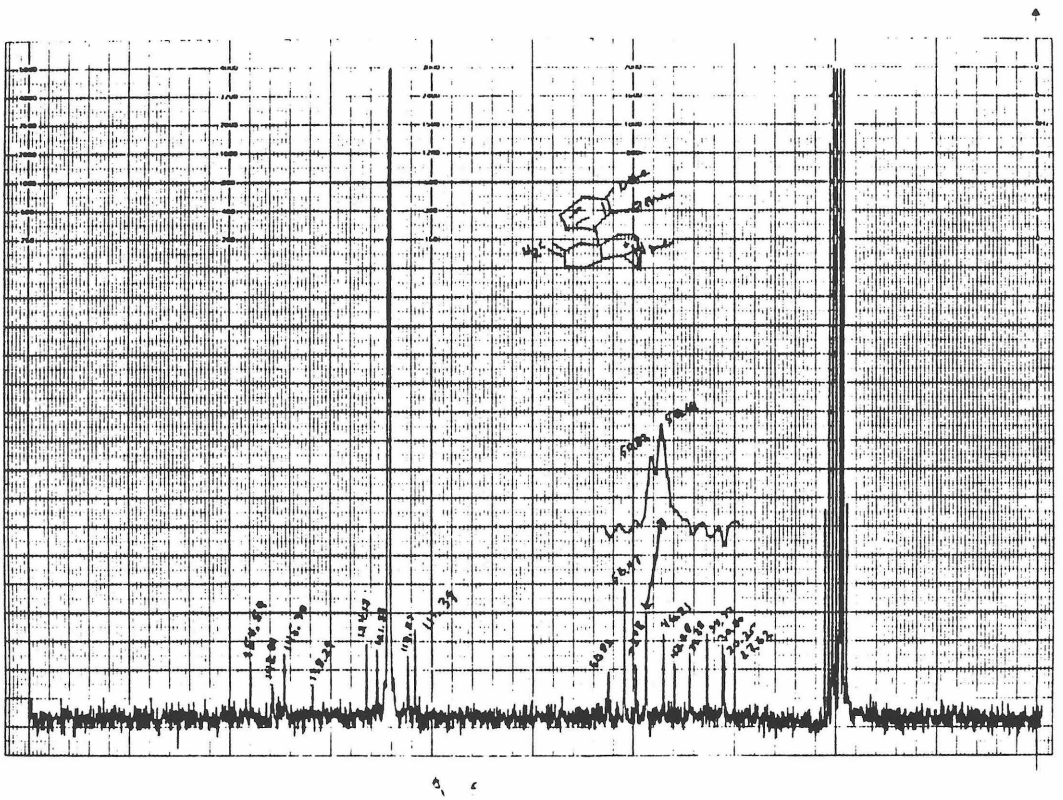


Page 61

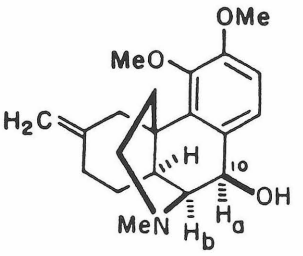


47

CD_3CN

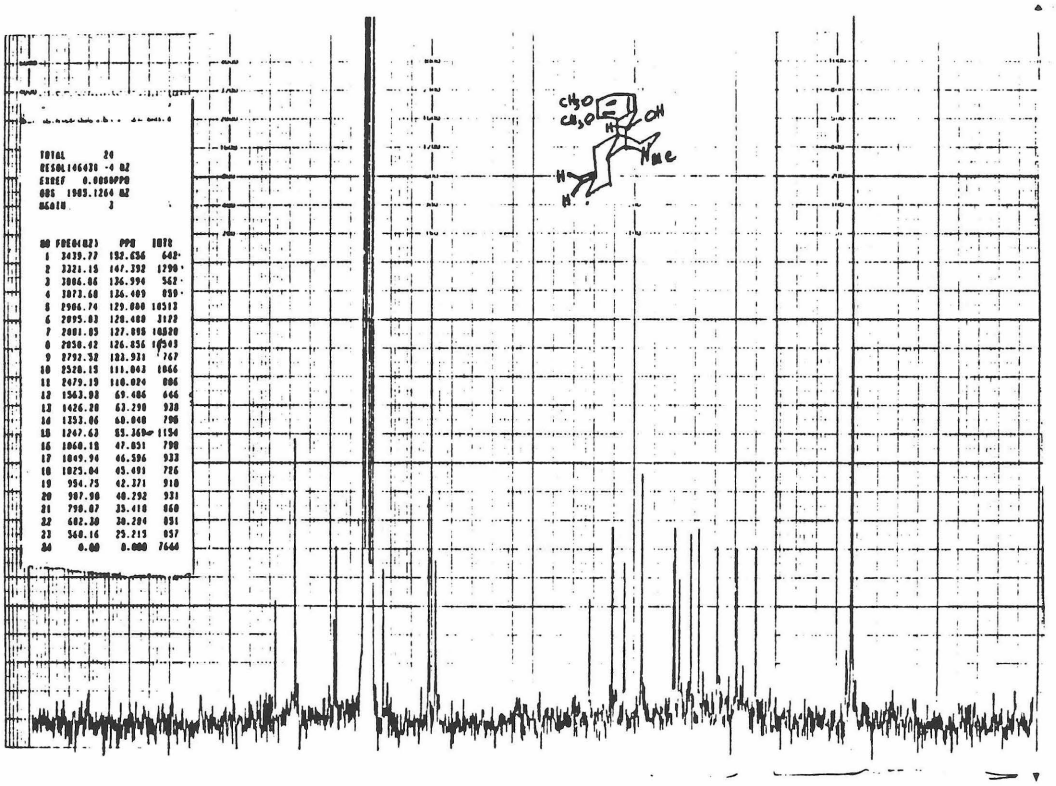


Page 63

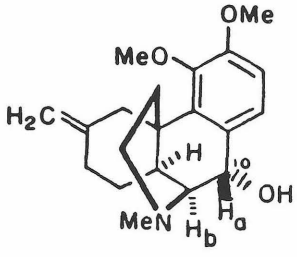


49

C_6D_6

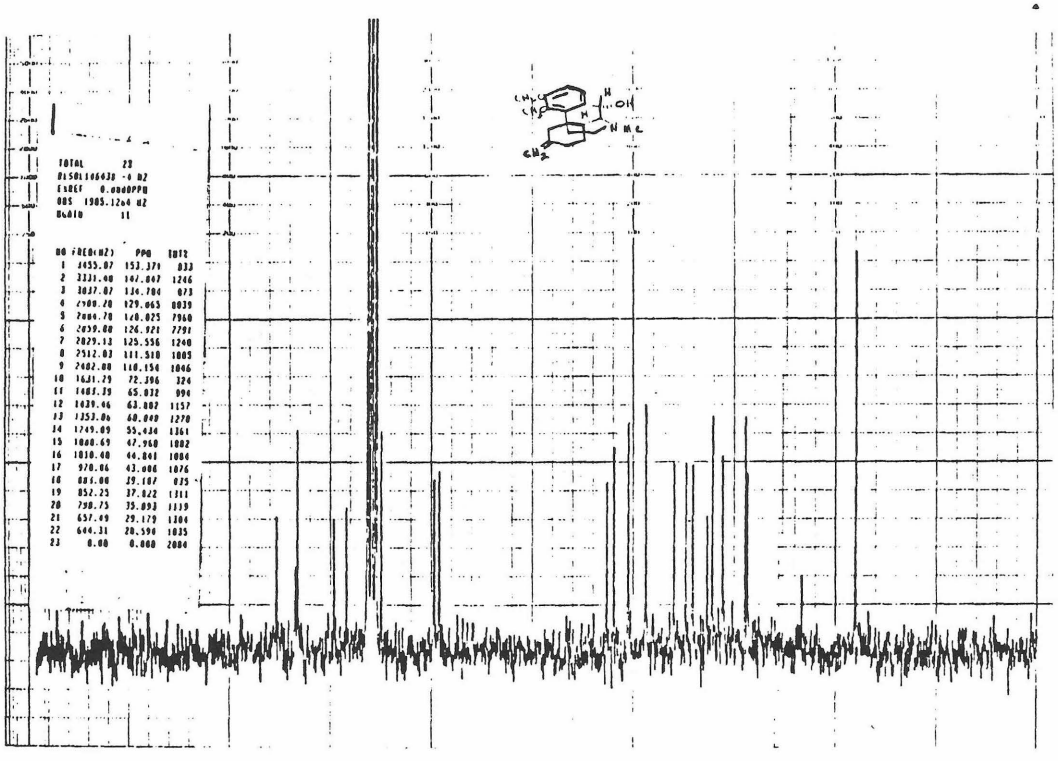


Page 63

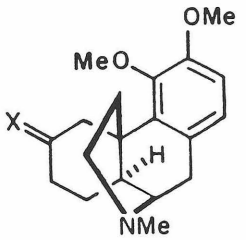


49a, 10α OH

C_6D_6

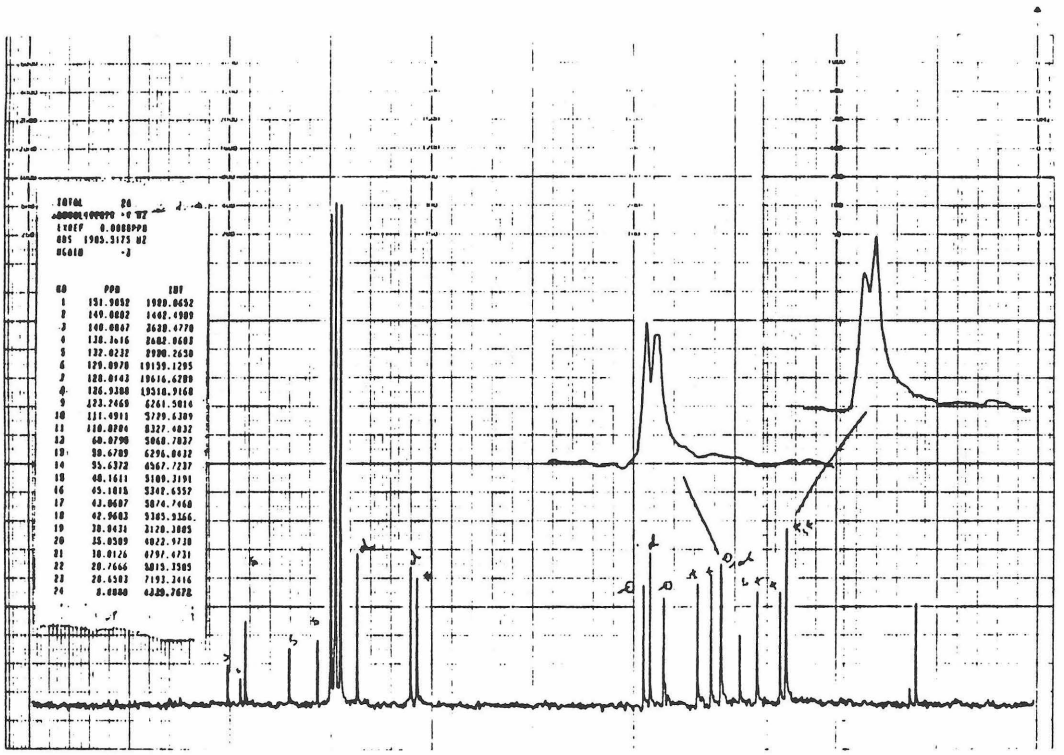


Page 64

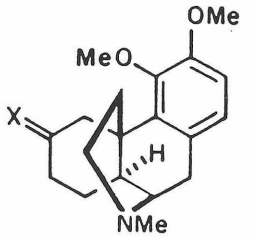


50, X = CH_2

C_6D_6

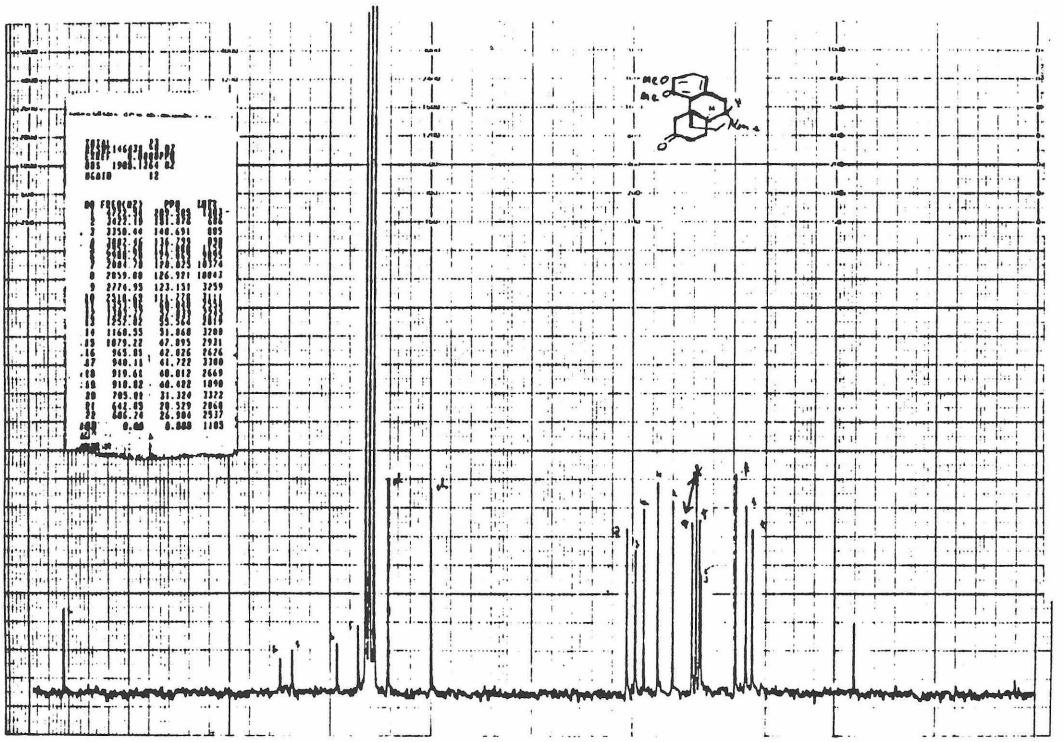


Page 66

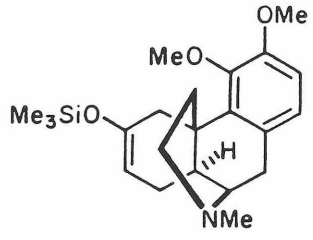


51, x = o

C_6D_6

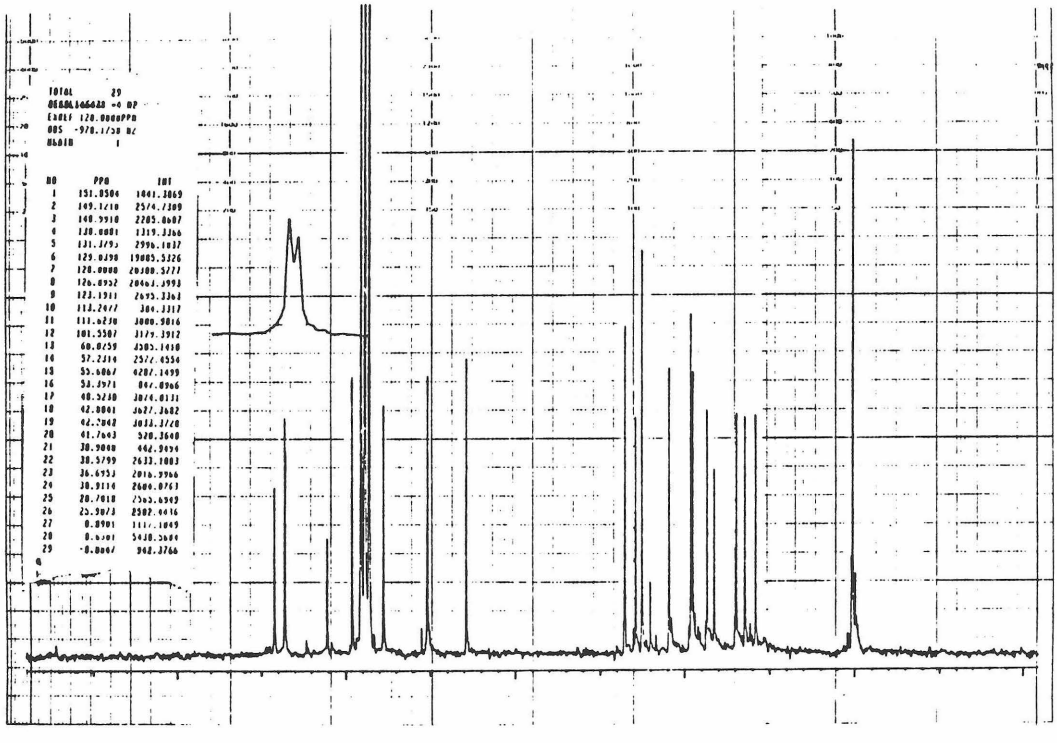


Page 67

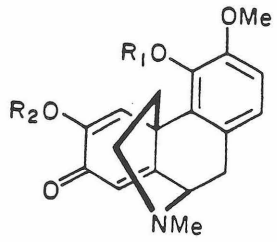


52

C_6D_6

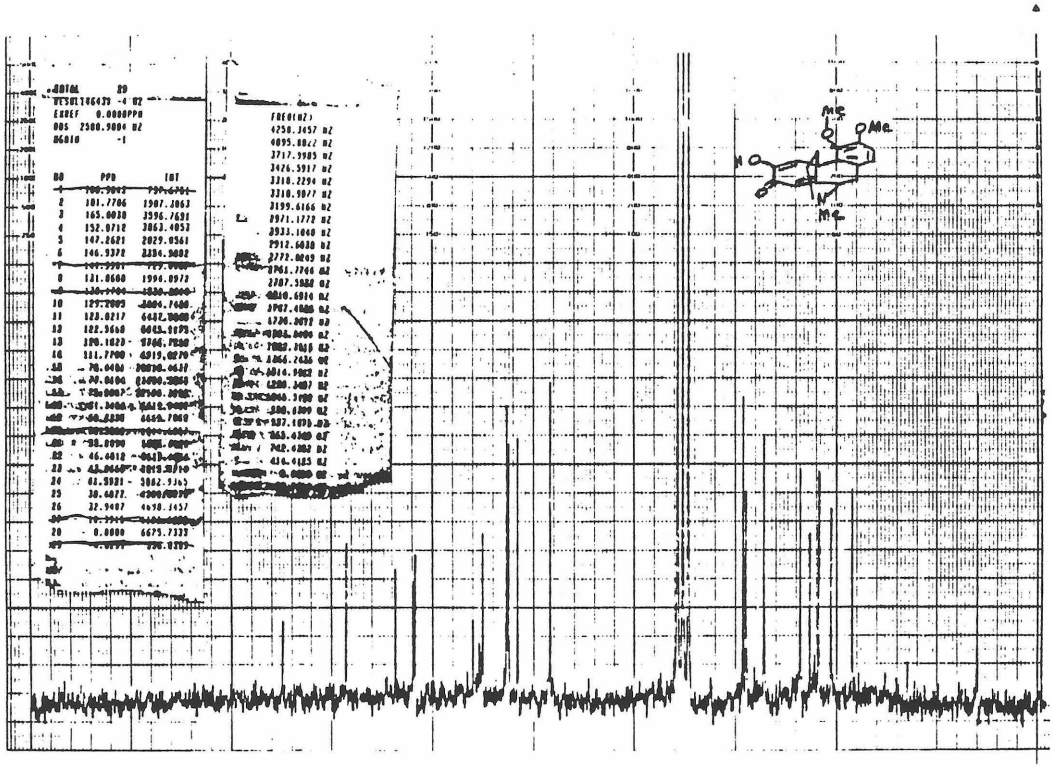


Page 70



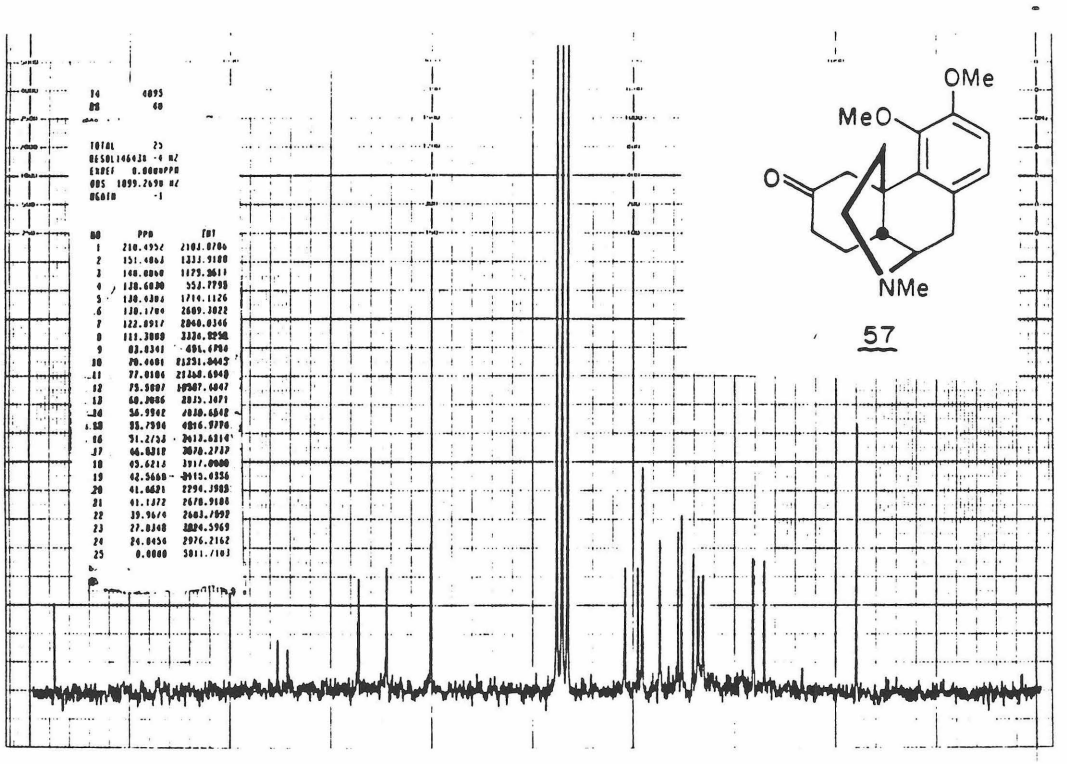
56a, R_1 = Me, R_2 = H

$CDCl_3$



Page 71

$CDCl_3$



57

Synthetic (PPM)	Literature[45b] (PPM)
210.5	210.3
151.5	151.5
148.9	149.1
130.4	130.6
130.2	130.4
122.9	122.9
111.4	111.6
60.3	60.4
57.0	57.1
55.8	55.8
51.3	51.4
46.5	46.7
45.6	45.9
42.6	42.7
41.5	41.6
41.4	41.3
40.0	40.2
27.0	27.2
24.0	24.2