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SYNTHETIC STUDIES IN INDOLE ALKALOIDS

by

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in the Department

of

Chemistry

We accept this thesis as conforming to the
required standard

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.....Edward Piers.....

.....

James P. Kutney

THE UNIVERSITY OF BRITISH COLUMBIA

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ABSTRACT

The total synthesis of a variety of indole and dihydroindole alkaloids, is described. More specifically, the dl-epimers of naturally occurring vincadine, vincaminoreine, vincaminorine, minovine, vincadifformine, N-methyl-quebrachamine and vincaminoridine have been obtained by appropriate modifications in the general synthetic scheme. This work also illustrates that the transannular cyclization reaction previously developed in our laboratories is of great versatility in the synthesis of alkaloids in the Vinca and Aspidosperma families.

In essence, the synthetic sequence involves the reaction of the aldehydo-ester (118) with either tryptamine or 6-methoxytryptamine to provide in high yield, the tetracyclic lactams (119 or 166). Lithium aluminum hydride reduction of the latter, followed by hydrogenolysis of the benzyl group provided the corresponding alcohols (94 or 165). These compounds were transformed via their mesylate derivatives to the quaternary salts (95 or 187) which served as the crucial intermediates for the preparation of the nine-membered ring alkaloids. Finally transannular cyclization of the latter substances leads to the pentacyclic Aspidosperma and Vinca alkaloids.

James P. Kutney

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TABLE OF CONTENTS

	Page
TITLE PAGE	i
ABSTRACT	ii
TABLE OF CONTENTS	iii
LIST OF FIGURES	iv
ACKNOWLEDGEMENTS	ix
INTRODUCTION	1
(i) General	1
(ii) Biosynthetic theories	3
(iii) Some Important Biosynthetic Reactions	22
DISCUSSION	29
(1) Reinvestigation and improvement of the quebrachamine total synthesis	29
(2) Introduction of functionalities at C-3 of quebrachamine	72
(3) Extension of the approach to alkaloids bearing an oxygen function in the aromatic ring	94
EXPERIMENTAL	136
REFERENCES	178

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LIST OF FIGURES

Figure		Page
1.	Incorporation of (±)-tryptophan-2-^{14}C into different indole alkaloids	4
2.	Incorporation of (±)-tryptophan-3-^{14}C into ibogaine	5
3.	The interconversion of the C_{9-10} unit and incorporation to the major indole alkaloid skeleton	6
4.	Basic units used to prove each of the four proposed hypotheses of the biogenetic origin of the non-tryptophan moiety	7
5.	Outline of Barger-Hahn-Robinson-Woodward hypothesis	8
6.	Basic transformations of prephenic acid hypothesis	10
7.	Incorporation of the SPF unit into ajmalicine (30, corynanthine (31), ajmaline (17) and sarpagine (32)	11
8.	Incorporation of the SPF unit into the Iboga and Aspidosperma alkaloids	12
9.	Postulated mechanism of Schlittler-Taylor hypothesis	14
10.	Incorporation of labelled acetate into ajmaline	14
11.	The "monoterpene" or Wenkert-Thomas hypothesis	15
12.	The incorporation of labelled 2-^{14}C mevalonate into the "aliphatic"part of the indole alkaloid skeleta	17
13.	Summary of detected radioactivity in the "non-tryptophan" part following labelled mevalonate administration	17
14.	Incorporation of geraniol-2-^{14}C to the indole alkaloid skeleta	18
15.	Monoterpenes used for checking "cyclopentanemonoterpene" theory	19
16.	Incorporation of loganin to all type indole alkaloid skeleta	20
17.	An attractive sequence leading to incorporation of the C_{10} unit into indole alkaloids	21
18.	Amino acids as alkaloidal building units	22

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Figure		Page
19.	Stereochemical correlation between condylocarpine and akuammicine	23
20.	Synthesis of flavopereirine by Wenkert (R=H or Et)	24
21.	Synthesis of vincadifformine analogues	25
22.	Transannular cyclization processes	26
23.	Retention of absolute configuration during the reactions	28
24.	Total synthesis of dl-quebrachamine (9) in our laboratories.	31
25.	Side products of mercuric acetate reaction	32
26.	Preparation of the uncyclized benzyl ether	34
27.	Application of Bischler-Napieralski reaction	35
28.	Kuehne's and Harley-Mason's selective cyclization to tetracyclic lactams	36
29.	Preparation of aldehydoester (118)	37
30.	NMR spectrum of allyloester (116)	38
31.	Mass spectra of the allylo-, diolo- and aldehydoesters	40
32.	Electron impact on allyl compound (116)	41
33.	NMR spectrum of dioloester (117)	42
34.	The diol (117) under electron impact	43
35.	NMR spectrum of the aldehydoester (118)	45
36.	Fragmentation of aldehyde (118) upon electron impact	46
37.	New improved reaction sequence for the total synthesis of quebrachamine (9)	47
38.	NMR spectrum of cyclized lactam (119)	48
39.	The main fragements of the lactam (119) upon electron impact	50
40.	Mass spectra of the cyclized lactam (119) and amine (93)	51
41.	NMR spectrum of the cyclized amine (93)	53
42.	The two diastereoisomeric dl-pairs of amine (93)	54

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Figure		Page
43.	NMR spectrum of alcohol-I (94)	55
44.	NMR spectrum of alcohol-II (94)	56
45.	Most favored conformation of the alcohols	59
46.	Conformations proposed for some reserpate derivatives (R=OH or 3',4',5'-trimethoxy benzoate)	60
47.	Stereochemical relations in some quinolizidine derivatives	61
48.	Conformation of the isomeric alcohols-I and II	62
49.	NMR spectrum of alcohol A' (97)	66
50.	Mass spectra of alcohols A', A (or I) and C (or II)	68
51.	Common fragments in the mass spectrameter of a substituted tetrahydro-β-carboline system	69
52.	Possible conformations of alcohols A' and B	71
53.	Introduction of functional groups in C-3 of the quebrachamine skeleton	73
54.	Introduction of cyanide in C-3 by other workers[76a,b]	74
55.	NMR spectrum of cyanide-I (139)	75
56.	Mass spectra of cyanide-I, II and III	76
57.	Postulated fragmentation of cyanide-I and cyanide-II	77
58.	NMR spectrum of cyanide-II (139)	79
59.	NMR spectrum of cyanide-III (145)	80.
60.	Fragmentation of cyanide-III upon electron impact	81
61.	Possible mechanism for the formation of cyanide-III	81
62.	Mechanistic aspects of some 3-vinylindole chemistry.[78]	82
63.	Synthesis of carbomethoxydihydrocleavamine (72)	83
64.	Prospective formulae showing the relative shielding of the C-3 proton due to its spacial orientation	85
65.	NMR spectrum of dl-vincadine (3)	87
66.	Mass spectra of dl-vincadine (3) and its epimer	88

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Figure		Page
67.	Plausible fragmentation of the epimeric vincadines upon electron impact	89
68.	NMR spectrum of dl-epivincadine	90
69.	Chemical interrelations of some natural alkaloids	92
70.	Relative configurations of dl-vincadine and dl-epivincadine.	93
71.	Transannular cyclization of vincadine and vincaminoreine to vincadifformine and minovine respectively	94
72.	Reaction sequence leading to total synthesis of dl-vincaminoridine (7)	95
73.	Preparation of 6-methoxytryptamine.[88]	96
74.	NMR spectrum of 6-methoxy imide (159)	98
75.	Mass spectra of 6-methoxy imide (159) and amine (160)	99
76.	NMR spectrum of 6-methoxy amine (160)	101
77.	The modified sequence to tetracyclic amine (161)	103
78.	NMR spectrum of 11-methoxy amide (166)	104
79.	Mass spectra of 11-methoxy amide (166) and amine (161)	105
80.	Some important fragements of the lactam (166)	106
81.	NMR spectrum of 11-methoxy amine (161)	108
82.	NMR spectrum of 11-methoxy alcohol-I (165)	110
83.	Mass spectra of 11-methoxy alcohol-I and II	111
84.	NMR spectrum of 11-methoxy alcohol-II (165)	112
85.	Preparation of 16-methoxyvincadine and its epimer	113
86.	NMR spectrum of 16-methoxy cyanide-I (168)	115
87.	Mass spectra of 16-methoxy cyanide-I and II	116
88.	NMR spectrum of 16-methoxy cyanide-II (168)	117
89.	Base induced introduction of cyanide ion	119
90.	Conversion of cyanides to carboxylic acid esters	119

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Figure		Page
91.	NMR spectrum of 16-methoxy-dl-vincadine (170)	121
92.	Mass spectra of 16-methoxy-dl-vincadine and its epimer	122
93.	NMR spectrum of 16-methoxy-dl-epivincadine (170)	123
94.	N-methylation of 18-carbomethoxydihydrocleavamine (172)	124
95.	NMR spectrum of the N-methylation reaction product	126
96.	Epimerisation of 18-carbomethoxydihydrocleavamine	127
97.	NMR spectrum of N-methyl-18-carbomethoxydihydrocleavamine (173)	128
98.	NMR spectrum of dl-epivincaminoridine (7)	130
99.	Mass spectra of dl-vincaminoridine (7) and its epimer	131
100.	NMR spectrum of dl-vinaminoridine (7)	132

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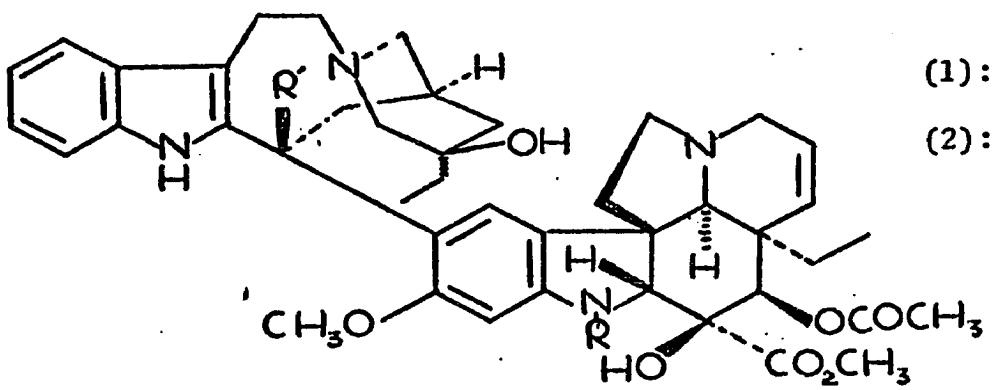
INTRODUCTION

(i) General

Of all the natural products studied by chemists in the last century, perhaps the most dominant study is that of alkaloids; particularly if one takes into consideration the companion medical aspects. Alkaloids have made a valuable contribution to medicine over many decades and one can be certain that this contribution will continue in the future despite the increasing attention to rigorous requirements for safety in governmental regulations on drugs.

In the 1950's, the periwinkle plant Vinca rosea Linn., was studied because of an interest in diabetes, but it was found that the extracts of the plant containing the dimeric alkaloids vinblastine (1) and vincristine (2),



(1): $R=CH_3$, $R'=CO_2CH_3$

(2): $R=CHO$, $R'=CO_2CH_3$

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were active against experimental leukemia in mice.

In the 1960's a new stimulus for investigation on alkaloids arose and the results were very encouraging, since many of them were found to cause cancer retardation. While no known drug, whether natural or synthetic, is as effective in the treatment of cancer as is desired, each new oncolytic drug, which has some positive effect in the treatment of clinical neoplasma is a temporary remission, a hope, and a prolongation of life.

By far, the alkaloids most extensively abundant in nature and most extensively checked for therapeutic use are the ones belonging to the indole family.[2]

This part of the thesis is concerned with the chemistry of the indole and dihydroindole alkaloids, especially of the Aspidosperma group, and with the biogenetic relations pertinent to their chemistry. The Aspidosperma type has been found in only a small number of plant families, and until only recently has been included in the postulated biosynthetic hypothesis. In this thesis, the first total syntheses of dl-vincadine (3), dl-vincaminoreine (4), dl-vincaminorine (5), dl-minovine (6), dl-vincaminoridine (7), and N-methyl-dl-quebrechamine (8) are described. In addition a new total synthesis of dl-quebrachamine (9), is presented and represents a considerable improvement over the sequence previously described.[3] Earlier literature on these alkaloids has been summarized.[4,5] It would be very interesting to see if, besides the above naturally occurring alkaloids, their epimers or derivatives, e.g. (10), which were synthesized also exist in nature as biogenetic intermediates

For the sake of clarity and consistency with previous publications we retain the numbering system originally employed in these families rather

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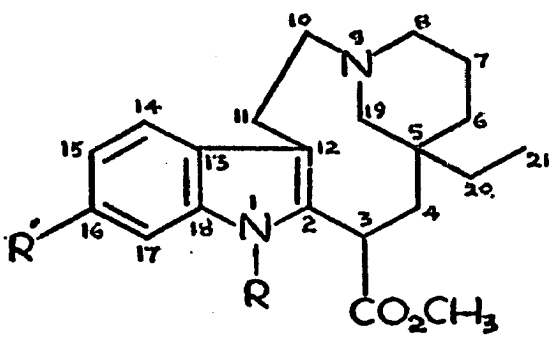
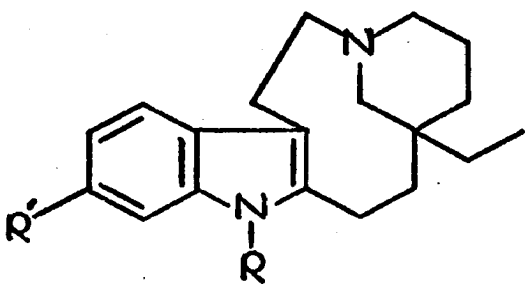
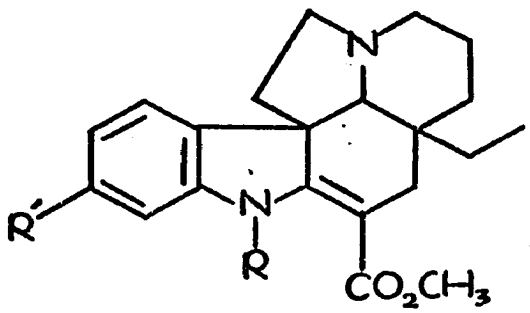


(3):R=H,R'=H
(4):R=CH_3, R'=H
(5):R=CH_3, R'=H
(7):R=CH_3, R'=OCH_3



(8):R=CH_3 R'=H
(9):R=H,R'=H



(6):R=CH_3,R'=H
(10):R=CH_3,R=OCH_3

than adopt the more recent proposal.[6]

(ii) Biosynthetic theories

It is not surprising that as soon as a new alkaloid is isolated the question arises: How is this complex natural product synthesized in the living system? In the past fifteen years or so, there has been an enormous progress in this field. Common building blocks, such as acetic acid, ornithine (11), and lysine (12), were proposed initially for the aliphatic part of the alkaloid and tyrosine (13), phenylalanine (14), 3,4-dihydroxyphenylpyruvic acid (15), and tryptophan (16), for the aromatic nucleus. In the indole family it was proven by appropriate labelling experiments that tryptophan was the important amino acid. For example, (±)-tryptophan-2-^{14}C

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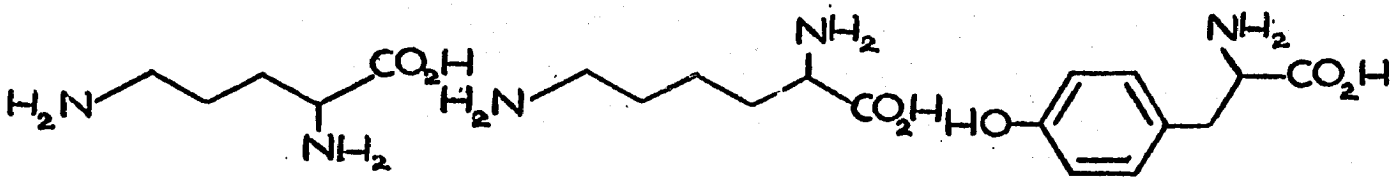
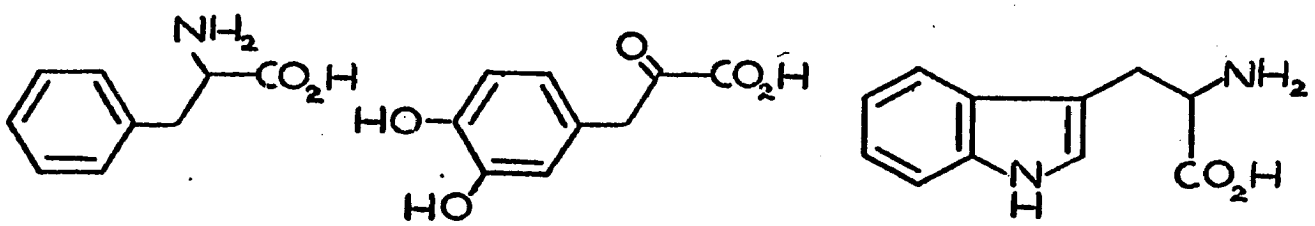
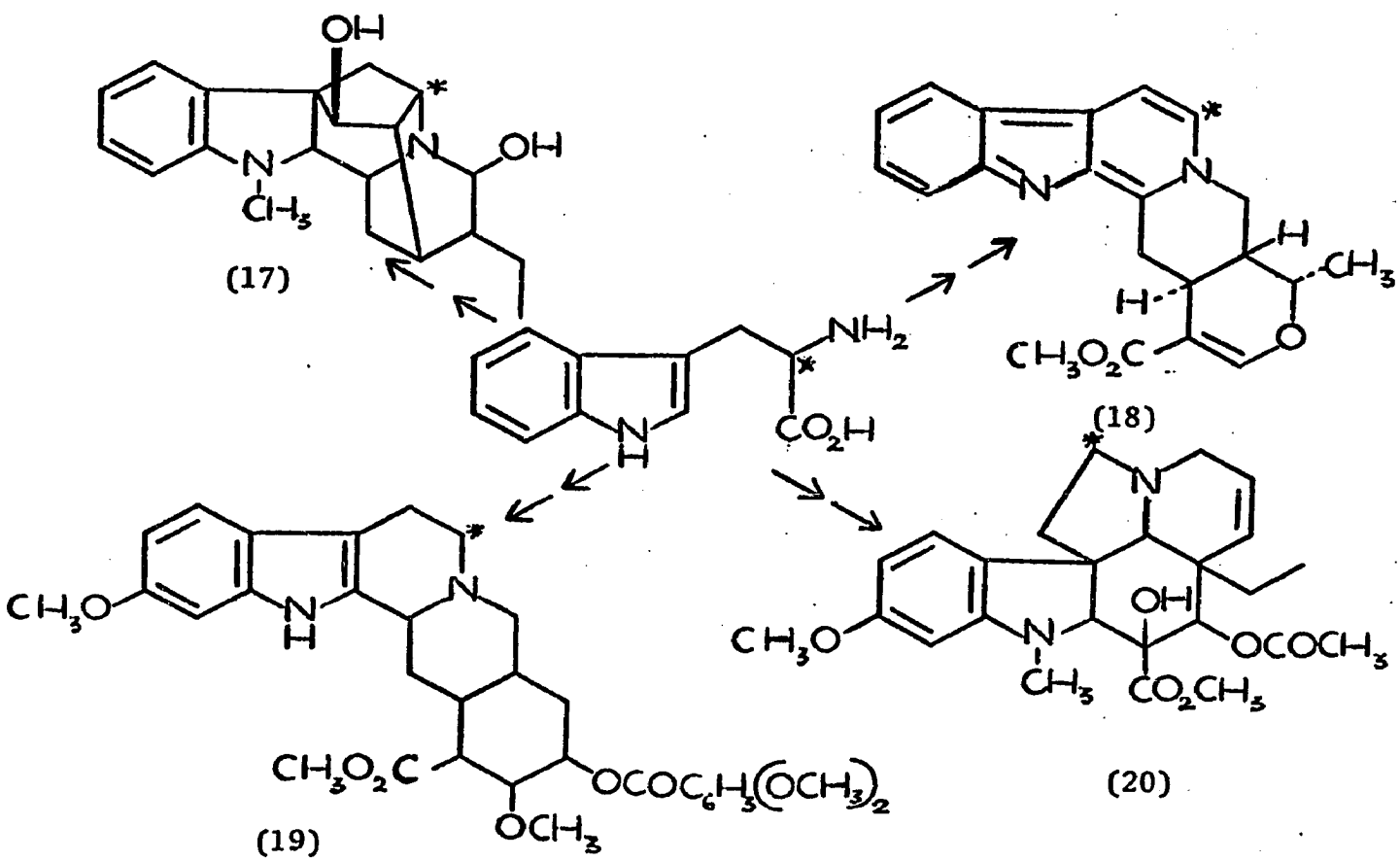


(11) (12) (13)



(14) (15) (16)

is incorporated by Rauwolfia serpentina into ajmaline (17), serpentine (18), and reserpine (19)[7,8], and by Vinca rosea L. into vindoline (20)[9], Figure 1.



(17) (18) (19) (20)

Figure 1. Incorporation of (±)-tryptophan-2-^{14}C into different indole alkaloids.

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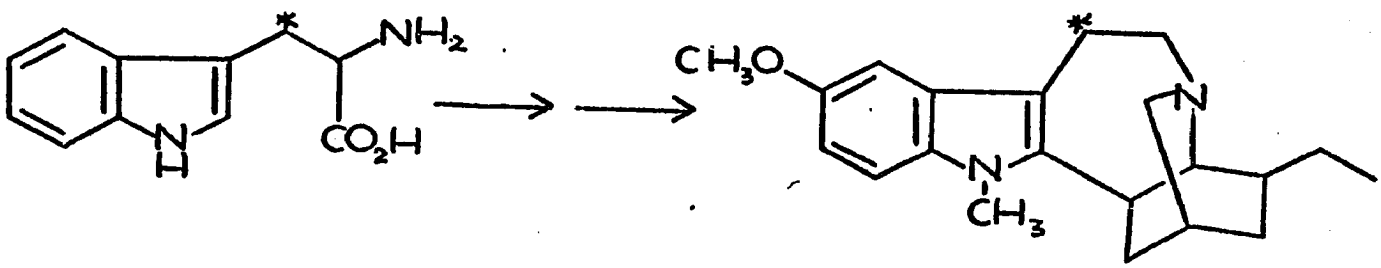
Also, (±)-tryptophan-3-^{14}C was incorporated by Tabernanthe iboga into ibogaine (21)[10], Figure 2.



(21)

Figure 2. Incorporation of (±)-tryptophan-3-^{14}C into ibogaine.

These experiments established that indole and dihydroindole alkaloids are derived partially from a tryptophan unit.

The biogenetic origin of the C_{9-10} "non-tryptophan" unit remained for a considerable number of years a matter of great argument and speculation. This unit could be produced by a variety of linear combinations from six carbon (C_6), one carbon (C_1) and three carbon (C_3) units connected as in Figure 3. This leads to three variants of "non-tryptophan" units which upon incorporation into the "tryptophan" moiety give rise to the three important indole-dihydroindole alkaloid families. In those alkaloids where only nine skeletal carbons appear in addition to the tryptamine residue, it is invariable that the carbon atom indicated by the dotted line has been lost.

Four hypotheses have been put forth to describe the origin of the "non-tryptophan" unit. These are illustrated in Figure 4, simply by the units involved and in the chronological order they appeared in the literature.

(A) The oldest hypothesis by Barger-Hahn suggested that a tryptamine skeleton is condensed via two Mannich type reactions with dihydroxyphenyl-alanine (22, R=H) and formaldehyde or its C_1-equivalent (α-condensation) and

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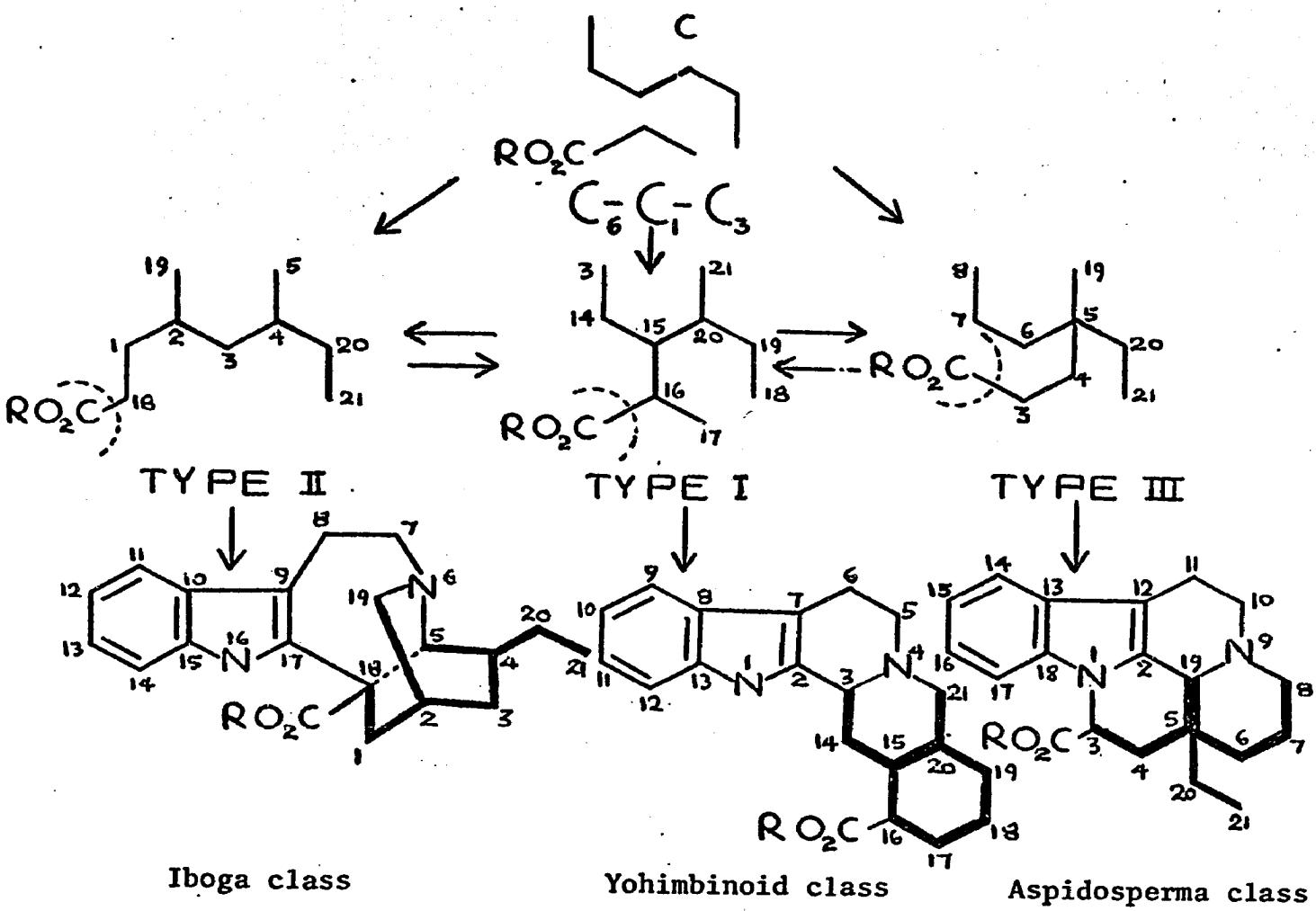
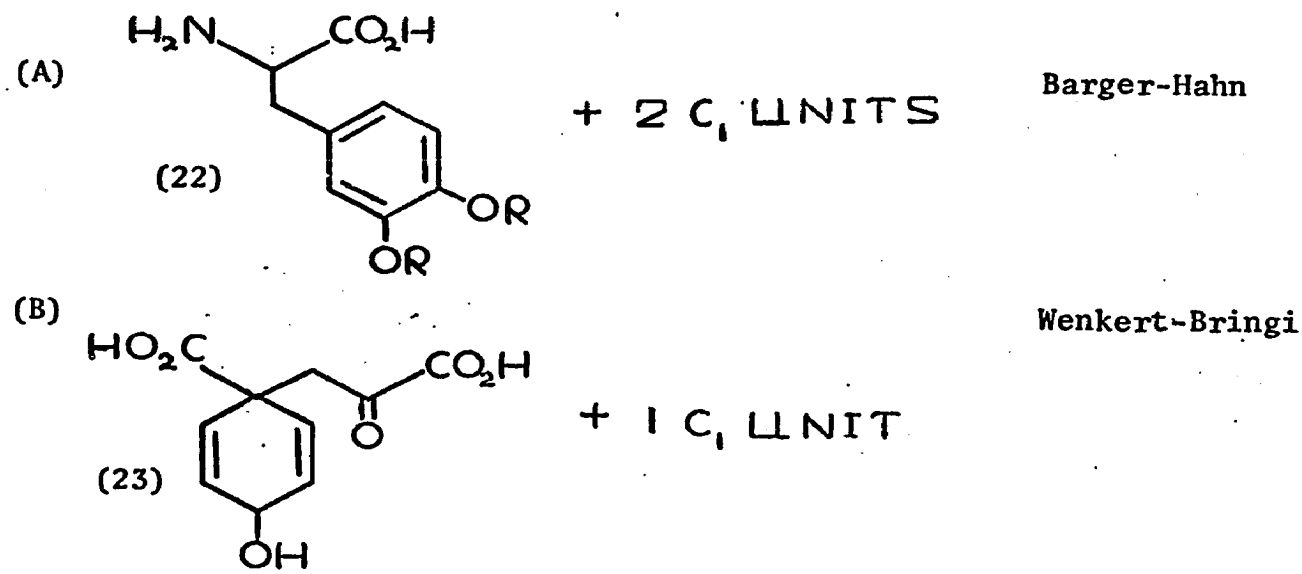


Figure 3. The interconversion of the C_{9-10} unit and incorporation to the major indole alkaloid skeleton.



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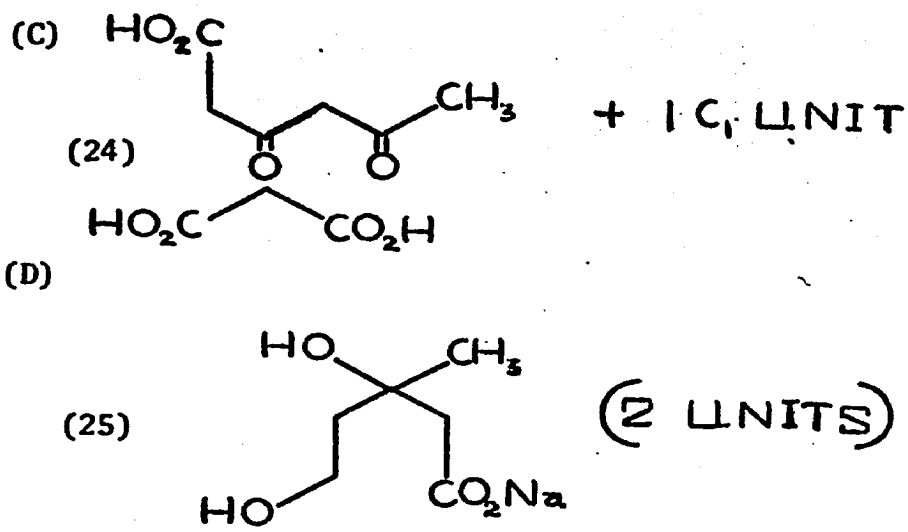

Figure 4. Basic units used to prove each of the four proposed hypotheses of the biogenetic origin of the "non-tryptophan" moiety.

can produce the yohimbine (27) skeleton, as in Figure 5.[11,12,13] It was already known that tryptamine undergoes condensation reactions in vitro with aldehydes to give carboline derivatives[14]. To account for the carbomethoxy group in (27) a tropolone intermediate (28) was proposed, which after second transformations gives a keto-acid or its ester.[14]

The Barger-Hahn hypothesis found support as a consequence of the ingenious suggestion by Woodward[15] in which instead of an α-condensation process there was condensation at the β-position with subsequent fission of the 3,4-dihydroxyphenyl moiety (26) to give strychnine (29) as illustrated in Figure 5. This concept was applied almost immediately to other indole alkaloids as ajmalicine (30), corynanthine (31), ajmaline (17)[16], sarpagine (32)[17] as well as to the bisisoquinoline alkaloid, emetine (33). However this hypothesis failed since:

(a) the administration of ^{14}C-labelled tyrosine (13) and phenylalanine (14) into Rauwolfia serpentina plants has resulted in only a low and nonspecific

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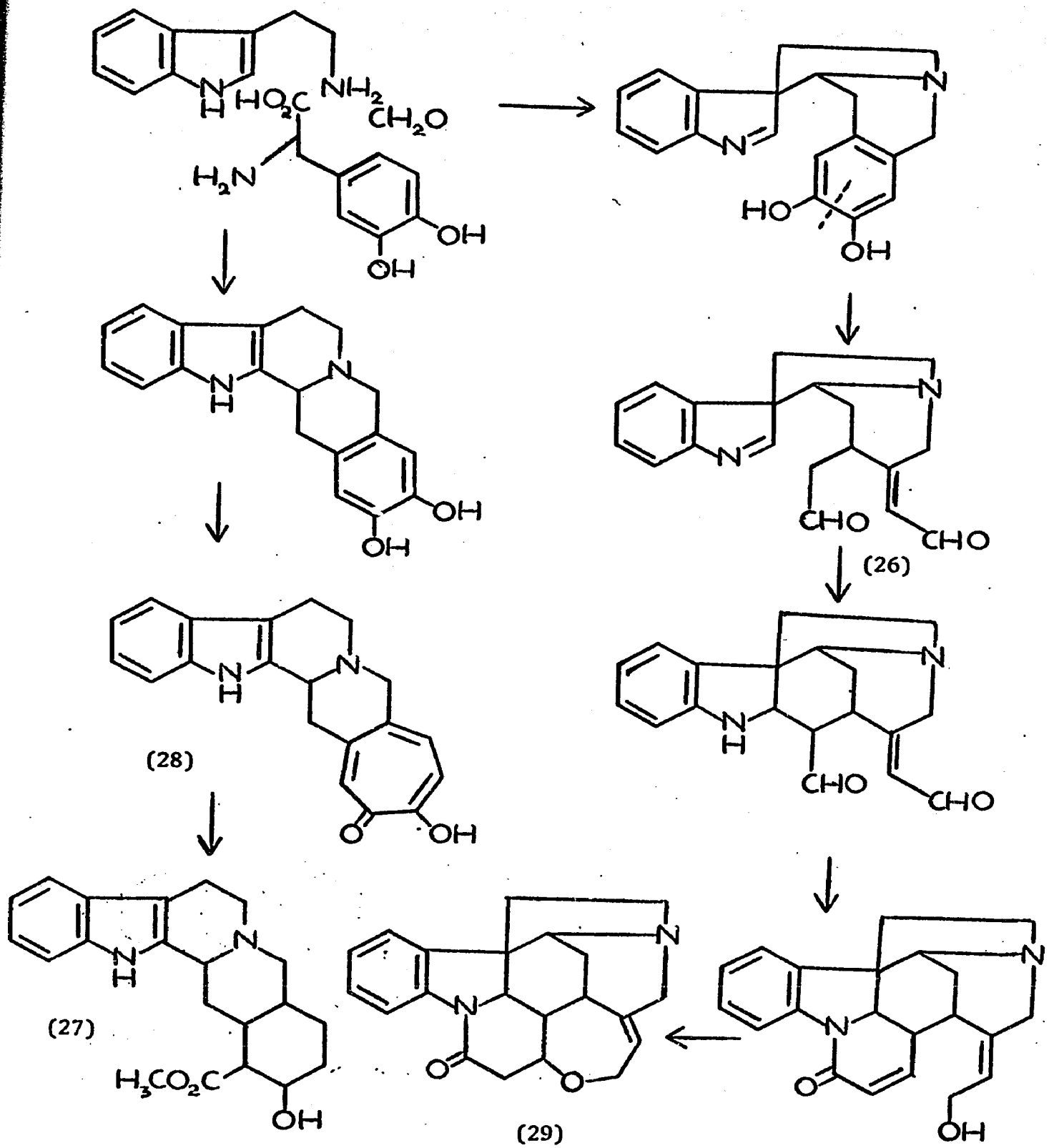

Figure 5. Outline of Barger-Hahn-Robinson-Woodward hypothesis.

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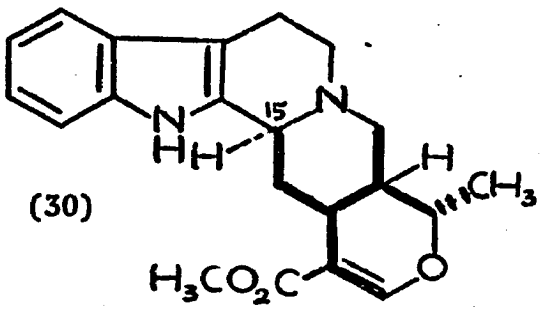

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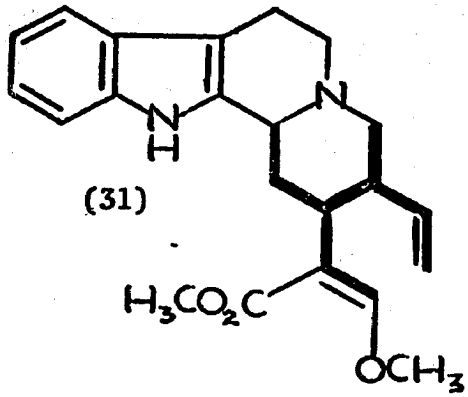

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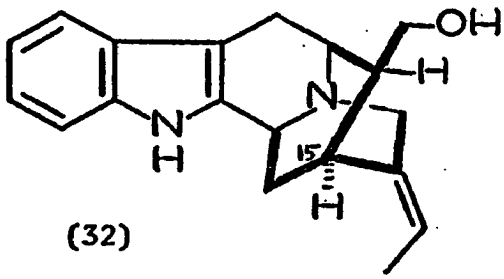

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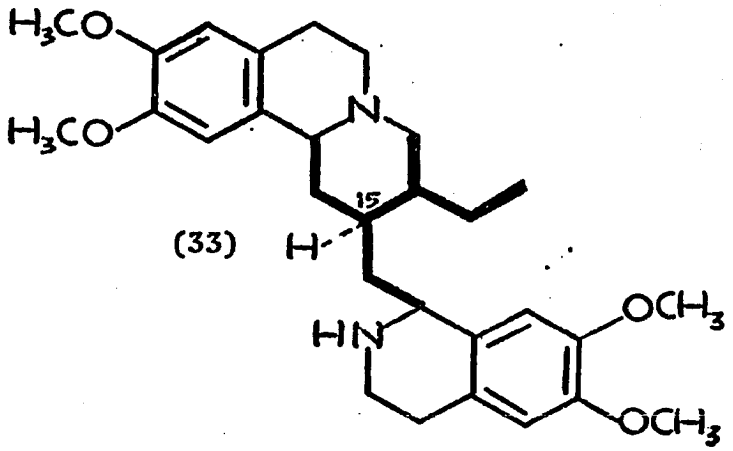

(33)

(radomization of labels) incorporation into alkaloids such as ajmaline (17) and serpentine (18);

(b) the aliphatic character of indole alkaloids containing a carbocyclic ring E was not taken into consideration;

(c) it was inconsistent with the observation that C-15 appears to have a unique absolute configuration;

(d) a tropolone intermediate is considered unlikely for the origin of the carbomethoxy group.

(B) The second hypothesis introduced by Wenkert and Bringi[18] known as the "Prephenic Acid Hypothesis" suggests that the "non-tryptophan" moiety is derived from carbohydrates via a pathway involving shikimic (35) and prephenic acids(36). The latter undergoes a stereospecific 1,2-shift of

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the pyruvyl chain with retention of configuration, followed by hydration and condensation with a C_1 unit to afford (37), possessing a Type I skeleton, see Figure 6.

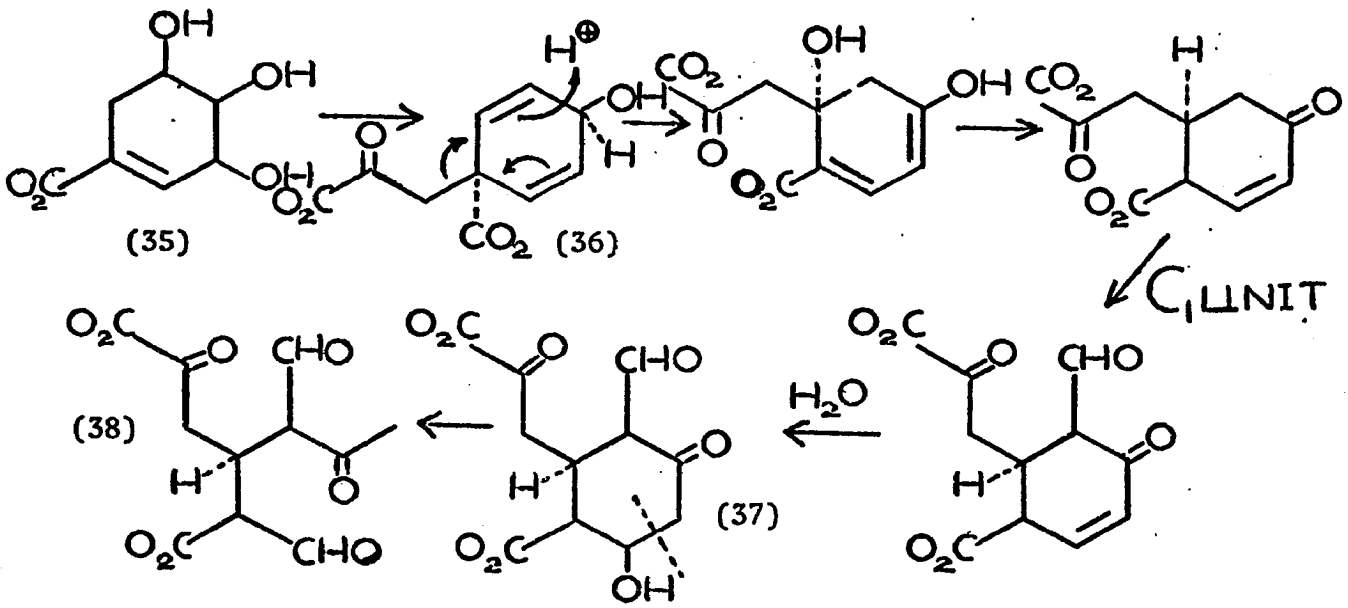

Figure 6. Basic transformations of Prephenic Acid Hypothesis.

The key unit (38) or "seco-prephenate-formaldehyde" (SPF) is then derived by a retro-aldolisation of the unit (37). This SPF unit gives rise to all Type I or yohimbinoid type alkaloids (see Figure 3) such as ajmalicine (30), corynanthine (31), ajmaline (17) and sarpagine (32), as shown in Figure 7.

This hypothesis accounts for the formation of strychnos, Iboga and Aspidosperma alkaloids also, as shown below, Figure 8, which possess the Type I, II, and III "monoterpene" units correspondingly.

It is obvious that a condensation of the formaldehyde group of (39) with the α-position of the indole ring gives intermediate (40) which then undergoes transannular cyclization across C-7 and C-3 or across C-7 and C-21 affording an intermediate (41) which gives strychnos bases or condylocarpine (Type I) bases respectively.

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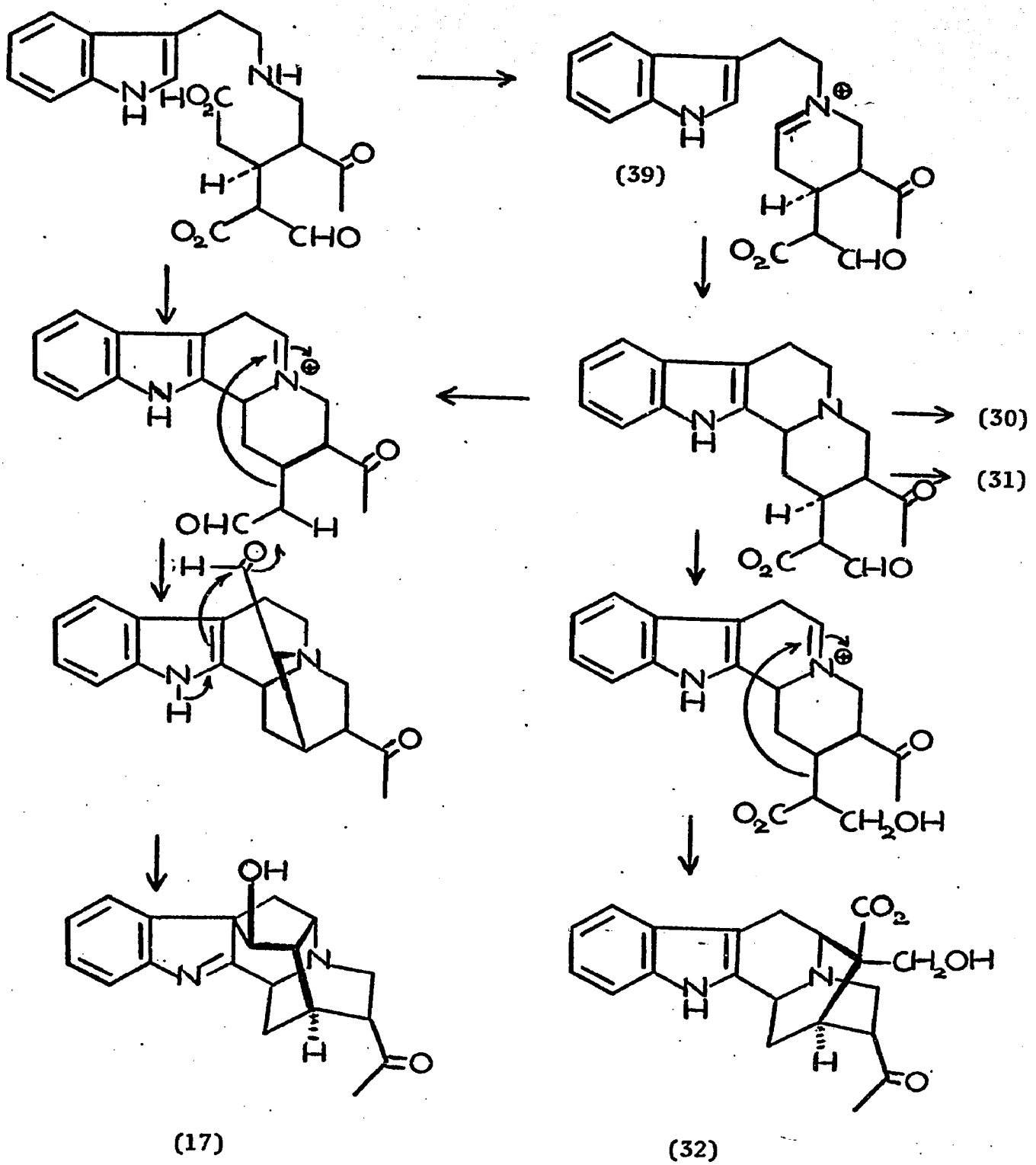

Figure 7. Incorporation of the SPF unit into ajmalicine (30), corynanthine (31), ajmaline (17) and sarpagine (32).

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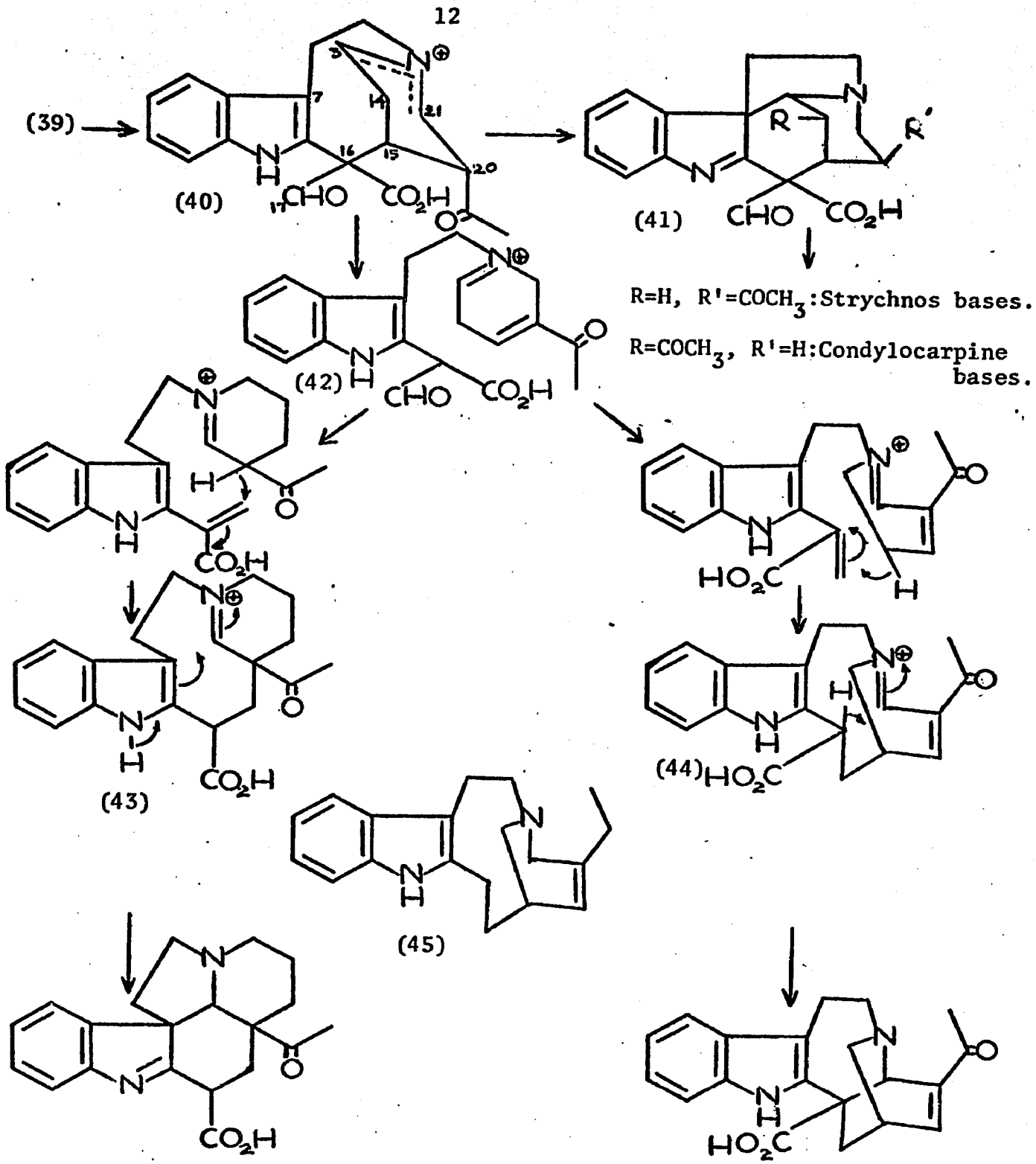

Figure 8. Incorporation of the SPF unit into the Iboga and Aspidosperma alkaloids.

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On the other hand rupture of C-16 and C-15 bond gives rise to (42), which can undergo several oxidation-reduction processes followed by Michael additions and by transannular cyclizations to give Iboga bases (Type II) or across C-17 and C-20 to give Aspidosperma bases (Type III) respectively. The nine-membered ring intermediate (43) and (44) resemble the structures of vincadine (3) and cleavamine (45) respectively.

Although this theory had taken into account the α-configuration of C-15 hydrogen found in almost all natural alkaloids, it could not stand up to experimental test. Feeding experiments with alanine-2-^{14}C to Rauwolfia serpentina plants expected to convert the amino acid thence to prephenic acid etc. showed that the actual uptake into ajmaline was extremely poor and randomized since only 2% of the incorporated radioactivity was at the predicted position[19]. The later developed modification of this theory, that is, that the SPF unit can be written in a number of equivalent ways and that the basic nitrogen of the indole alkaloids is not necessarily derived from that of tryptophan did not provide any strength to this theory.

(C) The third hypothesis was introduced by Schlittler and Taylor[20]. According to this hypothesis, an intermediate (47) closely related to Wenkert's SPF unit (38) is formed probably via an enzymatic condensation initially involving acetyl-coenzyme A. A poly-β-keto intermediate (46) is formed which then condenses with a C_1 unit - possibly formaldehyde - and a C_3 unit -- possibly malonyl-coenzyme A - as depicted in Figure 9.

The early experimental support of this theory came by feeding sodium acetate-1-^{14}C (48), mevalonic-2-^{14}C acid (49) or tyrosine-2-^{14}C (50) to Rauwolfia serpentina plants[21,22,23]. By administrating acetate, radioactive ajmaline (17) equally labelled at C-3 and C-19 was isolated, Figure 10.

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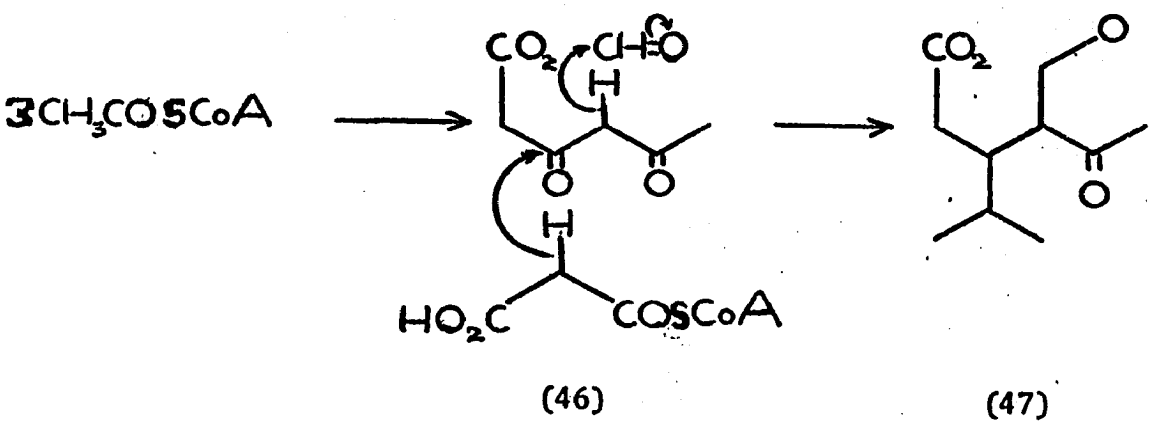
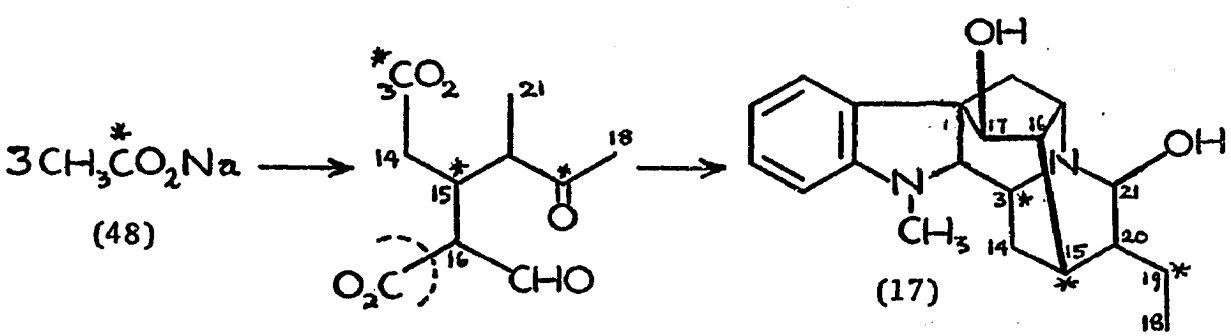
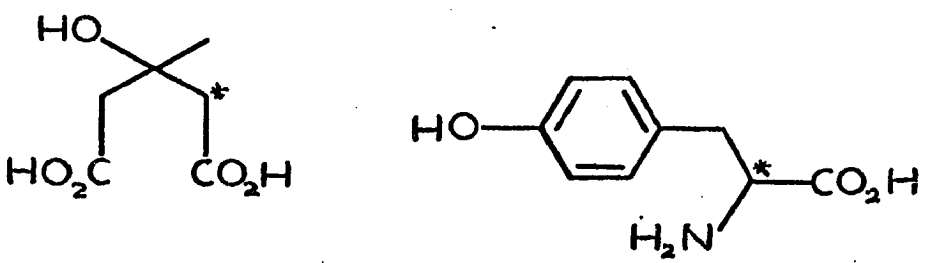


(46) (47)

Figure 9. Postulated mechanism of Schlittler-Taylor hypothesis.





(49) (50)

Figure 10. Incorporation of labelled acetate into ajmaline.

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On the other hand, feeding of mevalonic-2-^{14}C acid or tyrosine-2-^{14}C gave randomization of the labels, which excluded these compounds as biosynthetic intermediates as proposed by previous theories.

When the latter results were repeated by Battersby[24] incorporation of mevalonate took place indeed and since Leete was unable to reproduce his own results he was forced to withdraw[9]. Finally the failure to find radioactivity at C-15, as was expected from this theory (see Figure 10) as well as other results, caused it to be deserted.

(D) The only hypothesis which stands in accordance with up-to-date findings is that due to Thomas[25] and Wenkert[26], which suggests relationship of the C_{9-10} unit to a cyclopentane monoterpene skeleton (53). The so called "monoterpene hypothesis" is outlined in Figure 11 (cf. Figure 3).

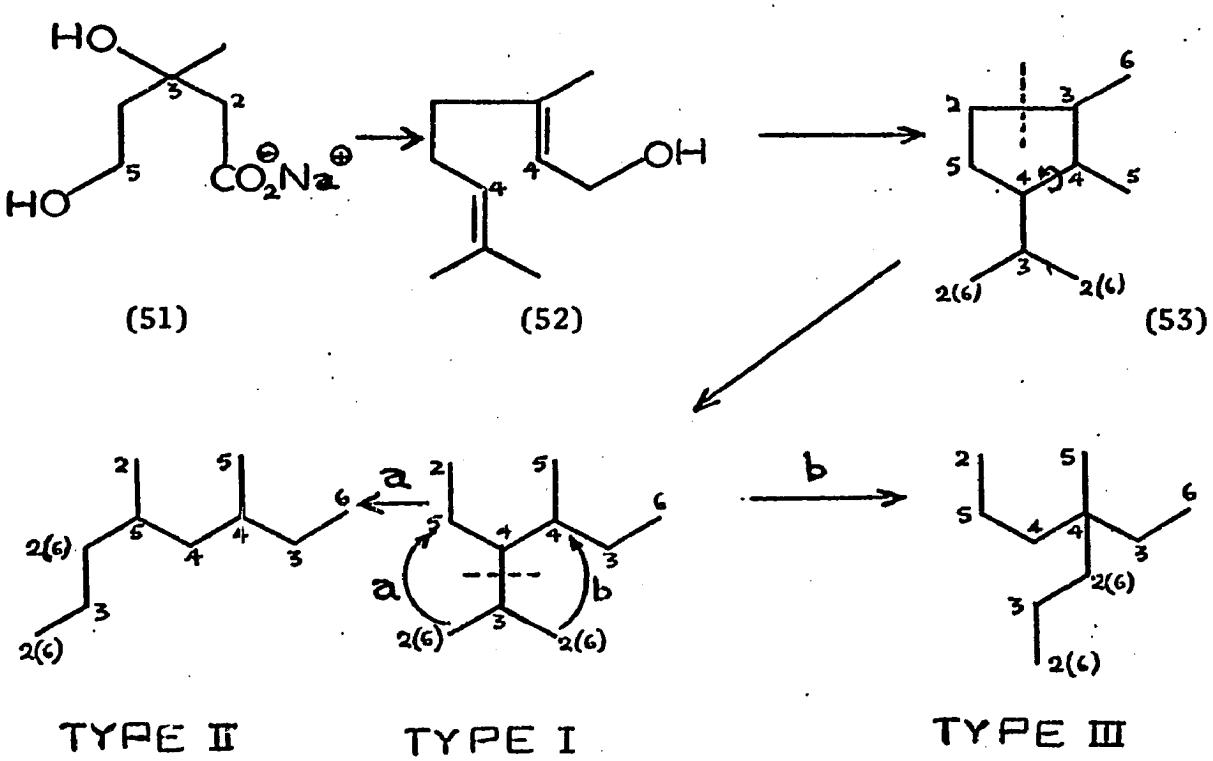

Figure 11. The "monoterpene" or Wenkert-Thomas hypothesis.

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The cyclopentane ring of some unknown monoterpene (53) - derived by a head to tail linkage of the mevalonate units - without any indication of its oxidation level, might undergo bond fission followed by bond formation in the direction either (a) or (b) as indicated. The "timing" that these changes take place or the favored pathway in the biosynthetic process is unknown as yet. The result of these processes is the creation of the three types of C_{9-10} units to give rise to the three basic skeleta of indole alkaloids (cf. Figure 3).

Sodium mevalonate (51) labelled in different positions was used extensively to check this theory. Battersby et al. found that satisfactory incorporation to Rauwolfia serpentina[27], Rhazia stricta, and Vinca rosea plants[28] occurred upon administration of sodium mevalonate-2-^{14}C. With R. stricta radioactive 1,2-dehydroaspermidine (54) was produced, while with V. rosea active vindoline (20), serpentine (18), ajmalicine (30), catharanthine (55) and perivine (56), Figure 12 were obtained. Reliable methods of degradation were used for locating the labels in the radioactive alkaloids isolated. Similarly, Arigoni et al.[29] and Scott et al.[30] independently carried out parallel experiments and more support of the "monoterpene" theory was found. These results are illustrated in Figure 13 and shown by underlined numbers are the positions in which they have been proven to be so labelled from the corresponding labelled mevalonate. Quantitative results are equally agreeable.

A logical substitute of mevalonate used would be geraniol (52) or any other C_{10} unit naturally existing in the plant. Geraniol is a biochemical intermediate during the transformation of mevalonic acid; therefore a potential precursor of the hypothetical cyclopentane system. Indeed this

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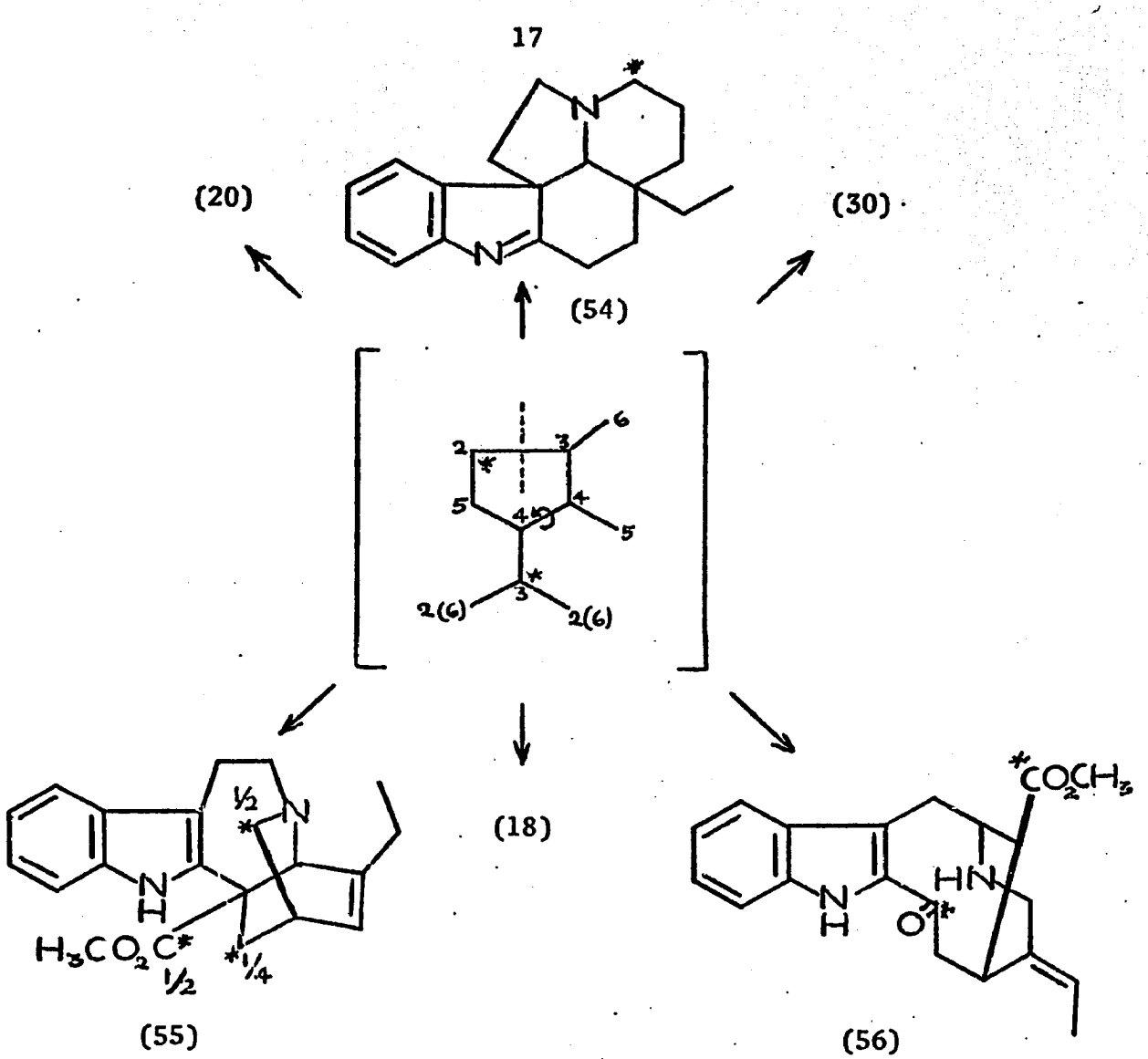

Figure 12. The incorporation of labelled 2-^{14}C mevalonate into the "aliphatic" part of the indole alkaloid skeleta.

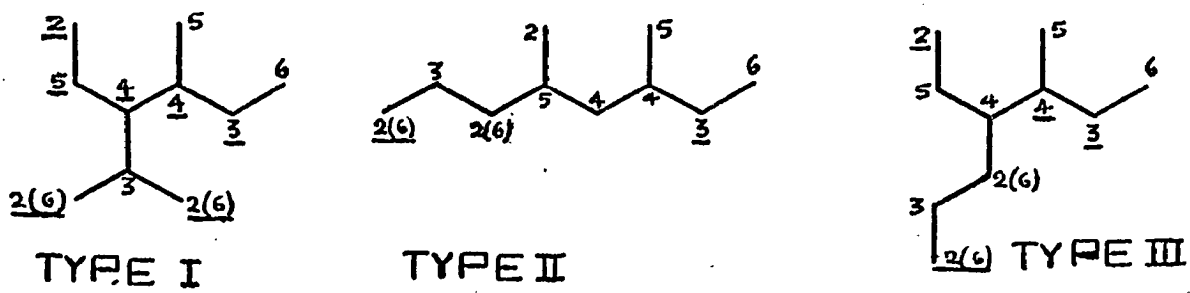

Figure 13. Summary of detected radioactivity in the "non-tryptophan" part following labelled mevalonate administration.

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was proven to be the case: geraniol-2-^{14}C-pyrophosphate or geraniol-3-^{14}C[31] was administered to Vinca rosea plants and incorporated in all three types of indole alkaloids[32,33,34] in higher yield than has been obtained using mevalonate, Figure 14. All the activity of these alkaloids was found at the

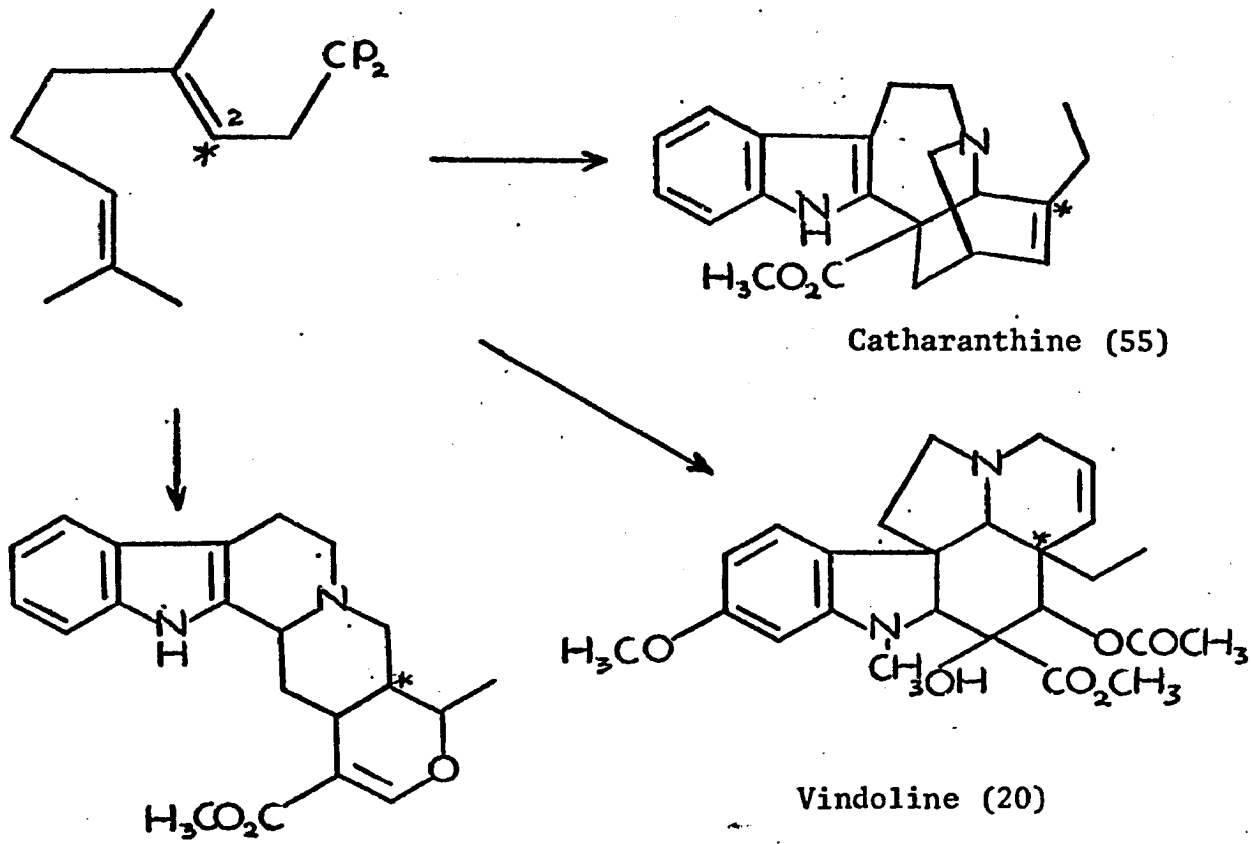

Figure 14. Incorporation of geraniol-2-^{14}C to the indole alkaloid skeleta.

indicated position in accordance with the cyclopentane-monoterpene theory.

Some other possible precursors were verbenalin (57), dihydroverbenalin (58), genepin (59), monotropeine ester (60) and loganin (61), Figure 15. When (57), (58), (59) or (60) labelled with tritium at the ester methyl were administered into Vinca rosea plants the isolated alkaloids were inactive. However, when loganin (61), occurring alongside indole alkaloids in strychnos

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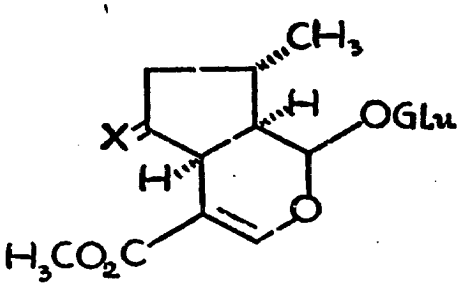
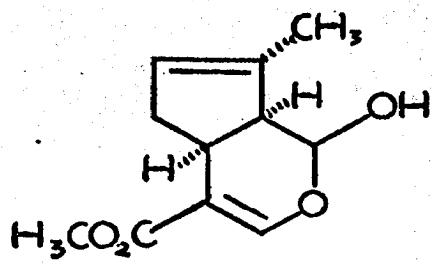
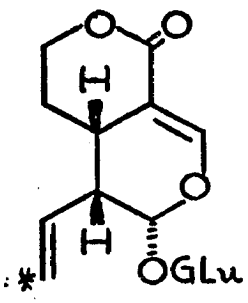


X=O:Verbenalin (57)

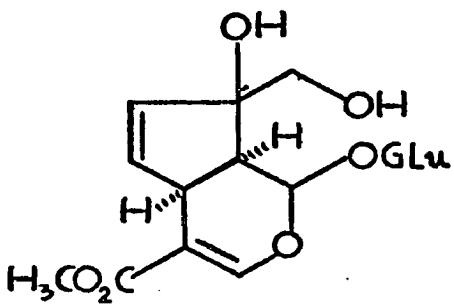
X=H,OH:Dihydroverbenalin (58)



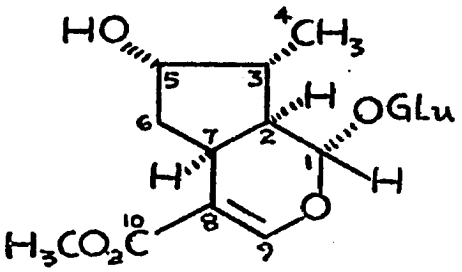
Genepin (59)



Sweroside (61a)



Monotropeine ester (60)



loganin (61)

Figure 15. Monoterpenes used for checking "cyclopentane-monoterpene" theory.

species[35], with tritium at the methyl ester group was administered, it gave good incorporation to all three basic indole alkaloid systems[36]. All the activity was found to be located at the methyl of the carbomethoxy group as expected, Figure 16. Recently, Arigoni et al.[37a] as well as Battersby et al.[37b] fed to Vinca rosea plants loganin labelled at ^{14}C-4 methyl or at ^{14}C-2. All of the basic indole alkaloids mentioned above were obtained with labels in the expected positions. Similarly, tritium labelled carbon atoms in other positions of loganin gave the expected results. All of these results established that loganin is a very likely precursor of the "non-tryptophan" moiety of the indole alkaloids. Very recently a Japanese group showed that sweroside (61a), labelled as indicated, is incorporated into

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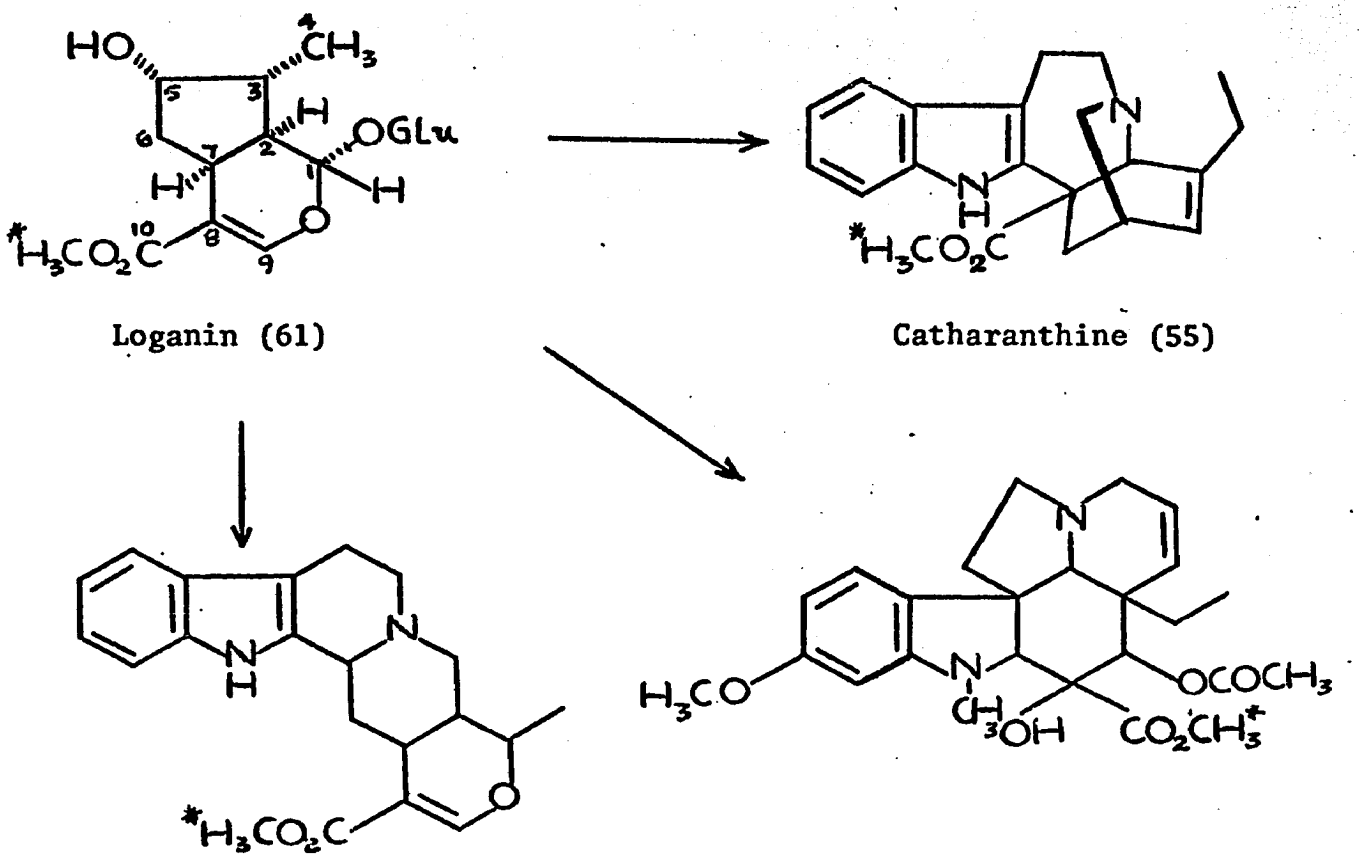

Figure 16. Incorporation of loganin to all type indole alkaloid skeleta.

these alkaloids. At least in the case of vindoline (20) the incorporation ratio was as high as 11%. These workers speculate that there "must be a biosynthetic pathway of the indole alkaloids from mevalonic acid via geraniol, loganin, and sweroside (61a) (or its equivalent)"[37c]. Today we may speculate at least in an approximate sense that the biosynthetic sequence in the plant may follow the pathway presented in Figure 17.

It is not known yet if rearrangements of the cyclopentane structure takes place before or after the condensation with the tryptamine structure. Although it is perhaps easier to think that the rearrangements take place before the introduction of the nitrogen, there is an indication that this

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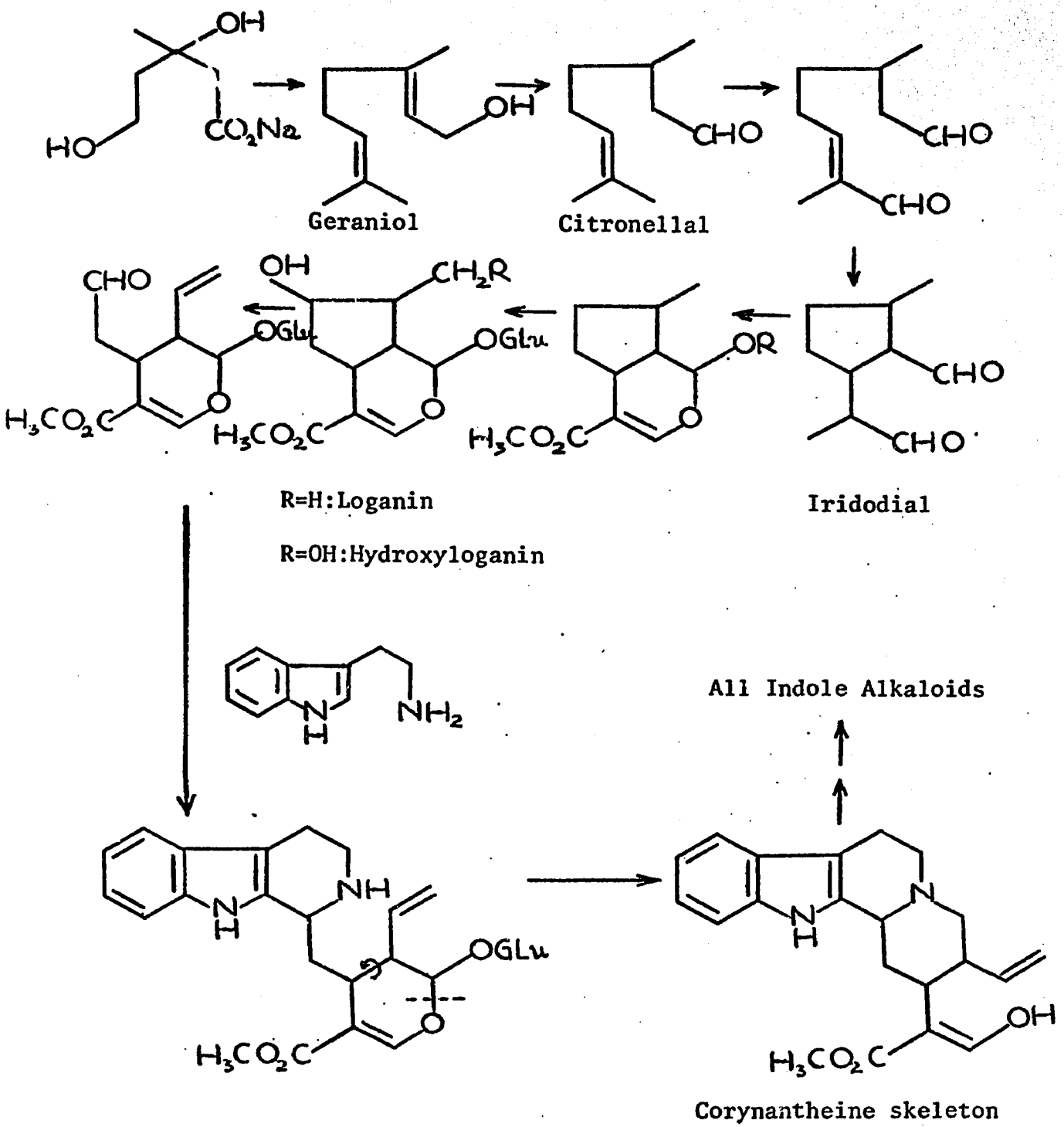

Figure 17. An attractive sequence leading to incorporation of the C_{10} unit into indole alkaloids.

might not necessarily be the case[38].

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(iii) Some Important Biosynthetic Reactions

It is well known that amino acids are alkaloidal building units. The precise way and timing of the procedure of the reactions involved is not known in most cases. However one plausible reaction sequence is illustrated in Figure 18.

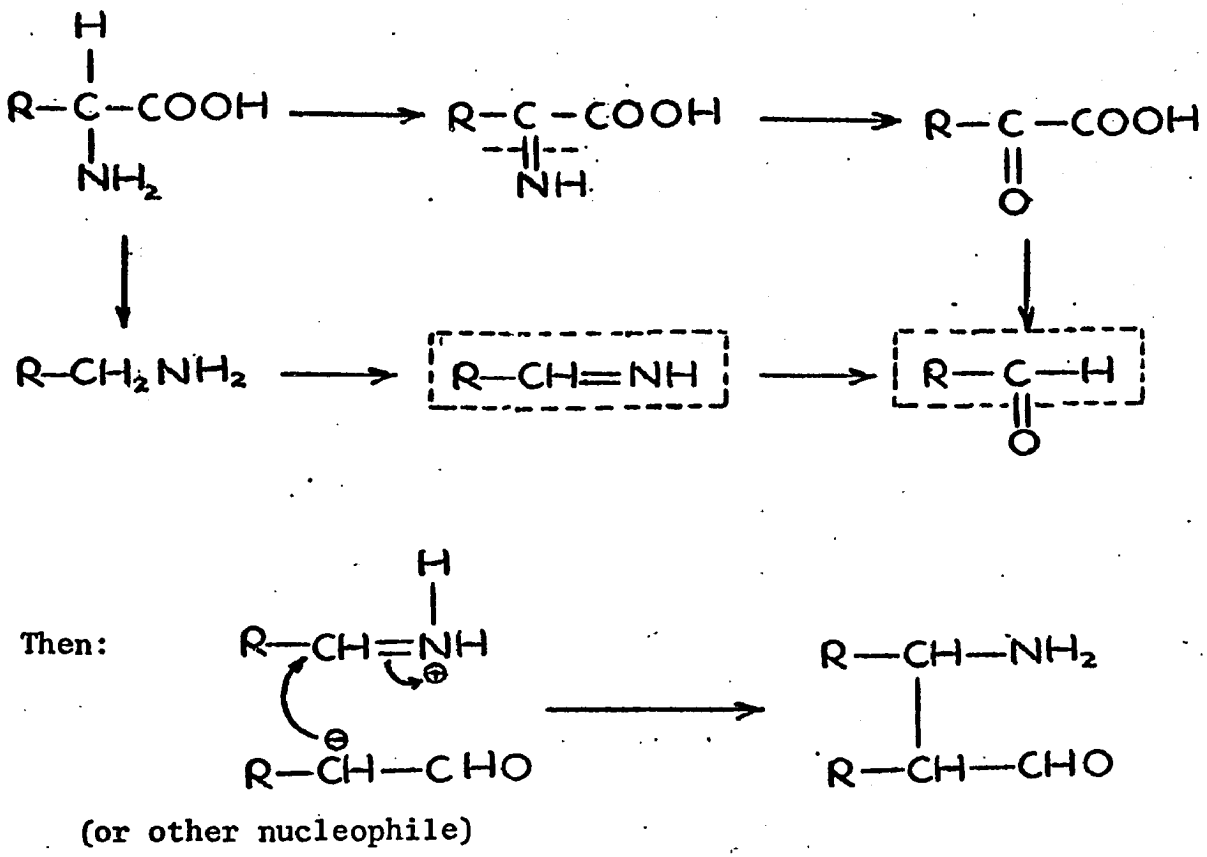

Figure 18. Amino acids as alkaloidal building units.

This series of reactions, performed in the laboratory as above, perhaps has nothing to do with the favored sequence that nature really used on the living system. However it is attractive and very interesting to speculate on reaction mechanisms as a basis for experimental work.

Wenkert's initial concept of formation of the iminium salt which then

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undergoes transannular cyclization (see Figure 8) to give several naturally occurring alkaloids found remarkable application. In this aspect the chemical correlation of condylocarpine (62) and akuammicine (63) reveals the absolute configuration of the former[39]. It is believed that the formation of iminium salt intermediates (66) and (67) is taking place, which then by transannular cyclization gives condyfoline (64) and tubifoline (65) respectively, being in equilibria, Figure 19.

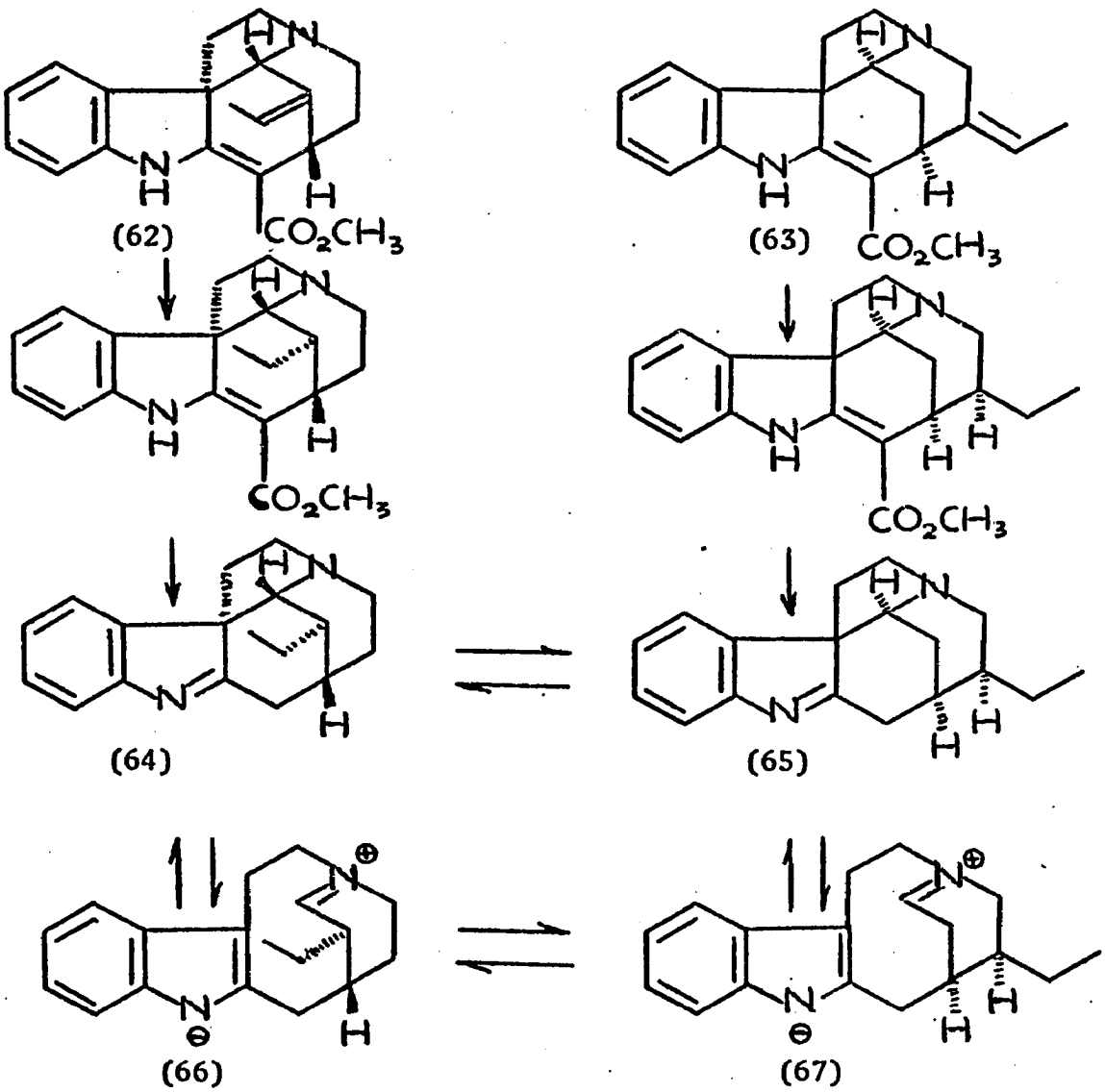

Figure 19. Stereochemical correlation between condylocarpine and akuammicine.

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Wenkert applied a related cyclization in the laboratory when by using mercuric acetate oxidation in methanol, a successful synthesis of flavopereirine (68) was obtained, Figure 20.

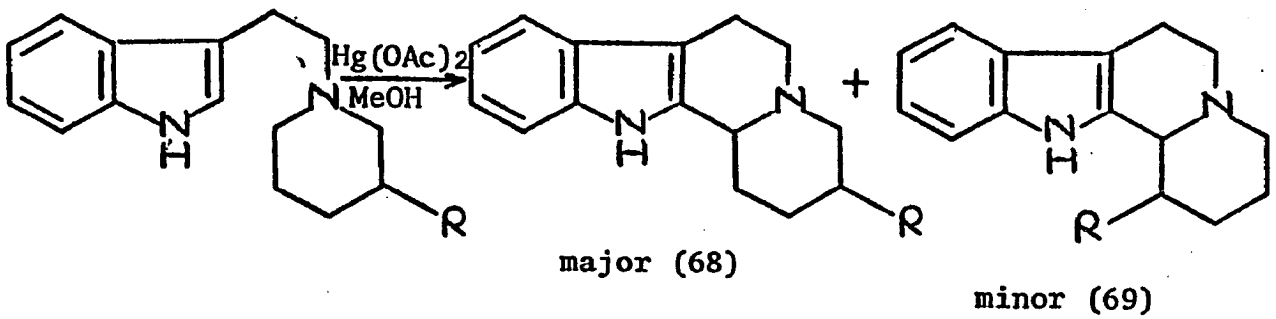
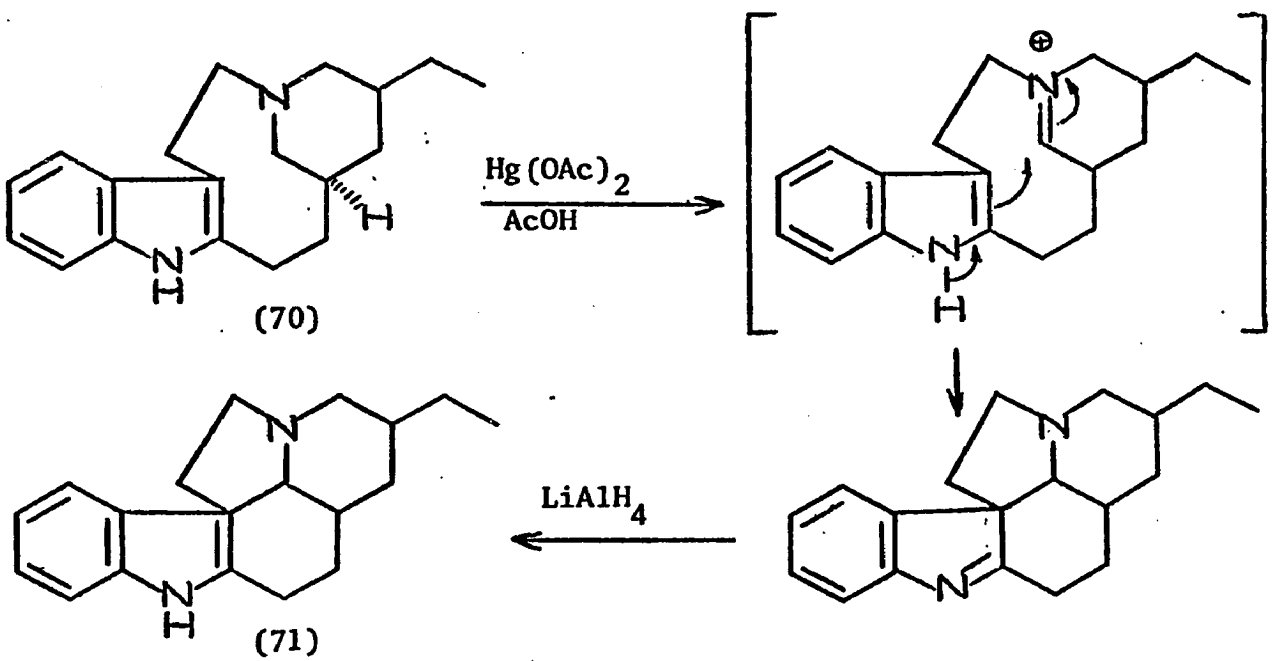


Figure 20. Synthesis of flavopereirine by Wenkert (R=H or Et).

The first application of this mercuric acetate oxidation and subsequent transannular cyclization to more complex alkaloid systems was by Kutney[41]. In this case using dihydrocleavamine (70), an aspidosperma skeleton (71) was obtained via the indolenine:



This type of cyclization was then used extensively in our laboratories later

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on to prove the versatility of this reaction. Several derivatives having different groups in various positions of the alkaloidal skeleton were used. For instance[49], carbomethoxydihydrocleavamine (72) gave 5-desethyl-7β-ethyl vincadifformine (73), which reduced to (74). Hydrolysis and decarboxylation of the latter gave another aspidosperma type structure (75), as shown in Figure 21.

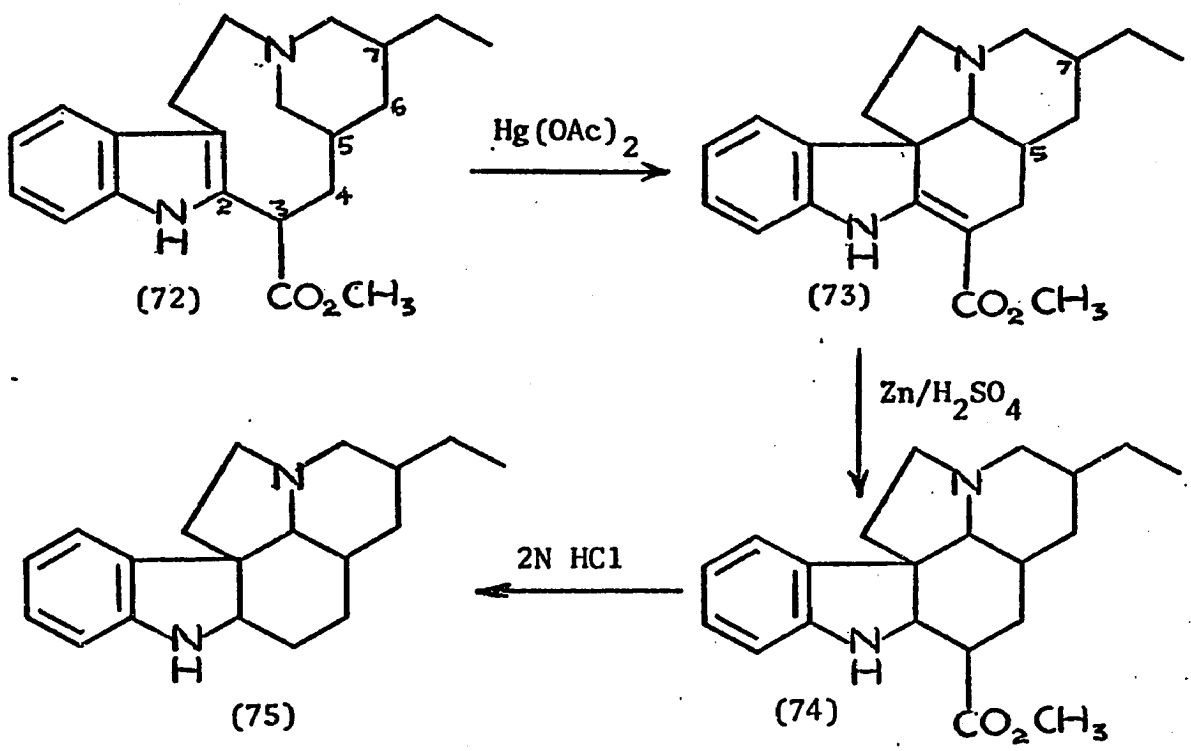

Figure 21. Synthesis of Vincadifformine analogues.

More careful investigation of the above reaction[43], (72) ⟶ (73), showed that besides (73), coronaridine (80, R=Et, R'=H) and dihydrocatharanthine (80, R=H, R'=Et) are also major products. This result was expected since generation of an intermediate iminium salt can occur in several ways, Figure 22. This epimerization at C-7 was expected, if we consider the

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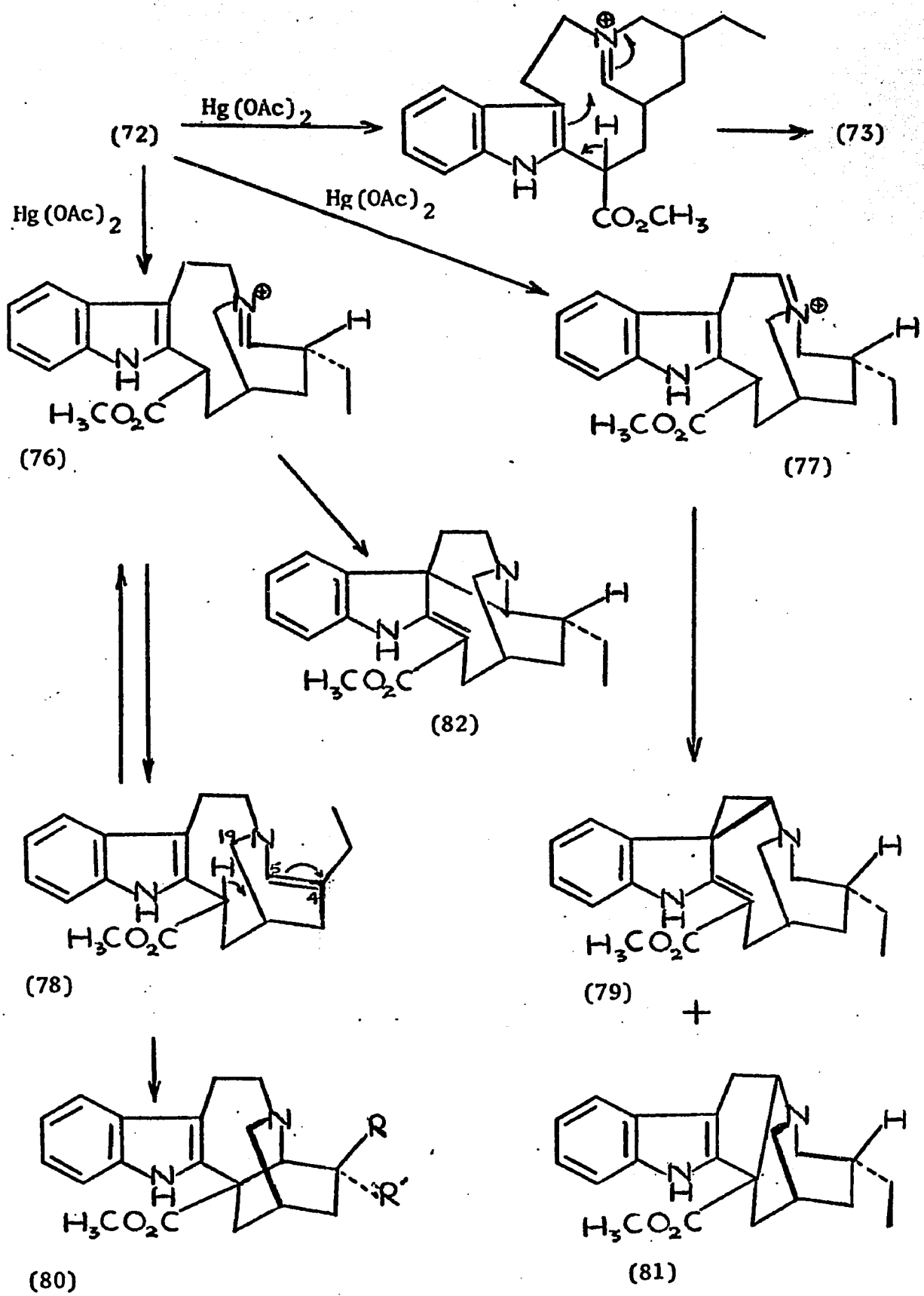

Figure 22. Transannular cyclization processes.

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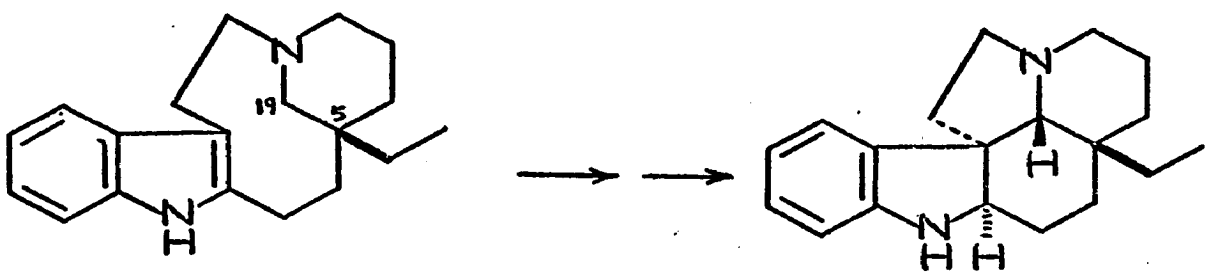
mobility of the enamine-iminium salt system[44] (76) ⟶ (78). On the other hand, we may expect products as (79), (81) or (82). All of them are unlikely to be formed because of the severe bond strain introduced, even though spiro components as (79) are formed in similar reactions[45].

The above chemical transformations of a common nine-membered ring intermediate such as (72) to both Iboga (80) or Aspidosperma (73) type homologues was established mainly by spectroscopic evidence[46]. In a similar manner, similar alkaloids with functional groups in other positions were studied[47]. For example, (-)-quebrachamine (83) was converted to (+) aspidospermidine (84). The absolute configuration of the latter was assigned



(83) (84)

as shown above, since it was proven by X-ray crystallographic studies that the absolute configuration at the crucial C-5 asymmetric center remains unaltered during such a chemical transformation[48]. Starting with catharanthine (85), we obtain cleavamine (86) with an established configuration at C-5. The resulting cyclic product (87) retains the same absolute configuration at C-5, as shown in Figure 23[47].

The transannular cyclization reaction was not only of great value as a synthetic tool, it also served to establish stereochemistry in some alkaloid families. Thus Kutney et al.[50,51] were able to utilize the stereospecificity of this reaction to derive the correct absolute configuration of the Iboga

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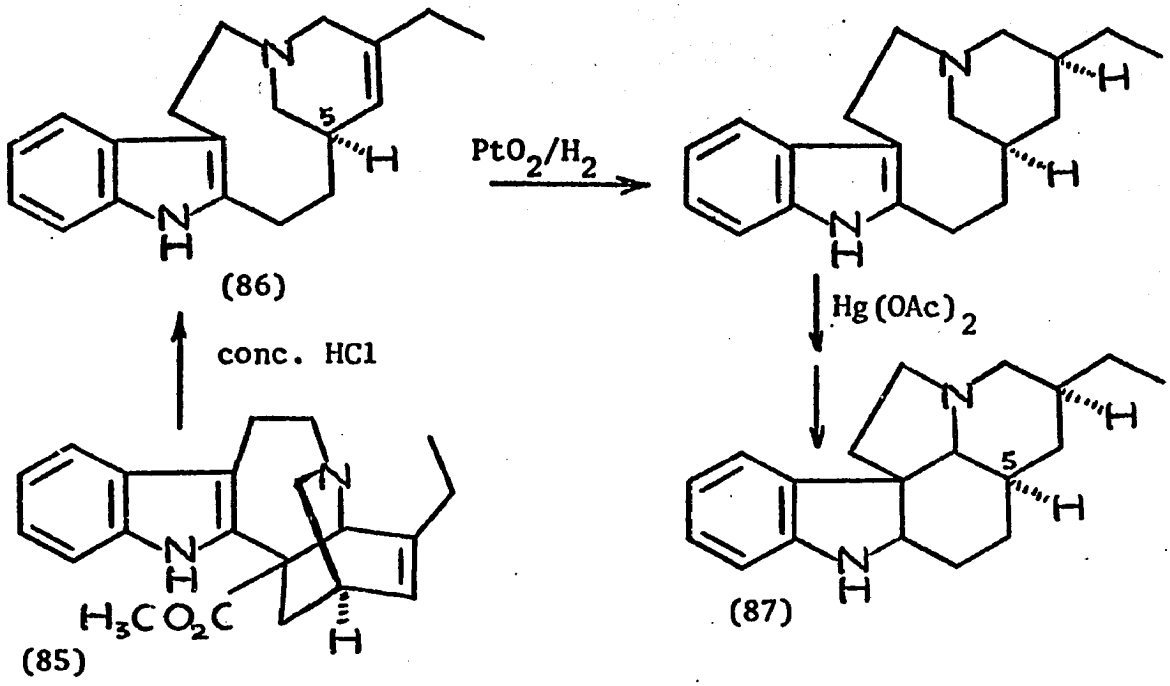
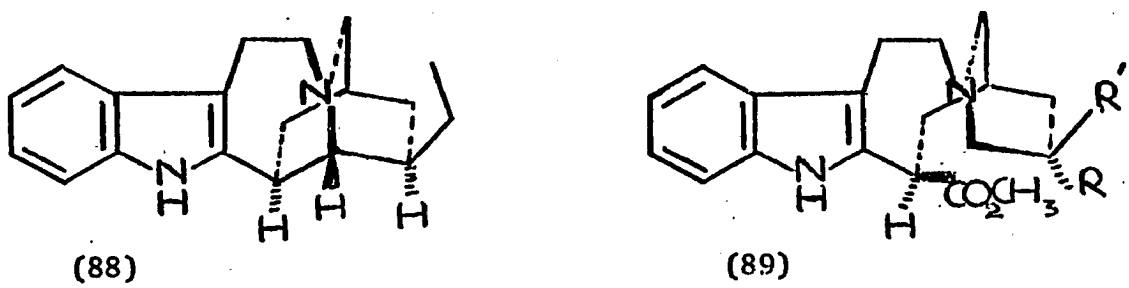


Figure 23. Retention of absolute configuration during the reactions.

alkaloids (88) and (89). Also one of the transannular cyclization products has been utilized as a key intermediate in the establishment of absolute configuration in the Aspidosperma family[52].



In conclusion it was now clear that the importance of the nine-membering ring intermediates which participate in the transannular cyclization process was sufficient to warrant an investigation into general laboratory syntheses of these molecules. The results in this direction represent the main theme of this thesis.

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DISCUSSION

In order to develop suitable synthetic method for the total synthesis of indole and dihydroindole alkaloids, a general cleavage approach was used to provide the desired nine-membered ring intermediates. A brief summary of this "ring cleavage approach" includes:

1) The reinvestigation and improvement of the quebrachamine total synthesis, completed by other workers in our laboratories.[53]

2) The development of a general reaction for introducing the appropriate functionality at C-3 of the quebrachamine system. The success of this reaction would lead to the first total synthesis of several naturally occurring Vinca alkaloids (vincadine, vincaminoreine, vincaminorine, vincadifformine and minovine).

3) The extension of the above sequence to alkaloids bearing an oxygen function (particularly $-OCH_3$) in the aromatic ring. In this manner, vincaminoridine a naturally occurring alkaloid would be available by total synthesis In addition other intermediates of particular value in the total synthesis of vindoline, one of the more complex Vinca alkaloids and the monomeric unit in the anti-tumor acting dimeric alkaloids, would be obtained.

1) Reinvestigation and improvement of the quebrachamine total synthesis

The total synthesis of dl-quebrachamine (9) via a novel approach was completed in our laboratories[3] and the successful sequence is depicted in

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Figure 24. Although the preparation of the diethyl ester (90) was fairly straightforward, as will be seen later, and the subsequent two steps (90) ⟶ (91) ⟶ (92) resulted in quantitative yields, the conversion of (92) to (93) gave low yields (mixtures of cyclized benzylethers were obtained in 30% yield). Furthermore, the catalytic hydrogenolysis of the mixture (93) + (96) gave (94) + (97) in 50% yield, while the reductive cleavage of the quarternary mesylates, (95) ⟶ (9) afforded dl-quebrachamine in extremely low yield.

A reinvestigation of the problem reveals several questions which require clarification:

a) Why were the yields of the $Hg(OAc)_2$ reaction so low? Is there any way to improve the yield?

b) Why were only three alcohols isolated from the hydrogenolysis reaction? In theory four dl-pairs are possible, two of these representing cyclization in the desired manner (93), while two pairs in the alternative direction (96)[40].

c) Which of the alcohols obtained in (b) represent the correctly cyclized structures and which represent the isomeric series?

d) How can the yield of the final reaction, e.g. (95) ⟶(9) be improved?

The following discussion considers each of these points in order and presents some of the results which we obtained in these areas.

Mercuric acetate is a well known oxidizing agent[54]. The low yields are mainly due to the variety of ways by which the formed iminium salts can react with a nucleophile system. Some of these processes can be visualized as in Figure 25, in addition to the main reaction products (93) and (96).

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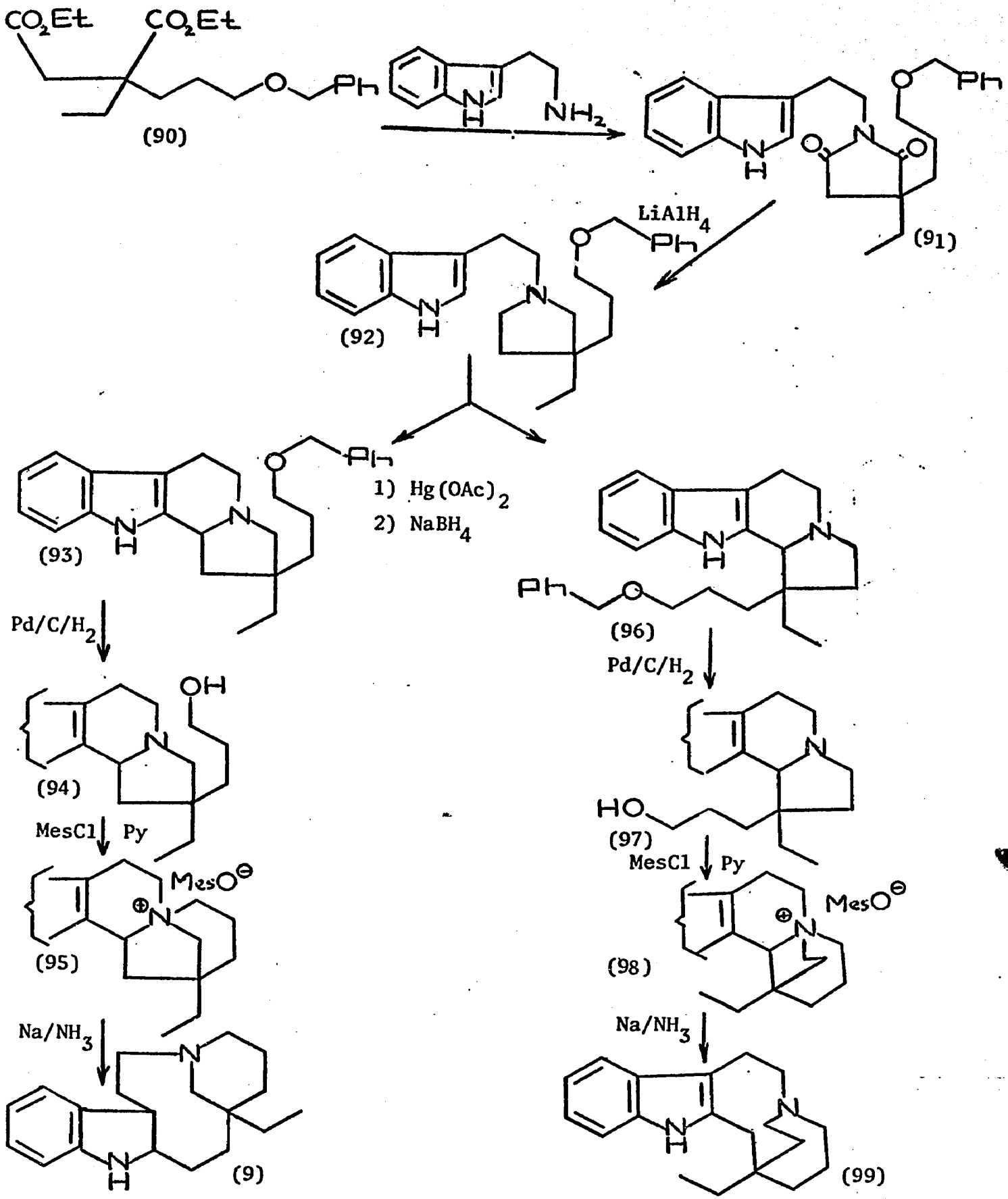

Figure 24. Total synthesis of dl-quebrachamine (9) in our laboratories.

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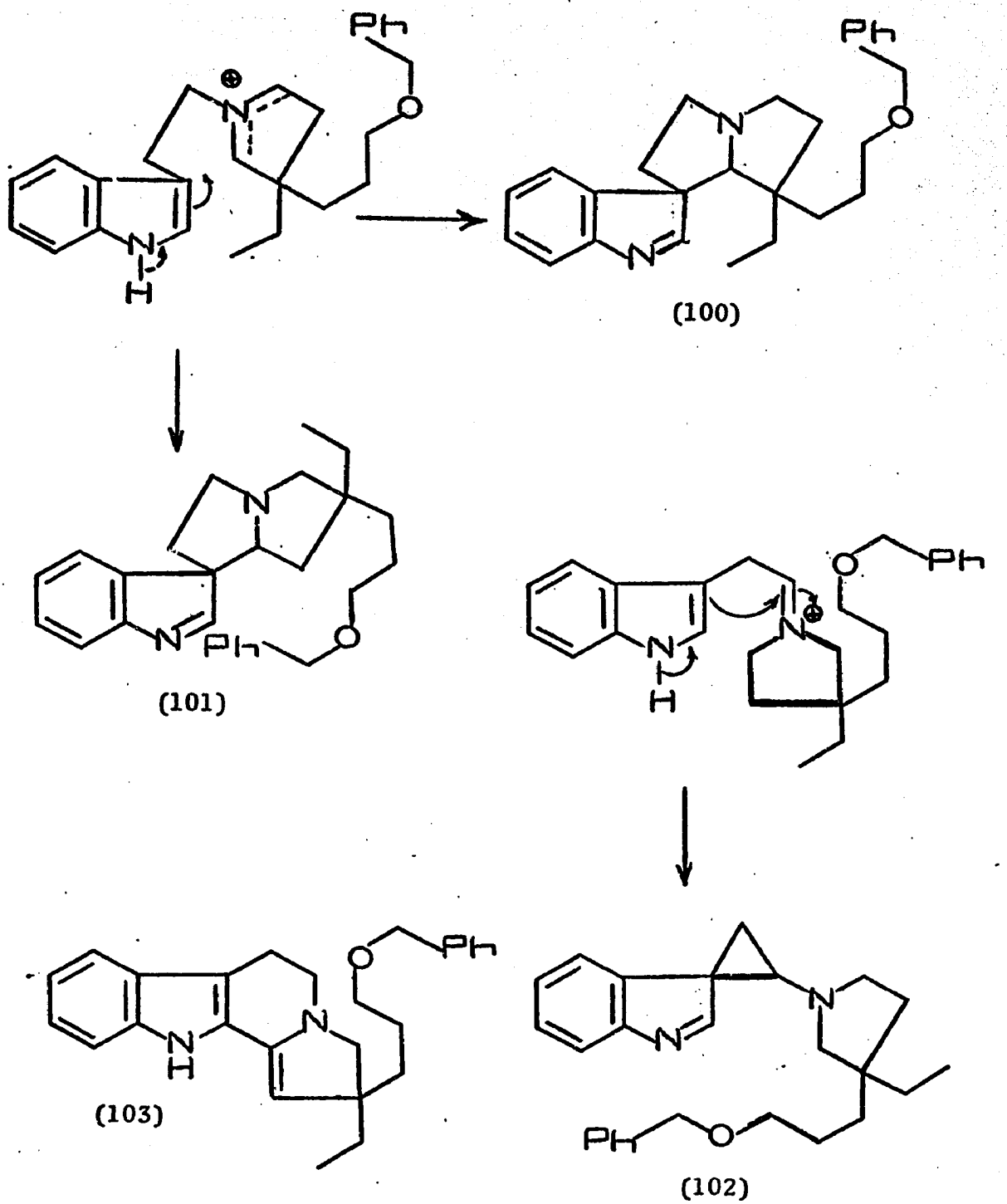

Figure 25. Side products of mercuric acetate reaction.

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It is known that the β-position of the indole ring has a higher electron density than the α-position, and spiro-indoles like (100) and (101) are not unlikely.[45] Finally, compounds as (102) might exist in small amounts, polymerization is possible and by-products similar to (103) have been isolated in this reaction under basic conditions.[55] All of the above possible reaction products have two asymmetric centers (except 103) and therefore stereoisomers may complicate the separation, although clearly the formation of some of these compounds is minimized through strain and steric factors.

To investigate this reaction, more starting material (92) was prepared according to known procedures. The reaction sequence is illustrated in Figure 26. All yields obtained were higher than anticipated in the literature,[3,56,57,58] because of improvement of reaction conditions and work up of the reaction mixtures.

The mercuric acetate reaction was repeated under a continuous atmosphere of highly purified nitrogen, utilizing higher dilution to avoid polymerization and working up the reaction mixture in as complete an exclusion of oxygen as possible. Finally decomposition of the complex with hydrogen sulfide and reduction with sodium borohydride gave the desired product. After purification by column chromatography on alumina a 38% yield of a mixture of (93) and (96) was obtained. This result was not an impressive improvement of the previously reported reaction yield (cf. 30%)[3]. Therefore we considered other ways to obtain (93) in higher yield.

The Bischler-Napieralski synthesis[59] has been used for cyclodehydration of amides of the type (91). Using several condensation reagents, Wenkert et al.[60a] was unable to cyclize (104) to (105). Morrison[60b] using phosphorus

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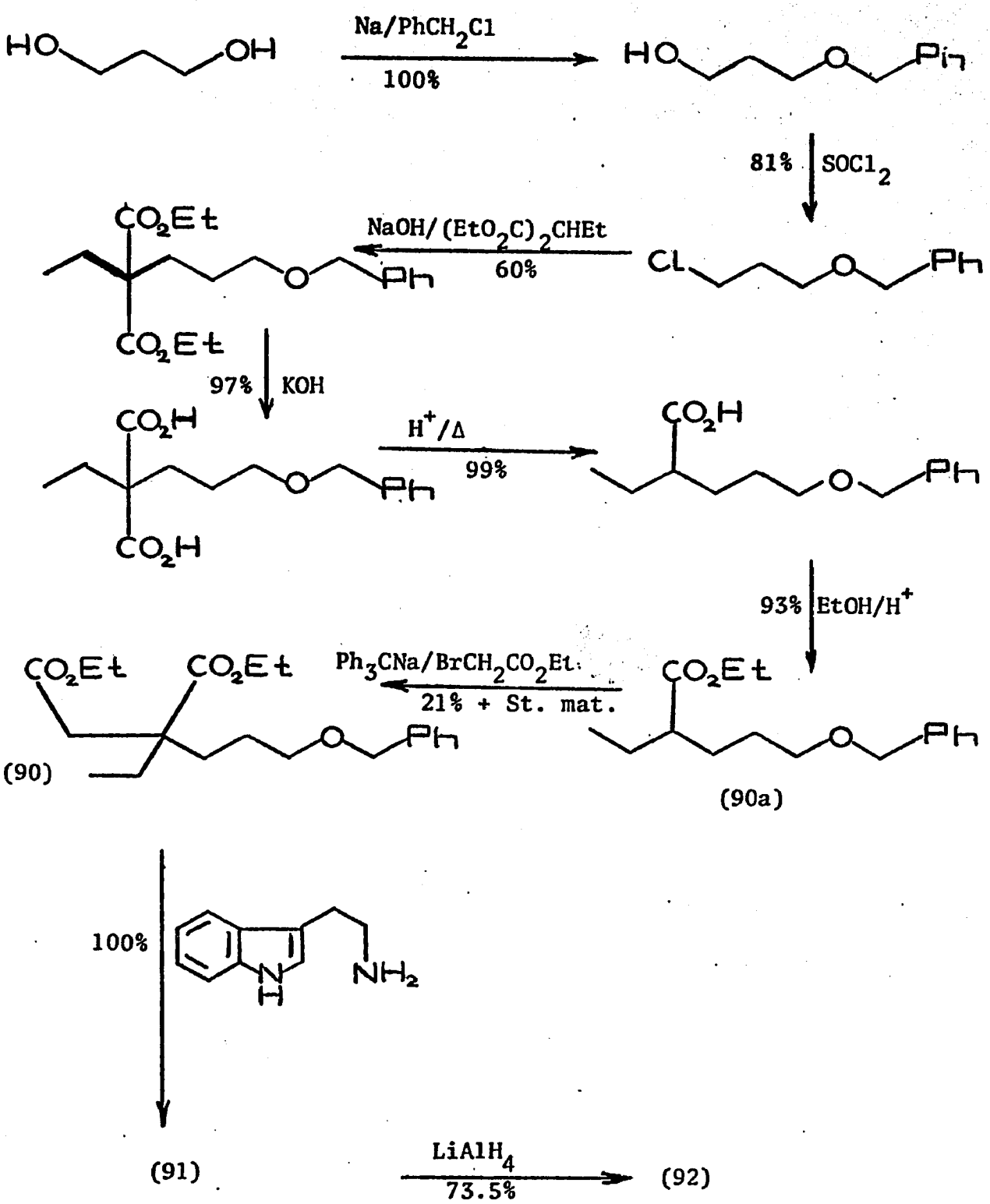

Figure 26. Preparation of the uncyclized benzyl ether.

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pentoxide was able to obtain the unsaturated lactam (107) from (106) in not very impressive yield (31%). However, an application of Morrison's conditions to imide (91) resulted in the loss of the benzyl group and subsequent dehydration to give the lactam (108) in very low yield (5%),[58] see Figure 27.

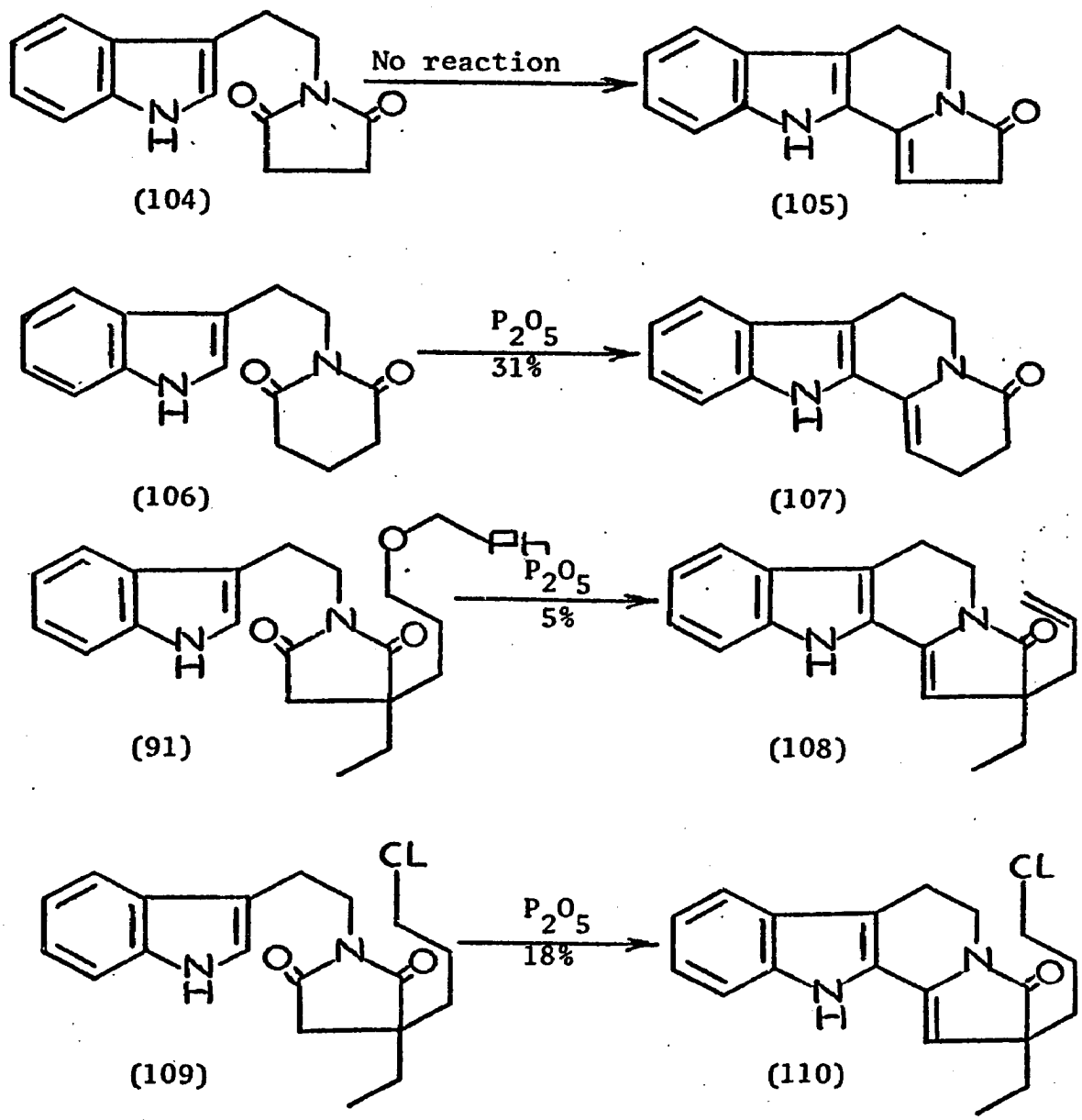

Figure 27. Application of Bischler-Napieralski reaction.

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By changing the reaction conditions and applying the condensation to chloro succinimide (109), compound (110) was obtained but again in low yield (18%).[58] Having all this previous experience in mind, we considered it a waste of time to try to develop or improve reaction conditions for the Bischler-Napieralski reaction.

The Pictet-Spengler reaction[61] has proved to be of considerable value in alkaloid syntheses. For instance Kuehne,[62] during the total synthesis of vincamine (113) condensed the aldehydo-diester (111) with tryptamine to get a mixture of epimeric lactam-acids (112) in 37% yield, Figure 28.

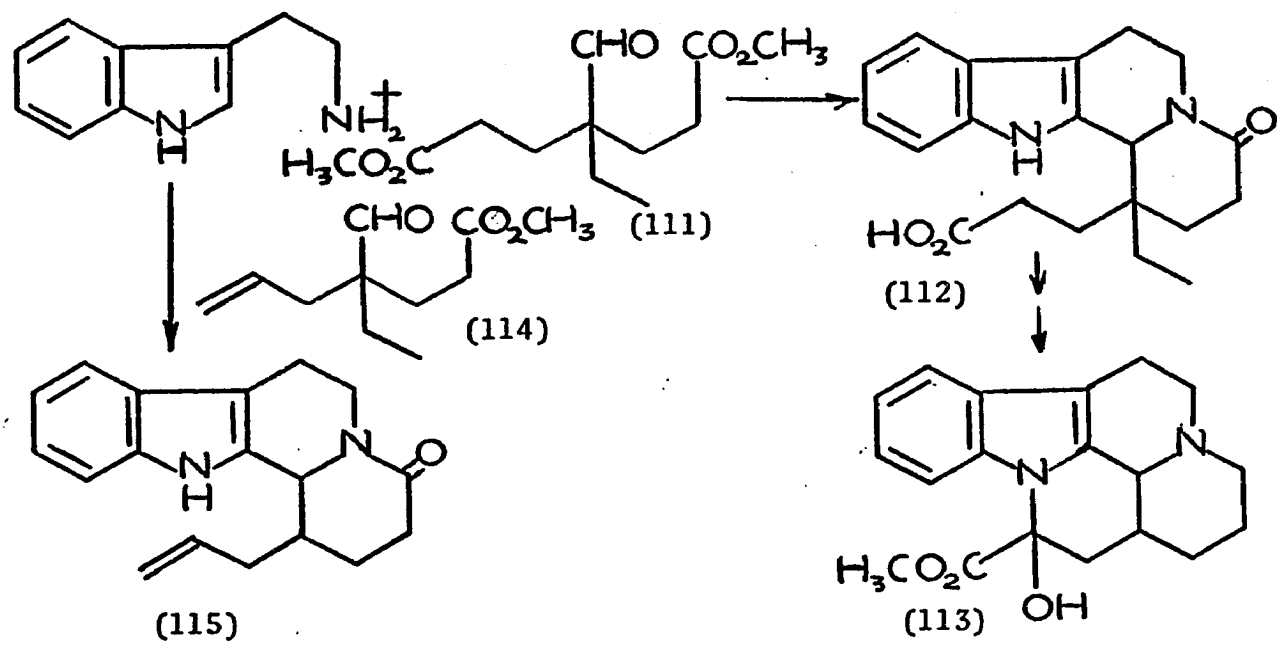

Figure 28. Kuehne's and Harley-Mason's selective cyclization to tetracyclic lactams.

Harley-Mason[63] also, using methyl 4-ethyl-4-formylhept-6-enoate (114) was able to prepare the tetracyclic δ-lactam (115) in 75% yield.

A convenient aldehydoester in our case would be (118) which was prepared from ethyl 2-ethyl-5-benzyloxypentanoate (90a) which was already available

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in large quantities from our previous experiments, see Figure 26. The sequence followed is shown in Figure 29.

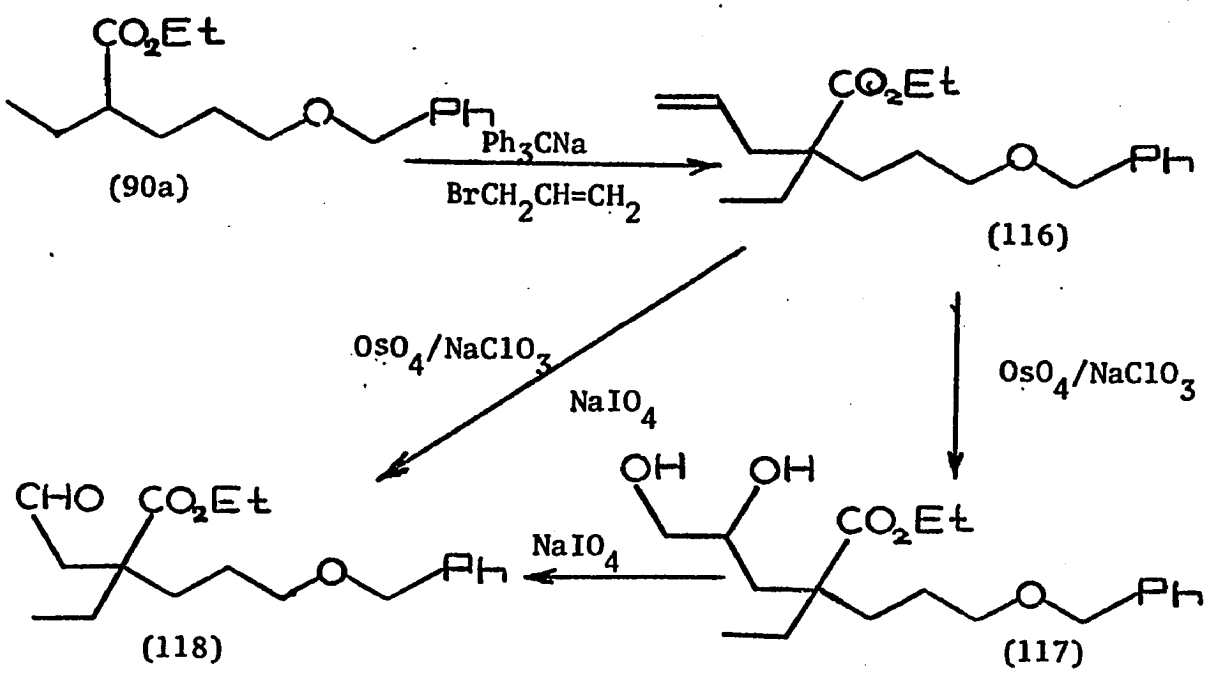

Figure 29. Preparation of aldehydoester (118)

When (90a) was treated with sodium triphenyl methyl as a strong base and allyl bromide we obtained a yellow oil. This oil was easily purified by column chromatography on silica gel (benzene elution) or by fractional distillation under reduced pressure to give a colourless viscous oil in 98% yield. The infrared spectrum of this oil indicated the presence of a saturated carbonyl absorption at 1725 cm^{-1}. The ultraviolet spectrum was typical of a mono-substituted benzene derivative with maxima at 257 and 222 mμ. The NMR spectrum was very informative, see Figure 30. A singlet corresponding to five aromatic protons at τ 2.72 was easily assigned to the benzyl group while a multiplet for two terminal allyl protons at τ 5.0 and one vinyl proton multiplet at τ 4.4 was very characteristic for the allyl group.[64] A doublet at τ 7.68 (J = 7 cps) was assigned to the two hydrogens

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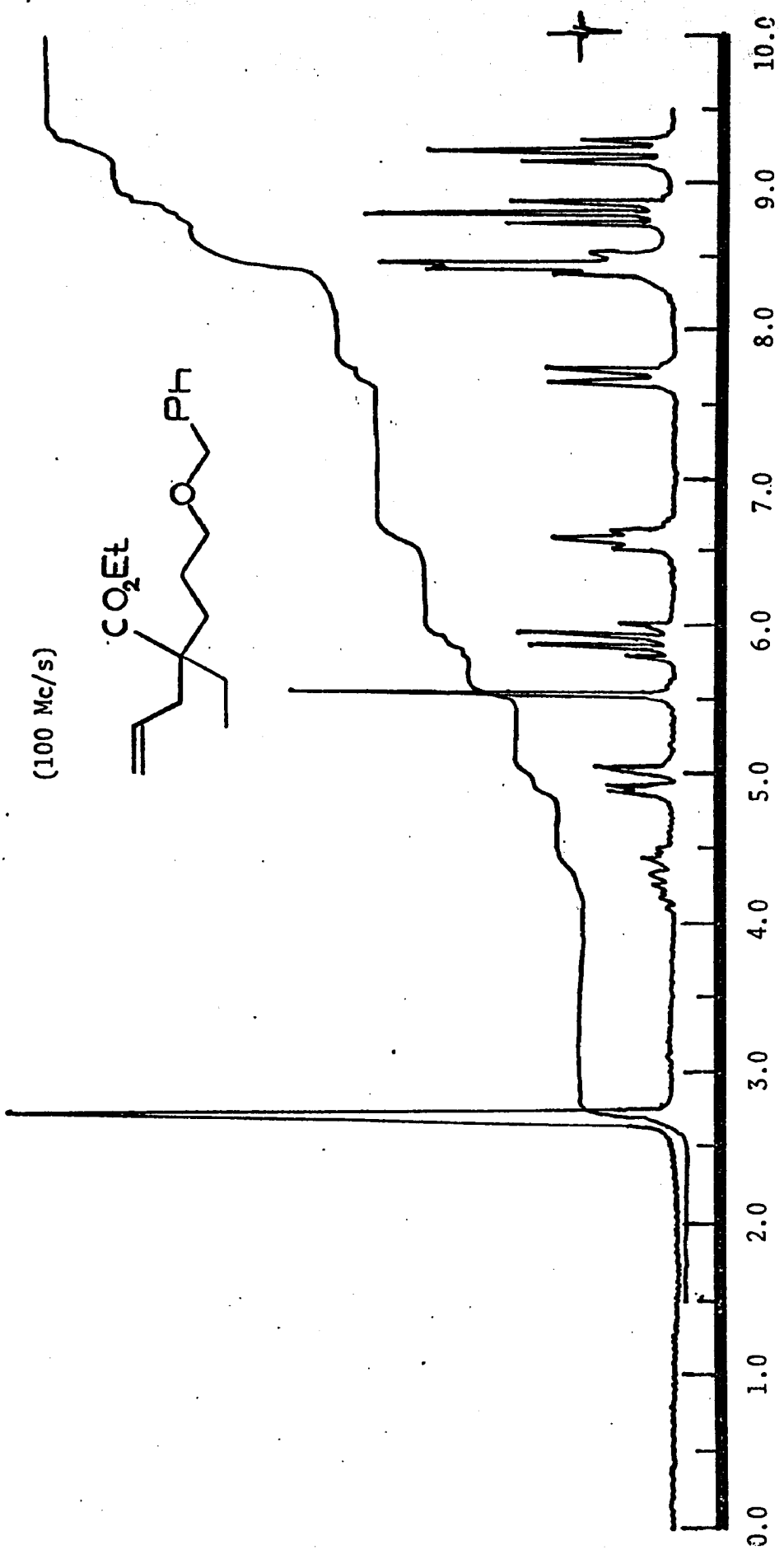

Figure 30. NMR spectrum of allyloester (116).

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next to the terminal double bond. A two-proton singlet at τ 5.57 arises from the two benzylic protons and a triplet at τ 6.60 was due to the other two hydrogens next to the oxygen atom. A quartet (J = 7 cps) at τ 5.92 was assigned to the methylene protons of the ester ethyl group, while two triplets of three protons each at τ 8.80 and τ 9.20 confirmed the presence of the methyl groups of the ethyl ester and of the ethyl chain respectively. The broad multiplet of the α-tertiary proton ($C\underline{H}CO_2Et$) at τ 7.8 of the starting material was no longer present. Furthermore, elemental analysis and the high resolution mass spectrum confirmed the formula $C_{19}H_{28}O_3$. The mass spectrum, Figure 31, indicated a loss of an ethyl group, m/e 275, and an ethoxy group m/e 259. The basic peak at m/e 91 was due to tropylium ion as expected from the benzyl group and other important peaks were at m/e 139, 156, 167, and 197. A plausible fragmentation of this molecule upon electron impact and the tentative assignment to each fragment is shown in Figure 32.

The allyl compound was treated with osmium tetroxide at moderate temperature and the osmate ester intermediate decomposed with sodium chlorate to give a mixture of the cis-diols (117). This mixture was purified by conventional methods. The absence of the vinyl protons in the NMR spectrum and the appearance of a broad singlet at τ 6.88 (two protons) which disappeared upon addition of deuterated water was in accord with this assignment. Furthermore, a broad strong absorption at 3400 cm^{-1} in the IR-spectrum supported the diol structure. Further evidence for the diol structure came from elemental analysis and mass spectrum (Figure 31) which established the formula $C_{19}H_{30}O_5$ for this compound. The yield in this reaction was 68%. The diol mixture on purification was obtained as a viscous clear oil which distilled at 240°/0.5 mm. When it was heated for longer periods it seemed

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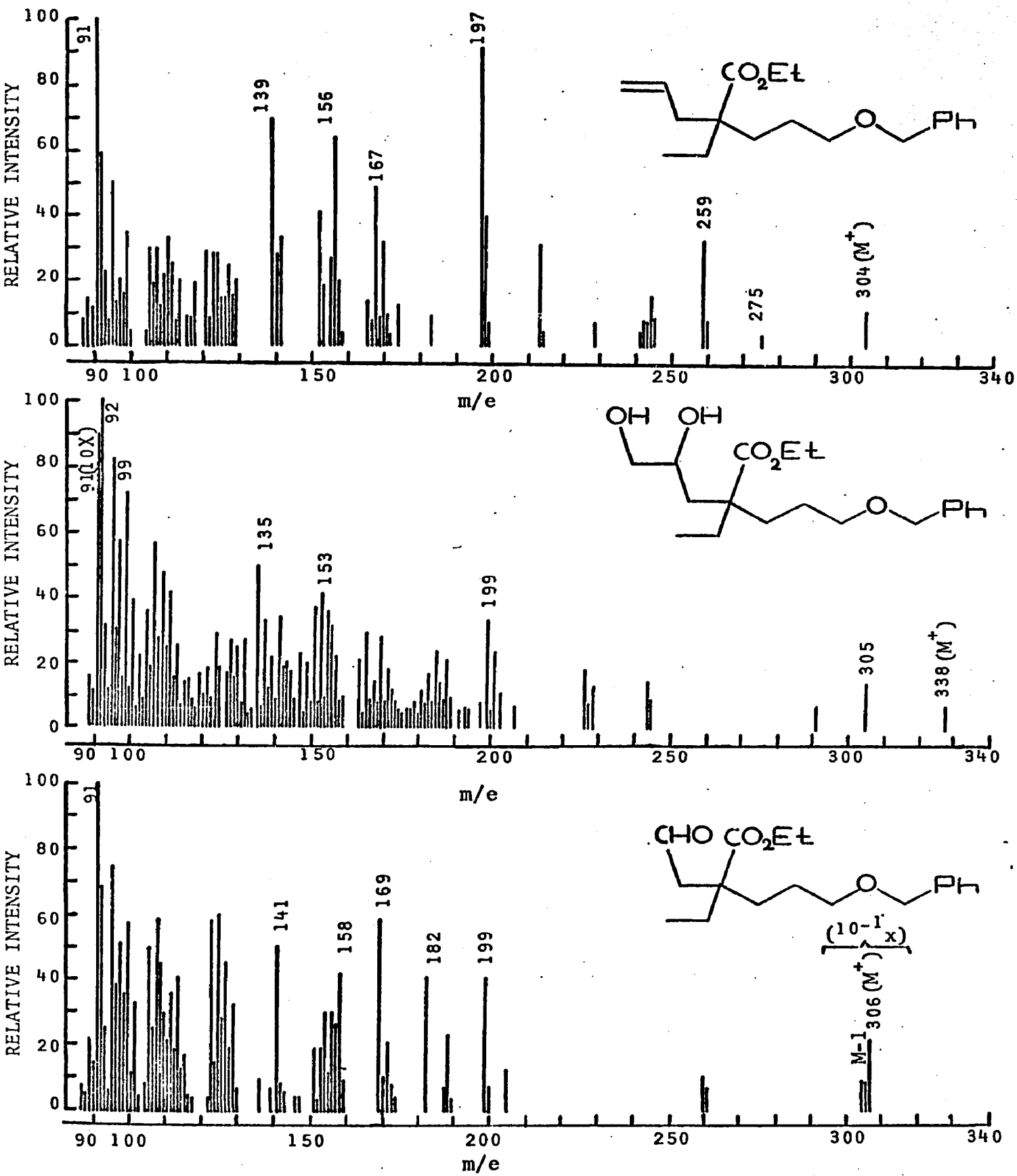

Figure 31. Mass spectra of the allylo; diolo- and aldehydo-esters.

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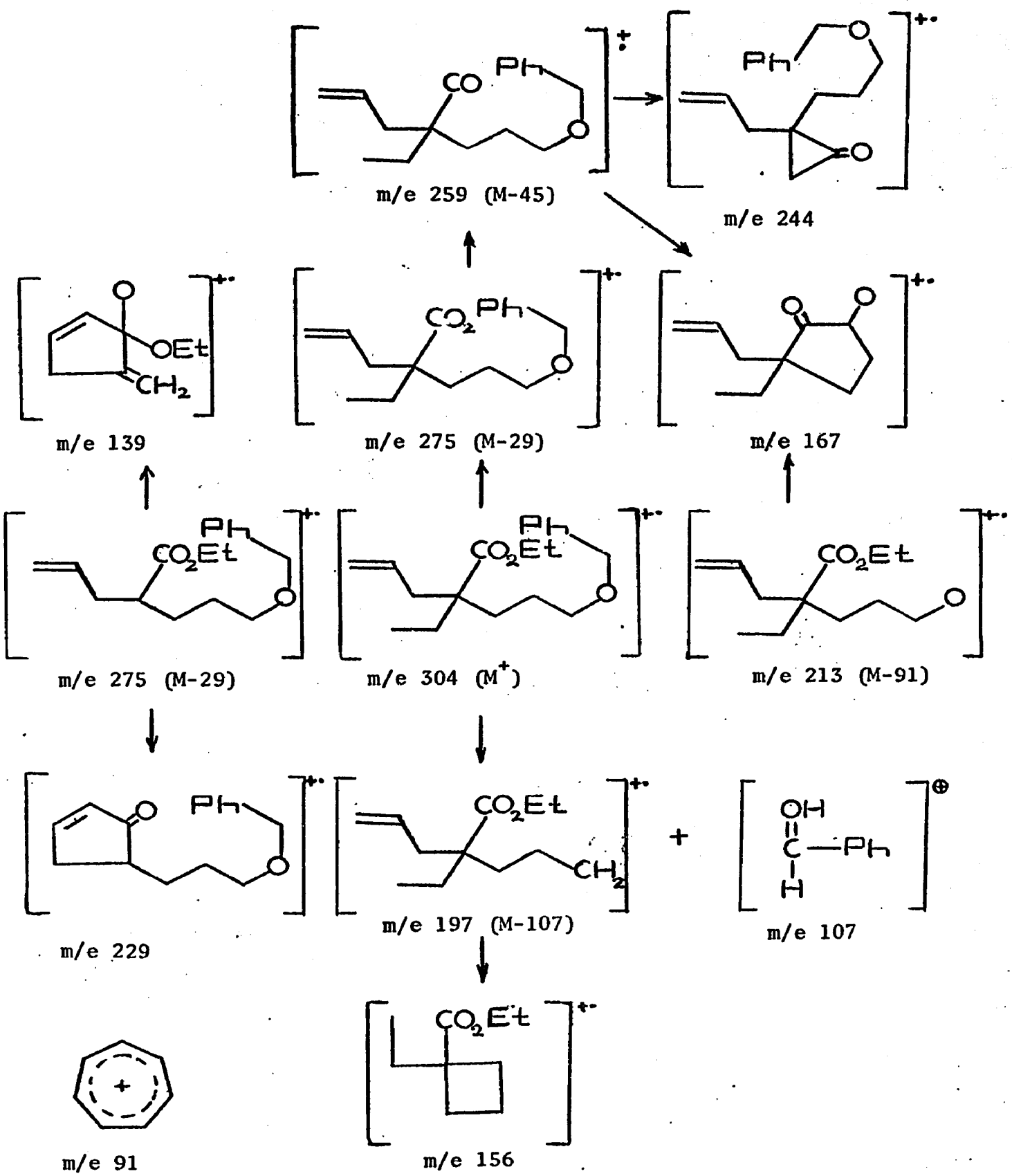

Figure 32. Electron impact on allyl compound (116).

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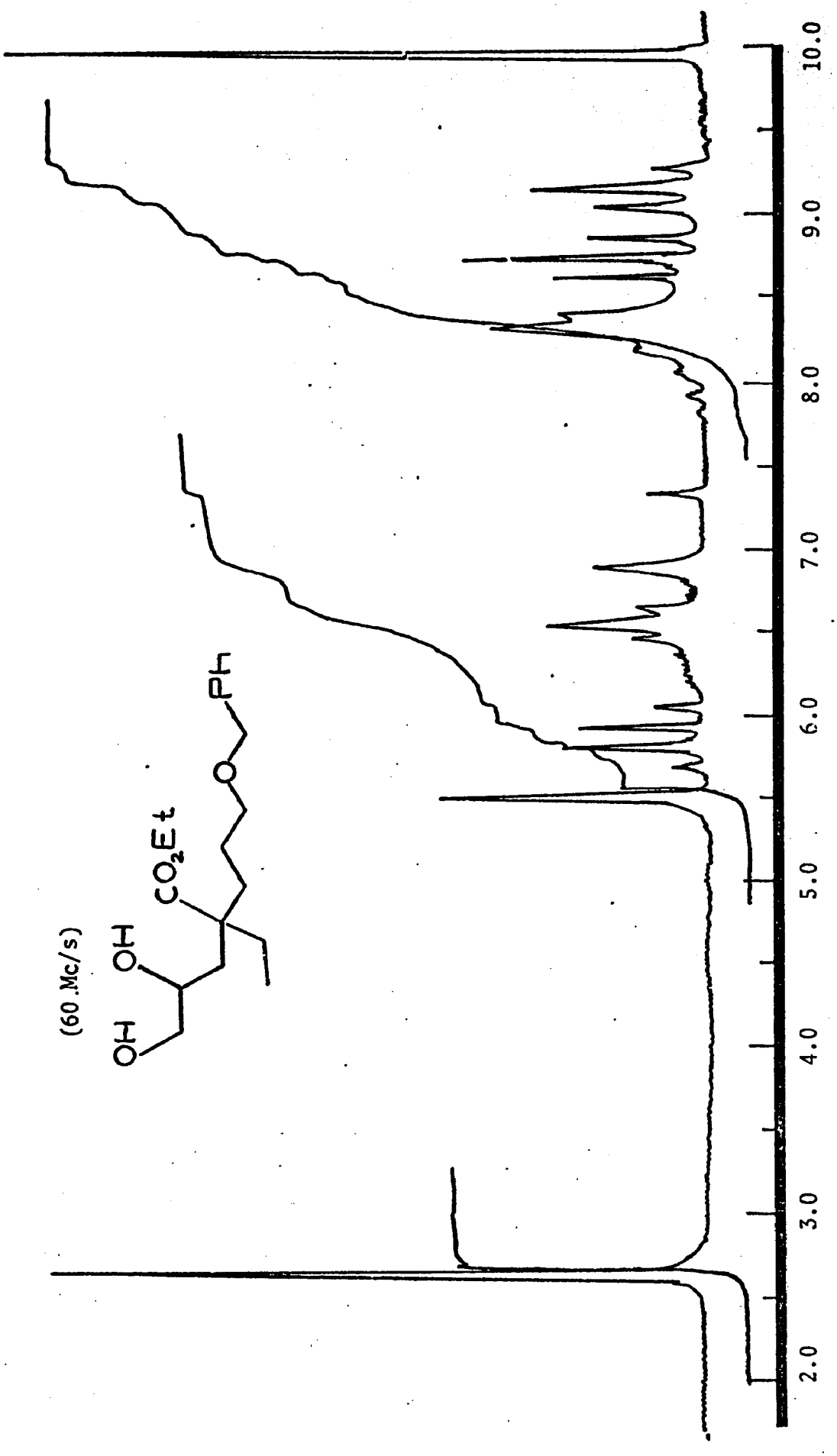

Figure 33. NMR spectrum of dioloester (117).

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partial lactonization took place to form a γ-lactone as suggested from the following data. The IR spectrum showed an additional strong peak at 1764 cm^{-1} besides the ester absorption at 1725 cm^{-1}, and this result accomodates best a five-membered ring lactone.[65] The NMR spectrum showed a shift of the broad singlet due to the alcoholic hydrogens from τ 6.88 to τ 7.70 and the relative area underneath the peak was about 1.5 protons indicating that approximately 25% of the lactone was present. This information was coupled with the results of the elemental analysis as well as of the appearance of a new less polar spot in the TLC. No attempts were made to separate the two epimeric cis-diols which were produced by the introduction of a new asymmetric center, since during the next step this asymmetric center was destroyed. The NMR spectrum of the two epimeric diols is shown in Figure 33. Some postulates for the significant fragments of the diols in the mass spectrum are shown in Figure 34.

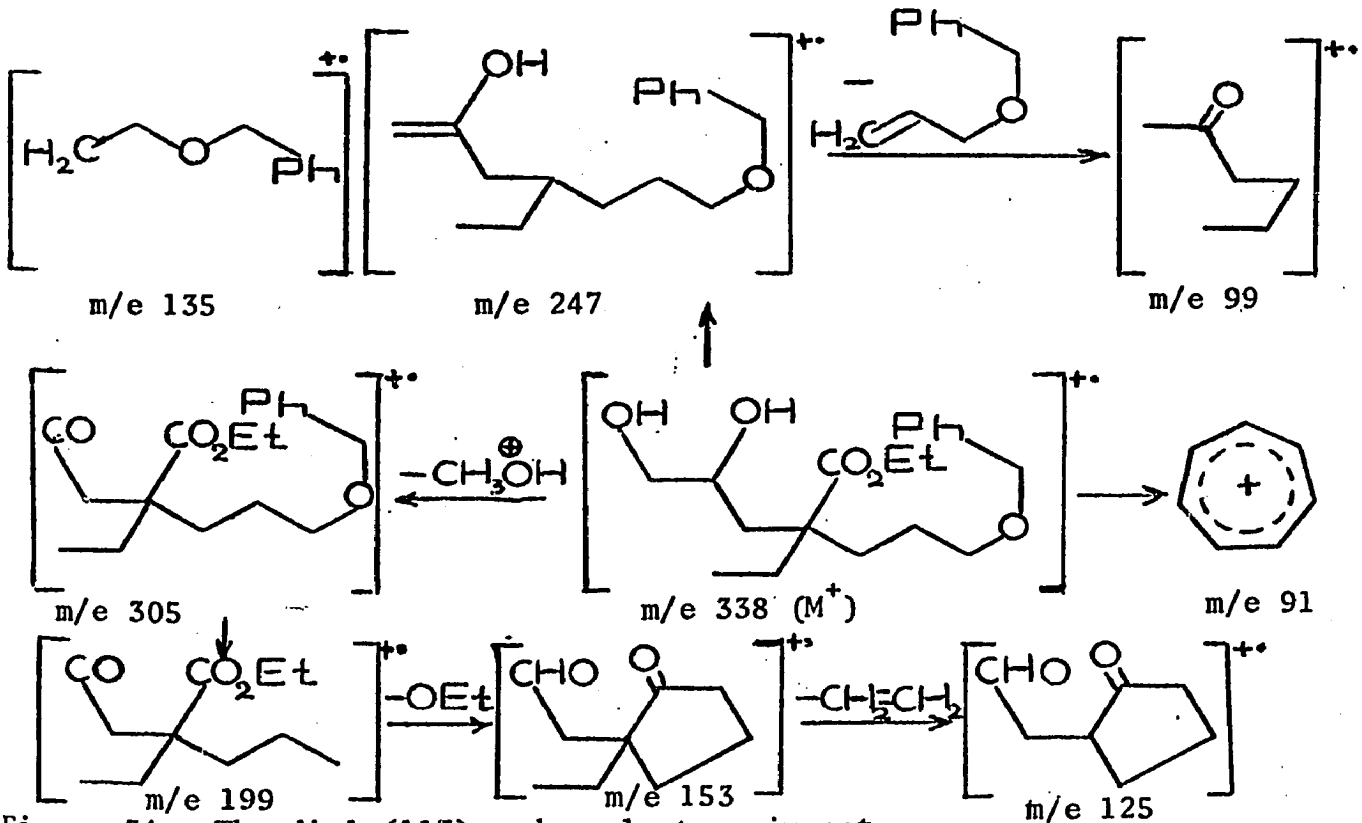

Figure 34. The diol (117) under electron impact.

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This mixture of cis-diols thus prepared was cleaved by sodium meta-periodate in aqueous tetrahydrofuran at room temperature to give the aldehyde (118) in 67% yield as a colourless oil after purification by column chromatography on silica gel (Woelm) or vacuum distillation. The infrared spectrum of this compound showed no absorption at 3400 cm^{-1} but an absorption at 2725 cm^{-1} characteristic for the C-H stretching frequency for aldehydes[65] in addition to the strong carbonyl band at 1725 cm^{-1}. In the NMR spectrum (Figure 35) a triplet (J = 2 cps) at τ 0.22 due to the aldehydic proton and a doublet at τ 7.36 for the two protons adjacent to the aldehydo group (J = 2 cps) were very characteristic. It was interesting also to note the shift of the other peaks in comparison with the NMR spectrum of the allyl compound (116). A downfield shift was apparent for the doublet at τ 7.36 being located at τ 7.68 (J = 7 cps) in the allyl compound. Finally, elemental analysis and high resolution mass spectrometry confirmed the formula $C_{18}H_{26}O_4$ for the aldehyde (118). The mass spectrum is reproduced in Figure 31 and some of the most important fragments are depicted in Figure 36. The weak molecular peak at m/e 306 and the favored β-bond cleavage are not uncommon for aldehydes.[66]

The one step preparation of aldehydes from the corresponding allyl compounds is a well known reaction. Since no complications or low yields were encountered during the previous reactions, it was worthwhile to try the preparation of aldehyde (118) from the allyl compound (116) in this manner. The osmium tetroxide, sodium chlorate and sodium meta-periodate were added successively to the reaction mixture at moderate temperatures or even at room temperature. The workup was as before and thus a yield of 70% of pure aldehyde was obtained from the allyl compound together with a mixture (11%) of diols. Since the overall yield by the stepwise method was 46%, this

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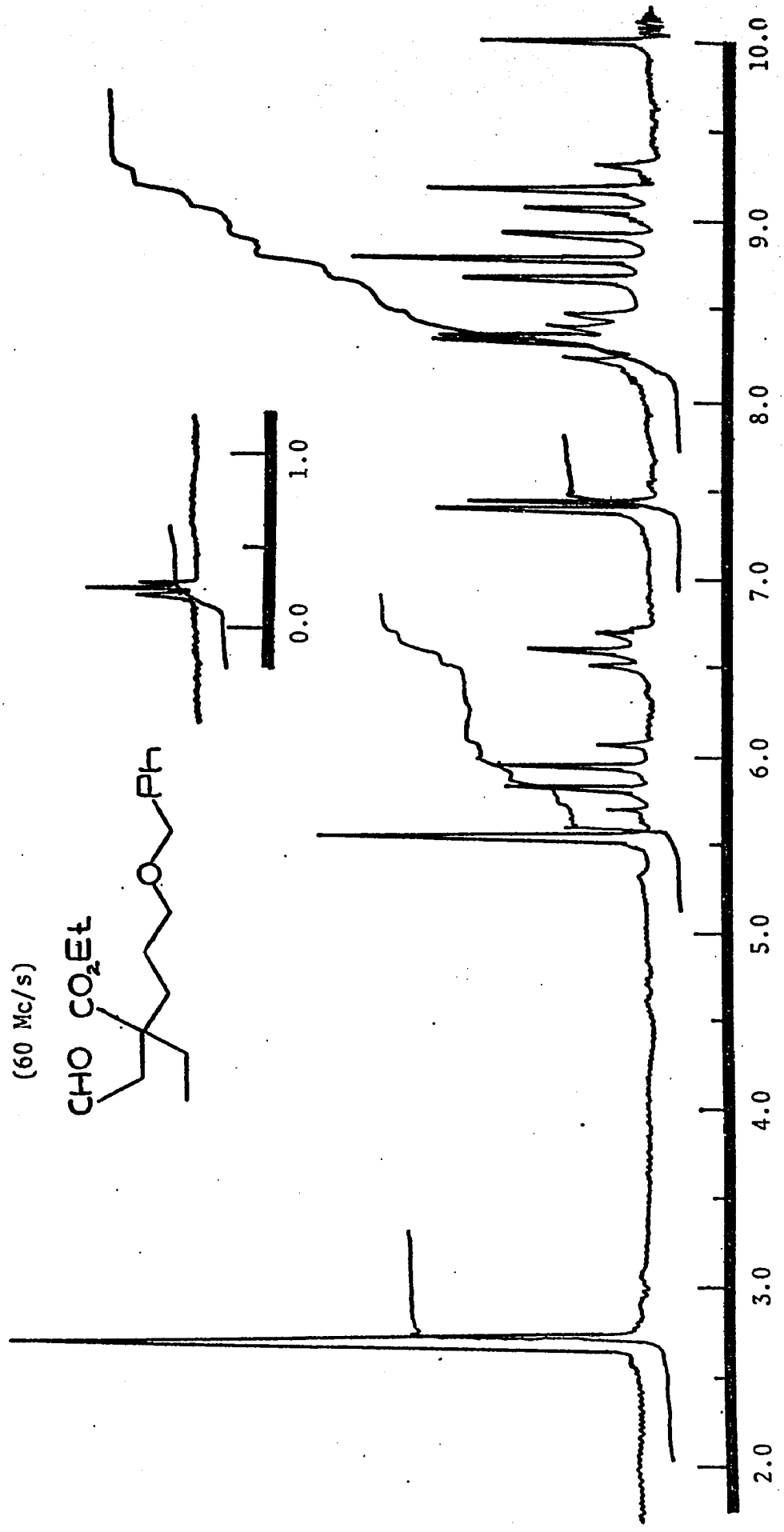

Figure 35. NMR spectrum of the aldehydoester (118).

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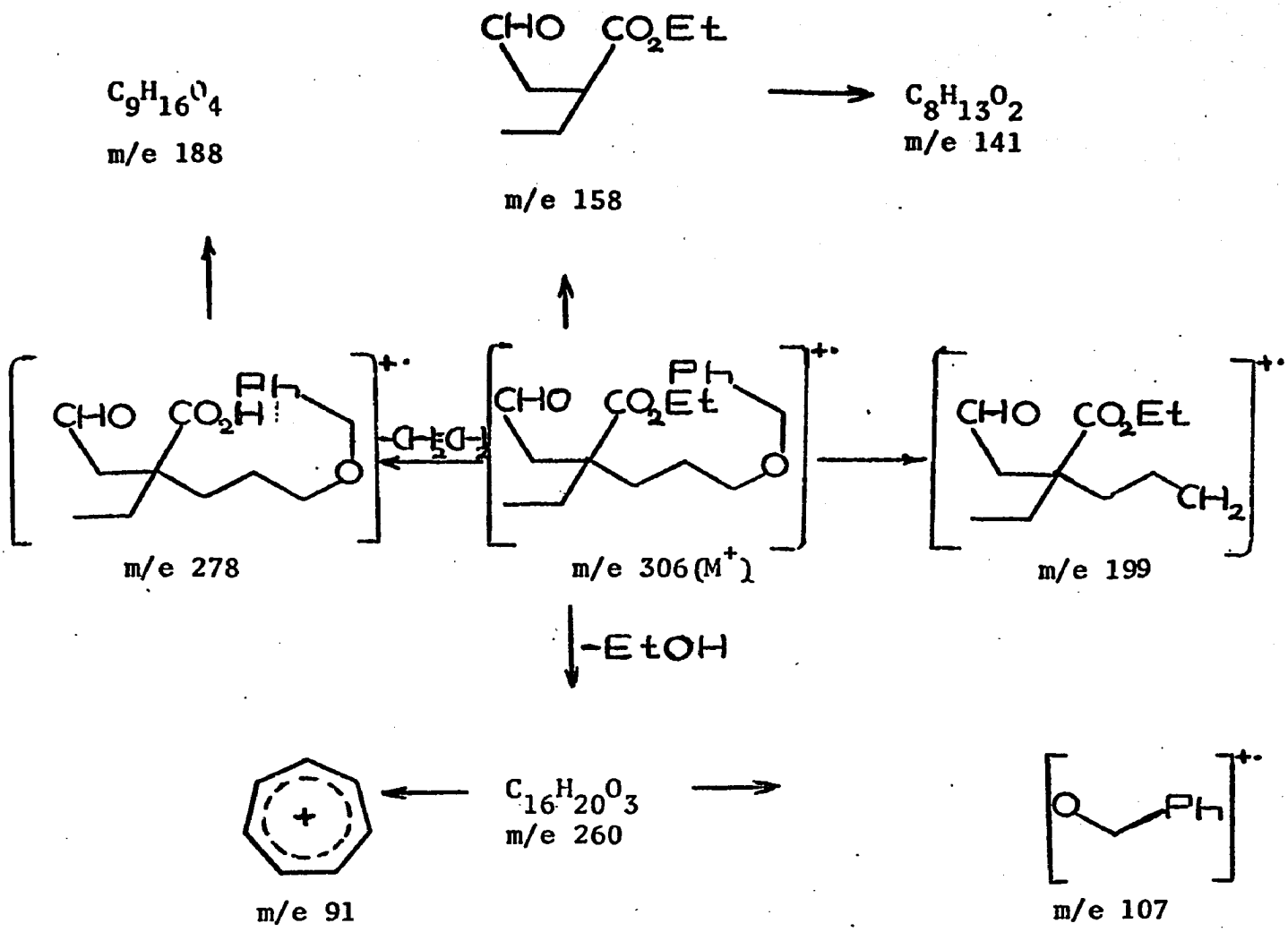

Figure 36. Fragmentation of aldehyde (118) upon electron impact.

procedure was obviously superior for obtaining the desired aldehyde (118). It is perhaps worthwhile to mention that during one of the purifications of this aldehyde by chromatography on alumina followed by some exposure to air and solvents a mixture was obtained. A five-membered cyclic lactam or simply partial oxidation took place as was suggested by TLC and infrared spectra. A new very strong carbonyl absorption at 1770 cm^{-1} besides the one at 1725 cm^{-1} as well as weak broad bands at 3400 cm^{-1} and 2940 cm^{-1} were apparent in the infrared spectrum.

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Having obtained the desired aldehyde (118), the next step was the condensation of it with tryptamine in an analogous manner as depicted in Figure 28. The reaction sequence followed is shown below (Figure 37).

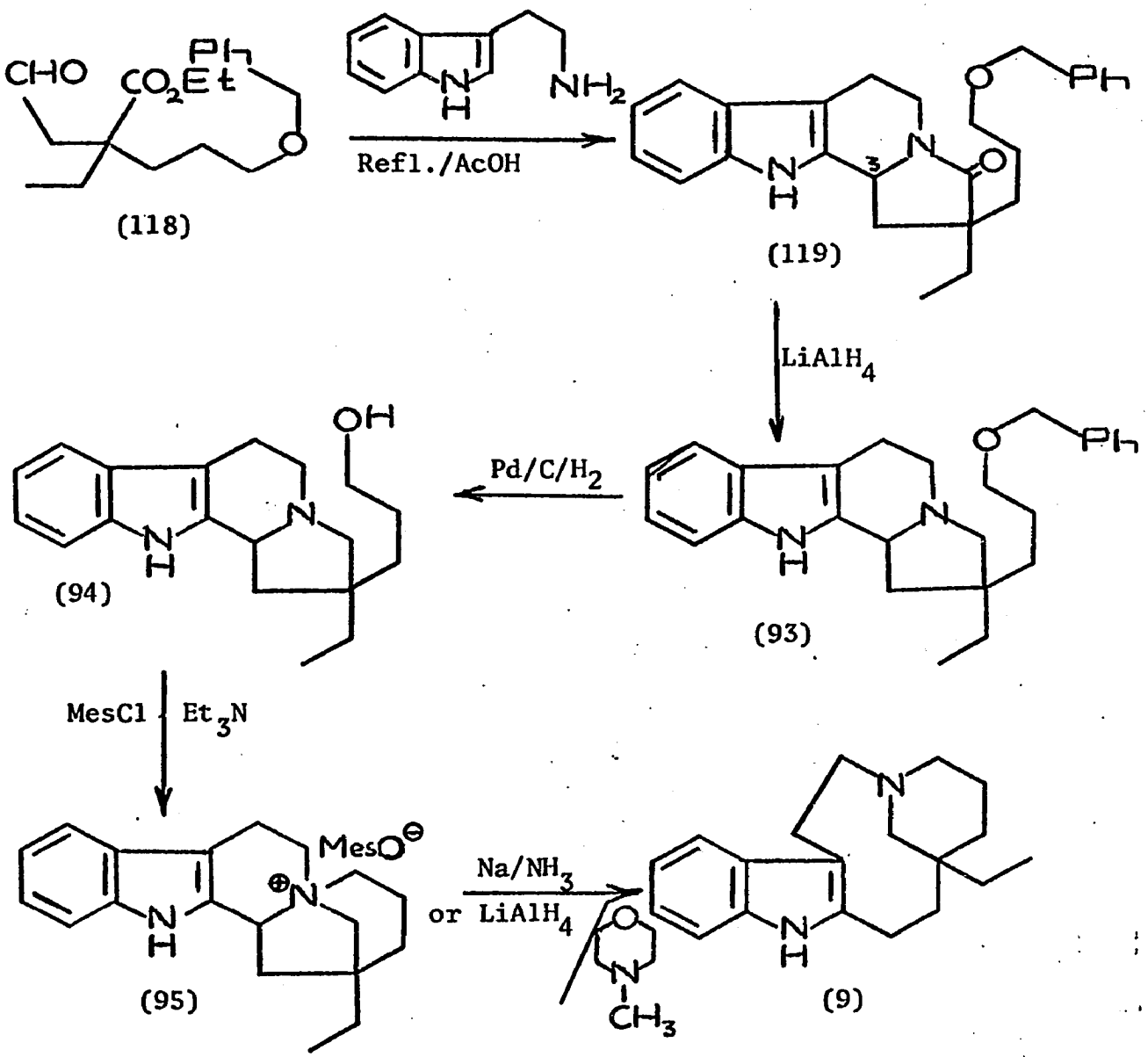

Figure 37. New improved reaction sequence for the total synthesis of quebrachamine (9).

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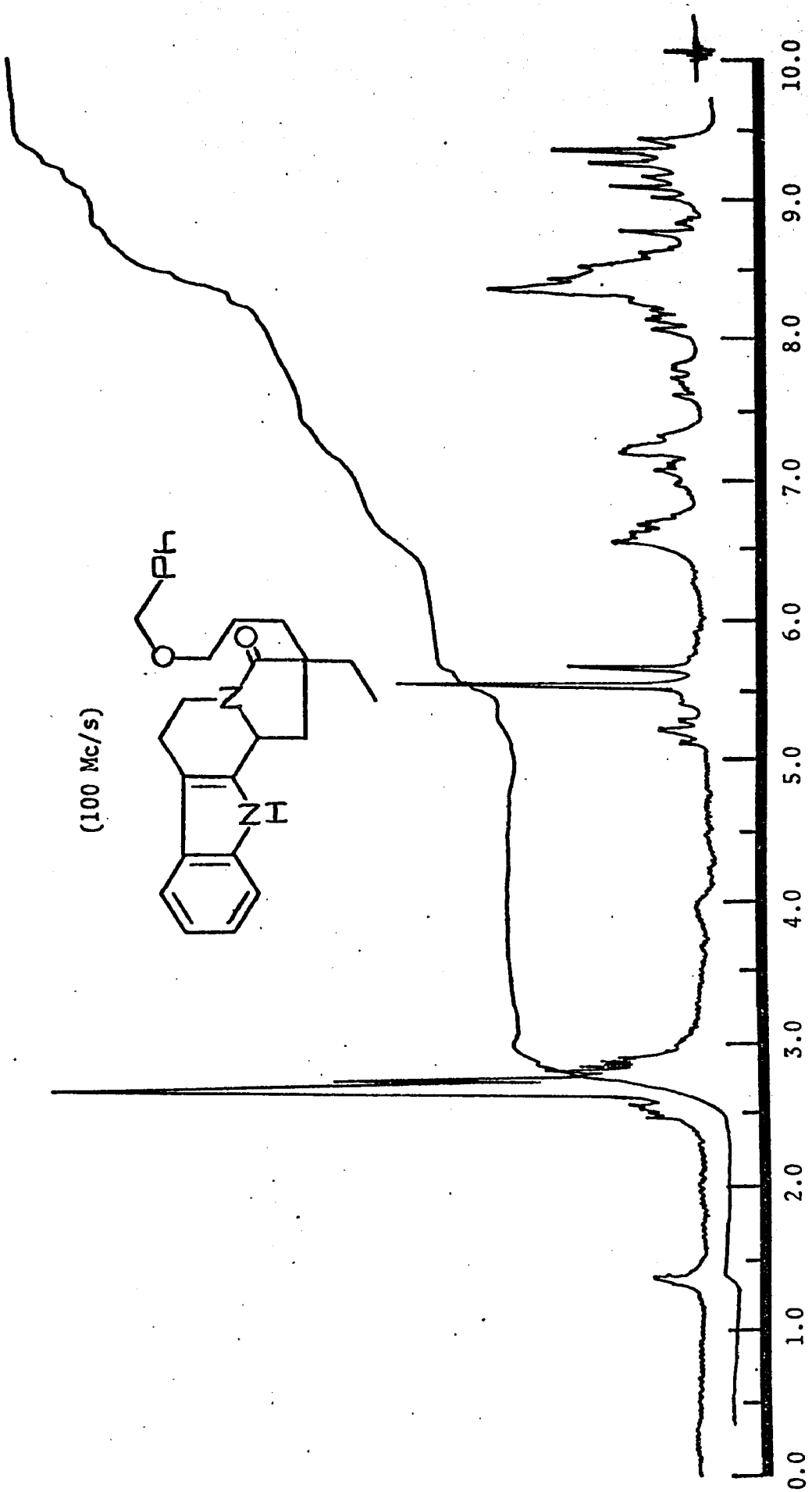

Figure 38. NMR spectrum of cyclized lactam (119).

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When the aldehyde (118) was refluxed with tryptamine in glacial acetic acid for one hour followed by conventional work up of the reaction mixture, a dark gum was obtained. This material was purified by column chromatography on alumina Woelm neutral (activity III, benzene elution) to give a yellowish glass in 90% yield. This compound could also be purified by distillation at 240°/0.1 mm. The structure (119) was assigned to this cyclic lactam on the basis of the evidence presented. It was actually obtained as a mixture of two inseparable diastereoisomers. The presence of the lactam was evident from the strong carbonyl absorption at 1675 cm^{-1} in the infrared spectrum. The NMR spectrum was most informative: signals for the α-proton on the indole ring were not present and at the same time two almost overlapping triplets at τ 5.21 and 5.24 (both J = 8 cps) indicated the presence of a C-3 proton on the lactam ring. The diastereoisomeric nature of this mixture was obvious throughout the whole NMR spectrum (Figure 38), but for our purposes it was not necessary to try to separate the two dl- pairs at this stage. The molecular formula $C_{26}H_{30}O_2N_2$, was established by high resolution mass spectrometry, which provided the value, 402.231 (calc. 402.230). Some of the more important fragments of this molecule are rationalized in Figure 39, while the mass spectrum is reproduced in Figure 40. The base peak at m/e 311 must result during the tropylium ion (m/e 91) formation and other expected peaks for this molecule were also present. Some very common fragments in indole alkaloids, such as the ones at m/e 129, 143 and 168, were also apparent.

The next step involved the removal of the lactam carbonyl and the subsequent hydrogenolysis of the resulting amino ethers (93) to the corresponding amino alcohols (94). Lithium aluminum hydride seemed a very

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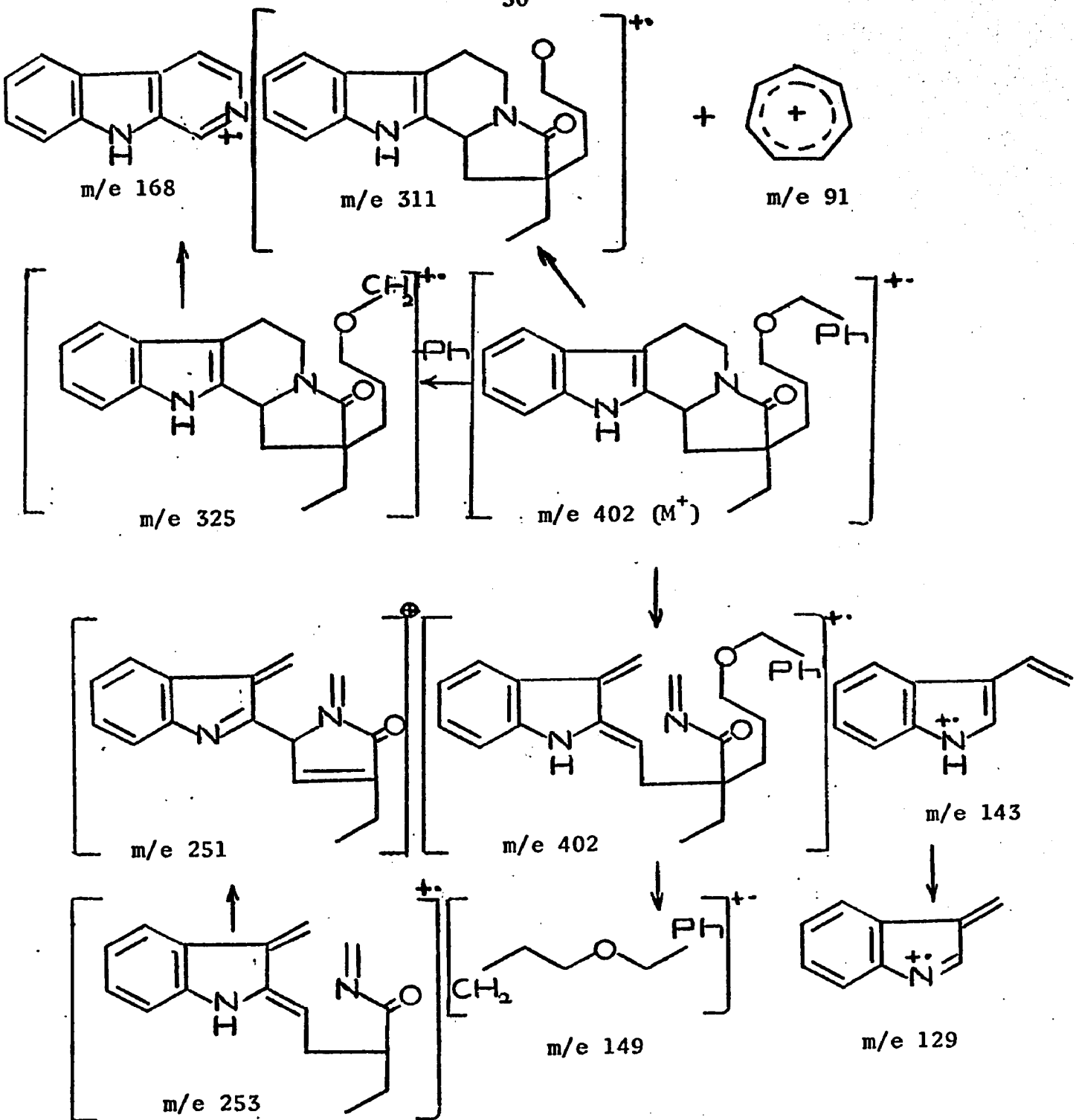

Figure 39. The main fragments of the lactam (119) upon electron impact.

promising reagent for this reaction. However when we attempted this reduction in refluxing tetrahydrofuran for 25 hours with a large excess of reagent (1:10 molar ratio), the reaction gave a product, which after chromatographic purification (alumina, neutral, activity II) and crystallization gave two compounds. The infrared spectra of both compounds were

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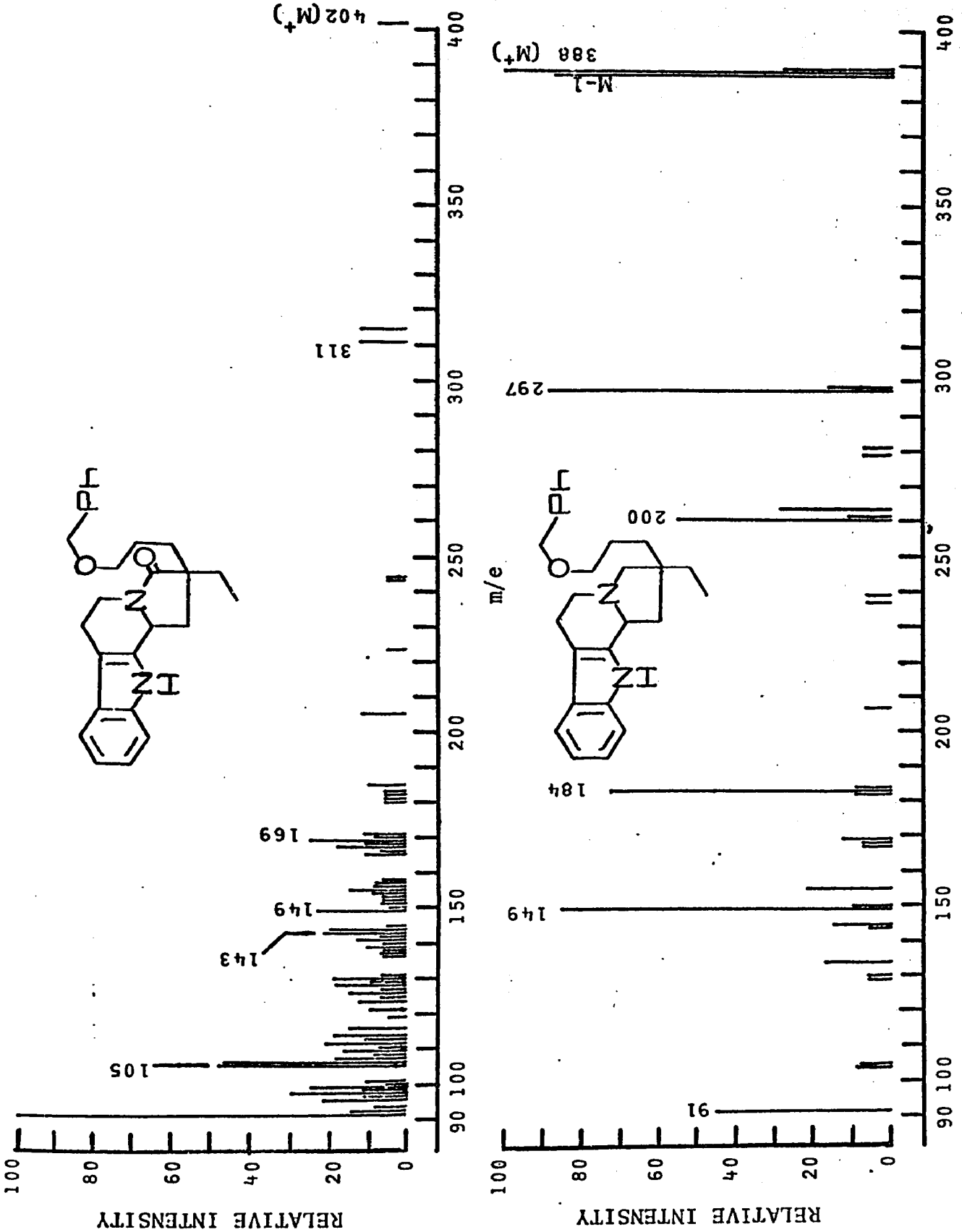

Figure 40. Mass spectra of the cyclized lactam (119) and amine (93).

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almost superimposable and strong hydroxyl absorption around 3330 cm^{-1} was apparent. The NMR spectra of these alcohols were quite similar with strong signals around τ 6.5 and in addition one of them had a strong singlet at τ 6.8. Their mass spectra were also very similar with main peaks at m/e 285 (M-15) and 210 (M-90) and a peak at m/e 300. This latter value corresponds to a structure with two protons more than anticipated for the desired alcohols (94). On this basis it was felt that the desired alcohols may have suffered further cleavage most likely involving the various bonds attached to the tertiary nitrogen atom. In view of this result we turned our attention to milder reaction conditions for this reaction. When a 1:3 molar ratio of reactants, a higher dilution and a shorter reflux period (8 1/2 hours) was employed the reaction product obtained as a yellow gum, could be easily purified by chromatography or distillation (240°/0.05 mm.). In this manner a 95% yield of desired material could be realized. This product was again a mixture of two dl- pairs and it was apparent that separation at this stage was going to be extremely difficult. The spectral data obtained was on this isomeric mixture. It was noted that the latter no longer showed a carbonyl absorption in the infrared spectrum. From the NMR spectrum (Figure 41) we noticed that this mixture of epimers was in a 1:1 molar ratio from the two singlets at τ 5.50 and 5.61 which were almost exactly 1:1 in area (benzylic hydrogens). Further support of the above statement came from the two overlapping triplets for the two methyl groups at τ 9.13 and 9.30 (J = 7 cps), which were also 1:1 in relative intensity. The expected shift to higher field of the two overlapping triplets at τ 5.2 (due to the C-3 proton) was observed as a new triplet at τ 5.88. Mass spectrometry and analysis confirmed the formula $C_{26}H_{32}ON_2$ for this mixture. The mass spectrum is shown in Figure 40.

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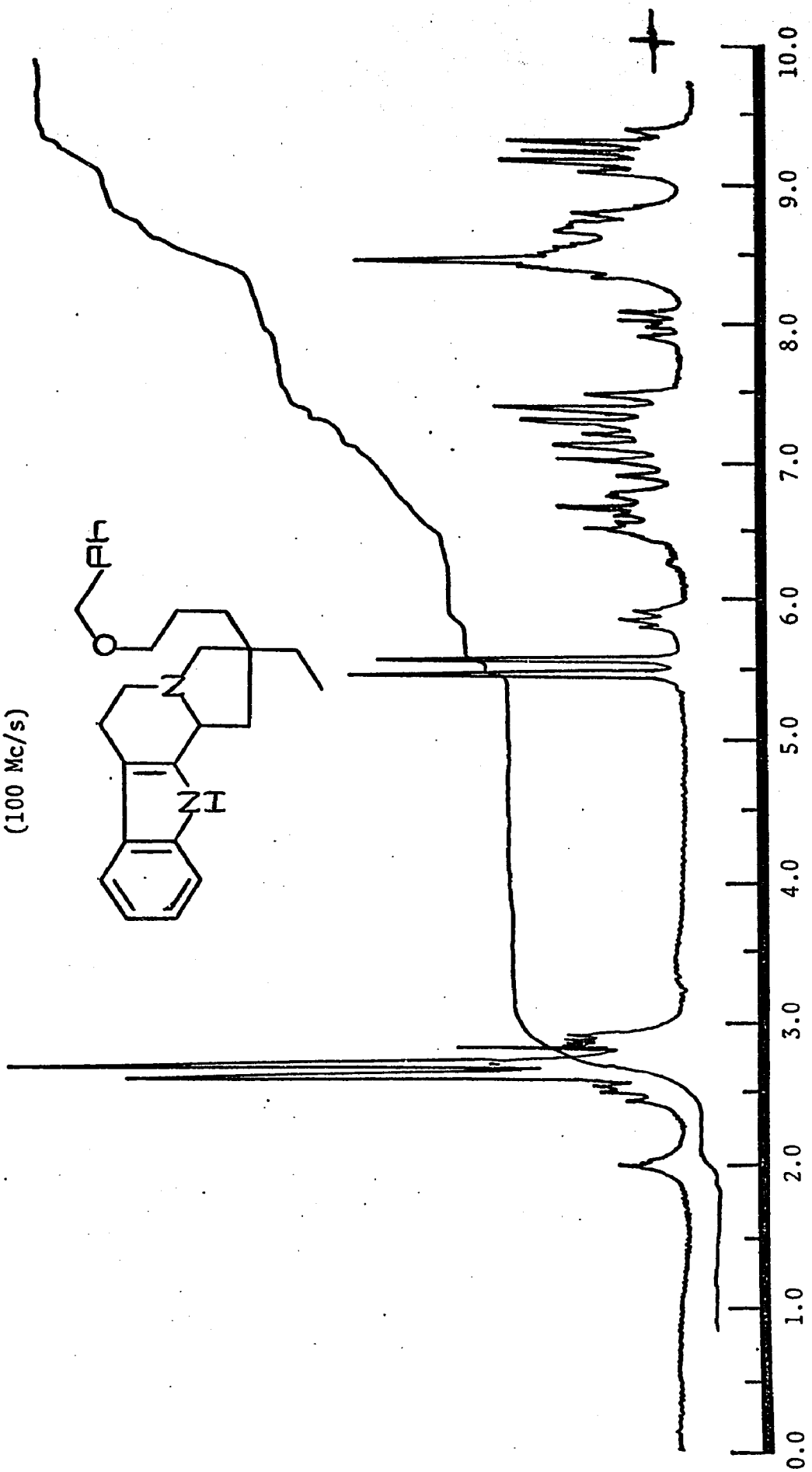

Figure 41. NMR spectrum of the cyclized amine (93).

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The two dl- pairs of this amine (93) are indicated in Figure 42. For

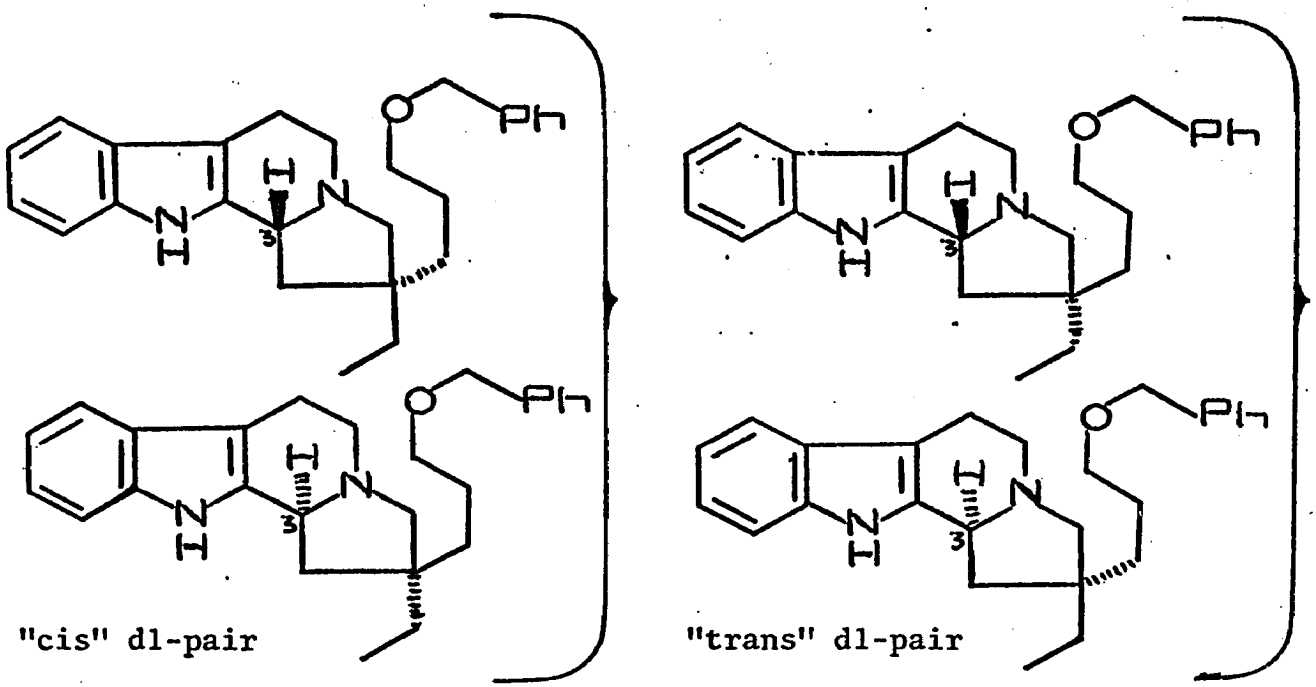

Figure 42. The two diastereoisomeric dl- pairs of amine (93).

the sake of convenience, we will call "cis" the dl- pair in which the proton at C-3 is in a "cis" relation with the ethyl side chain, while "trans" is the one with a "trans" orientation of these functions.

The benzyl group of the above mixture was removed by catalytic hydrogenolysis (10% Pd on charcoal, acetic acid) to provide in 84% yield a mixture of isomeric alcohols which could now be separated. Chromatography on alumina allowed the isolation of alcohol-I (less polar) and of alcohol-II (more polar). Both alcohols were crystallized easily from methylene chloride. Alcohol-I, m.p. 166-167° with its NMR spectrum shown in Figure 43, had triplets at τ 5.86 (C-3 proton), τ 6.55 ($\underline{CH_2}OH$) and at τ 9.15 ($CH_2\underline{CH_3}$). On the other hand, alcohol-II, m.p. 168-170°, with its NMR spectrum shown in Figure 44 showed corresponding triplets at τ 5.78, 6.38 and 9.30 respectively. The isomeric nature of these compounds was established

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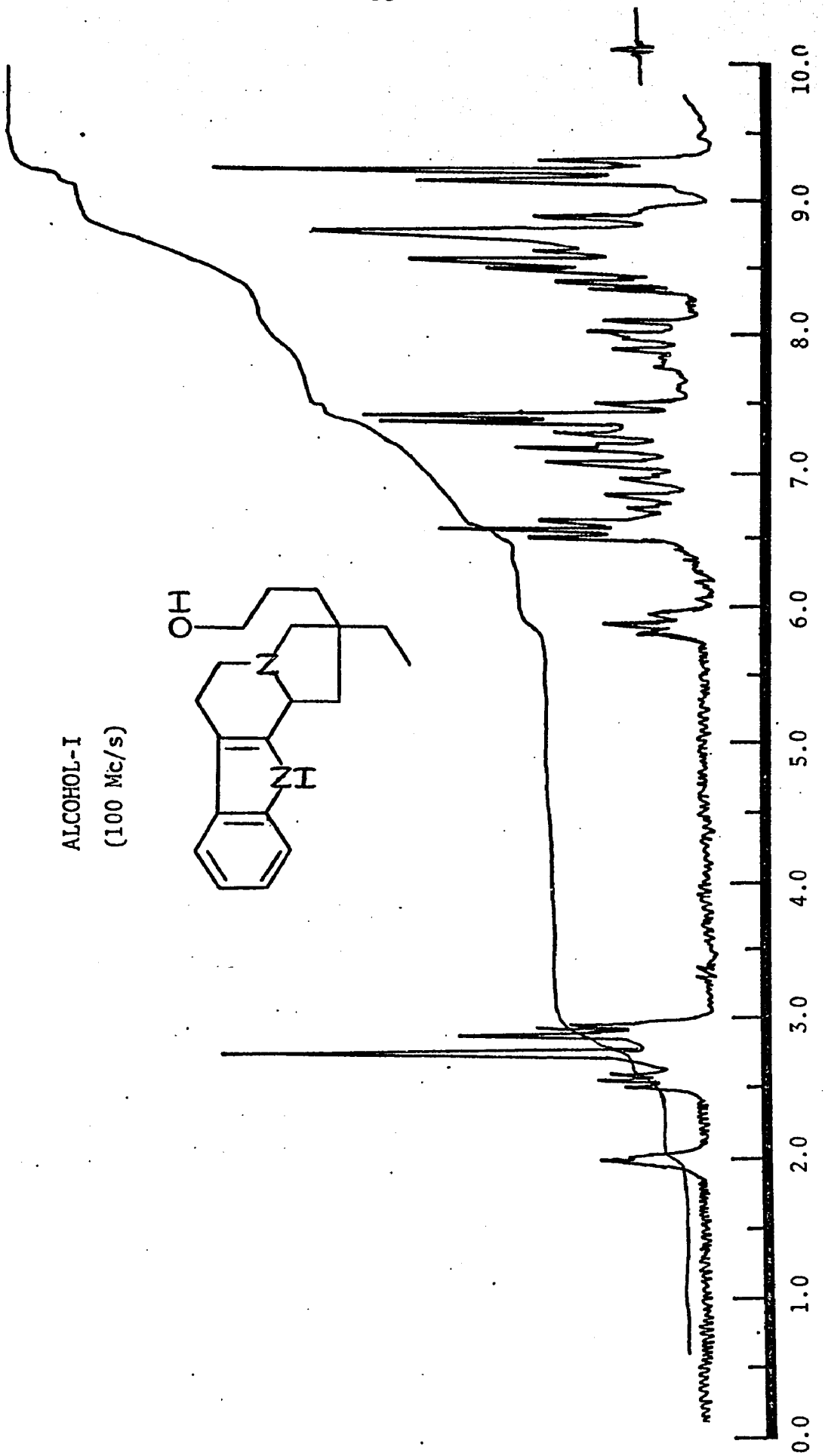

Figure 43. NMR spectrum of alcohol-I (94).

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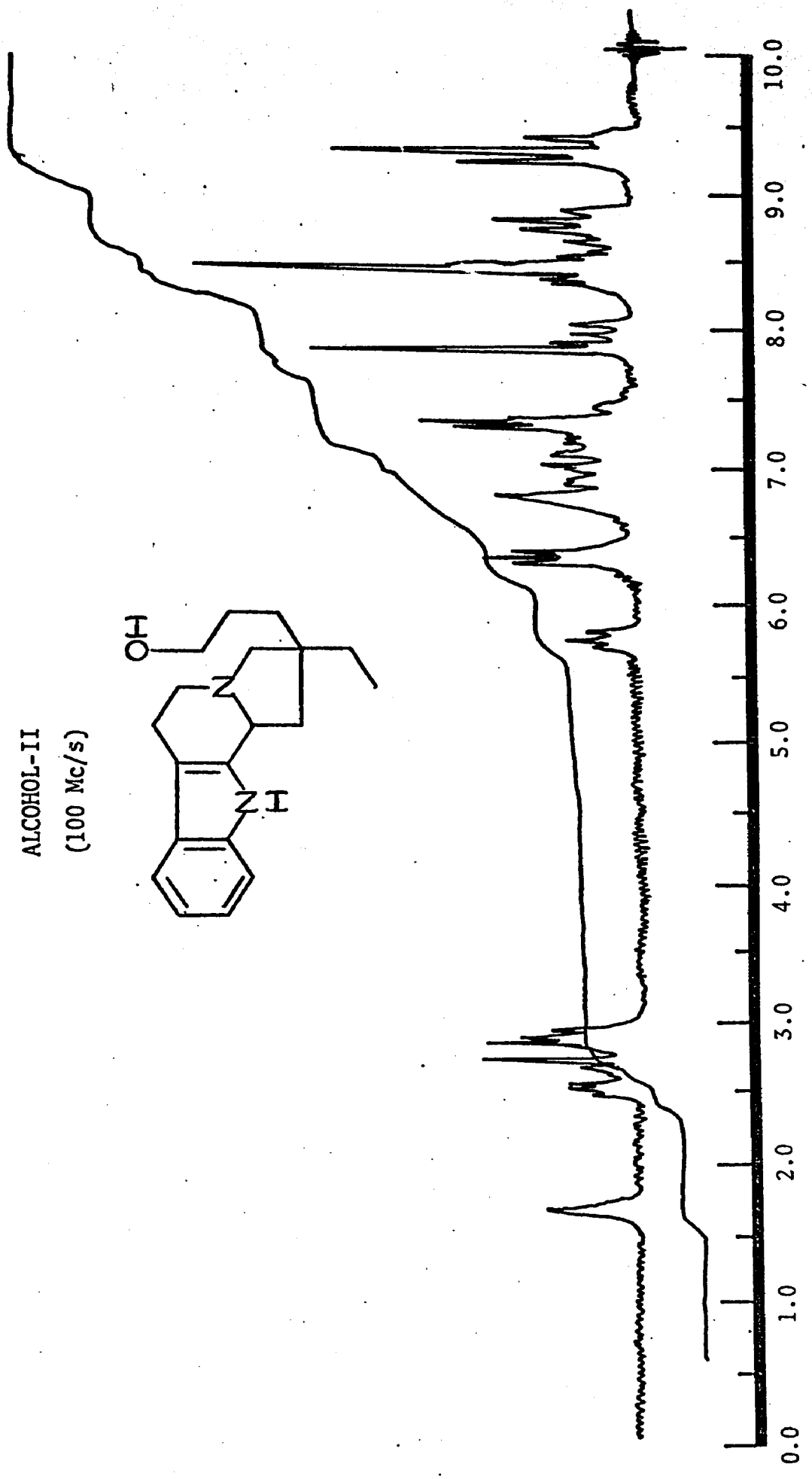

Figure 44. NMR spectrum of alcohol-II (94).

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by high resolution mass spectrometry and from the fact that both alcohols - as we will see later - afforded dl-quebrachamine.

At this point it is important to establish some stereochemical relations between these two dl- pairs of alcohols. First of all, since we are dealing with dl- pairs it is not advisable to refer to different functionalities of the molecule as being α- or β-, since what is α-oriented in one case becomes β-oriented in the mirror image of the same dl- pair. Therefore a cis - trans usage as shown in Figure 42 seemed more suitable.

Molecular models provide some information about the stereochemistry of these alcohols although it is clearly difficult to be very conclusive about it. It is reasonable to assume that ring C is in a most favored half-chair conformation in both alcohols, while the C/D ring junction can be cis or trans. Accordingly we may draw the most favored conformations for these various alcohols as in Figure 45 and we may then concentrate on the experimental and spectral data to identify them.

It must be recognized that in either the "cis" or "trans" dl-pairs, one of the members must have a 3α-H orientation, while the antipodal member must have the 3β-H. In other words we can have a 3α-"cis" isomer (122) and a 3α-"trans" (120) or a 3β-"cis" isomer (123) and a 3β-"trans" (121) one. Clearly then, any given environment around the C-3 position is available in either the "cis" or the "trans" dl-pair and therefore any special shielding or deshielding of the C-3 proton signal in the NMR spectrum by the indole ring or the adjacent electrons on nitrogen is cancelled out, since a particular isomer in either series has a similar environment. One must therefore consider the "cis" or "trans" relationship of the C-3 proton and the ethyl group to try to explain the observed NMR result.

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Molecular models reveal the following information:

i) When the C-3 proton is trans to the lone pair of electrons on nitrogen - as in (121), (123) and (124) - its dihedral angle with the 14β-proton is large (about 140-150°, circled hydrogens) and we would expect a large coupling constant (around 12 cps). Its dihedral angle with the 14α-proton is about 20-30° and a smaller coupling (J around 7 cps) is expected. Therefore a quartet is expected for the C-3 proton. In fact we find a triplet (J = 6 cps). When R = Et ("trans" case) or R' = Et ("cis" case) the ethyl group and side chain are far removed from either the C-3 proton or the nitrogen. Therefore it should have little effect on the chemical shift of this proton.

ii) When the C-3 proton is cis to the lone pair of electrons on nitrogen - as in (120), (122) and (125) - the dihedral angle with the 14β-proton is about 15° (J ≃ 9 cps) while with the 14α-proton it is about 108° (J = 1-2 cps) in what appears to be the most favored conformation. Here again we would expect a quartet rather than the observed triplet.

In the latter instance when R is ethyl as in (122) and (125), it is in reasonably close proximity to the N-electrons and to the 3β-proton. Therefore we feel that the 3β-proton would be shielded by the ethyl group while the latter in turn is deshielded by the nitrogen atom. As a consequence the "cis" dl-pair has the C-3 proton triplet to higher (τ 5.86) field and the ethyl triplet to lower (τ 9.15) field, while the "trans" dl-pair has these signals at τ 5.78 and 9.30 respectively. Support for these assignments is available from the literature.

Rosen and Shoolery[68] in their work on Rauwolfia alkaloids (Figure 46) generally assumed that axial protons absorb at higher fields than the equatorial ones and on this basis they made their assignments. When, as

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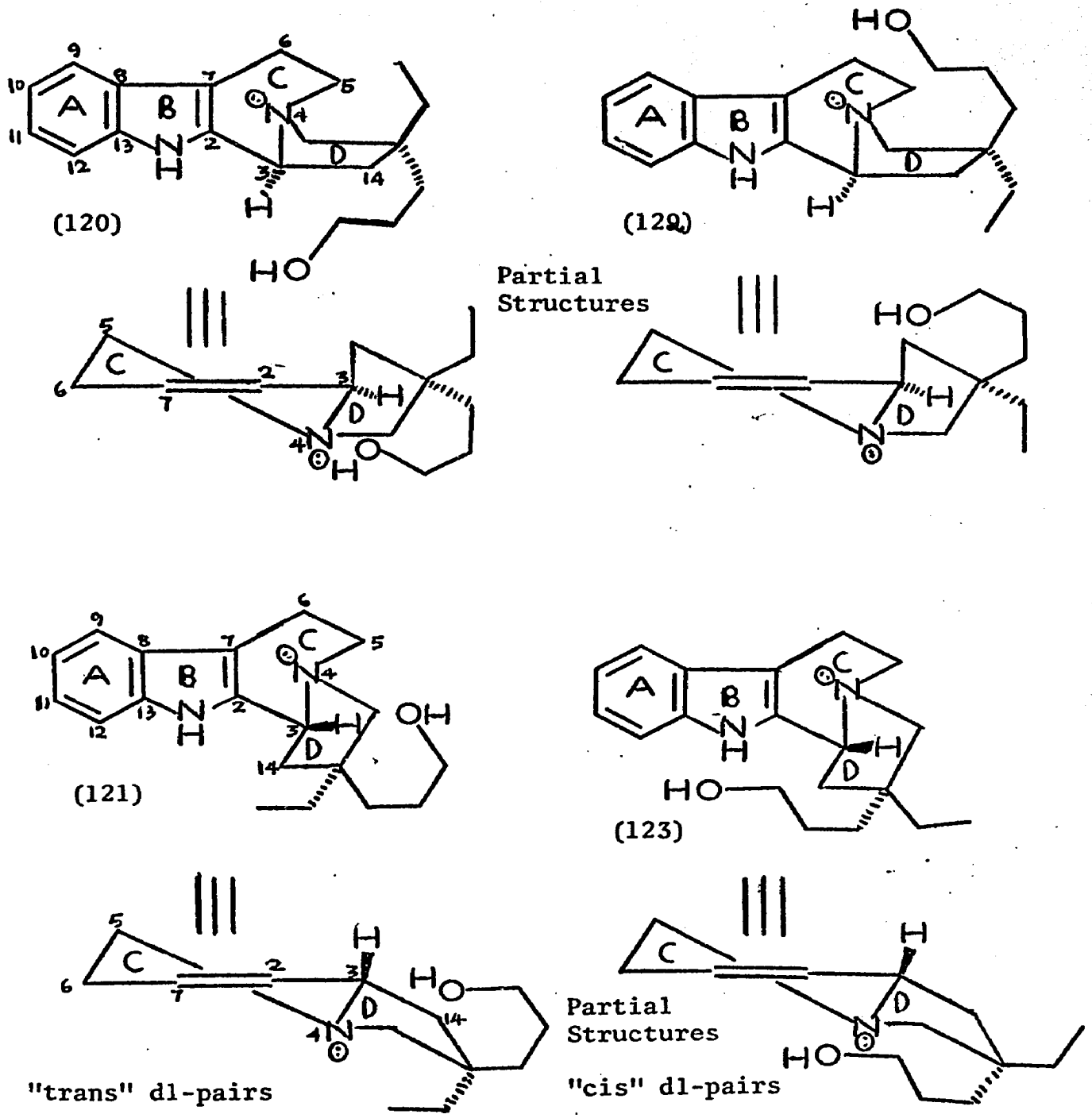
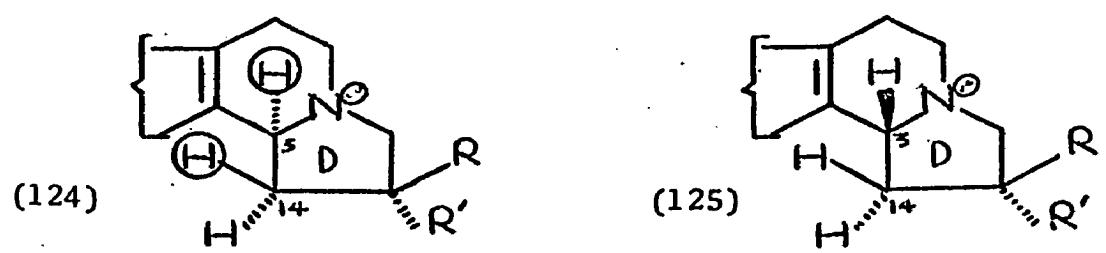


Figure 45. Most favored conformation of the alcohols.



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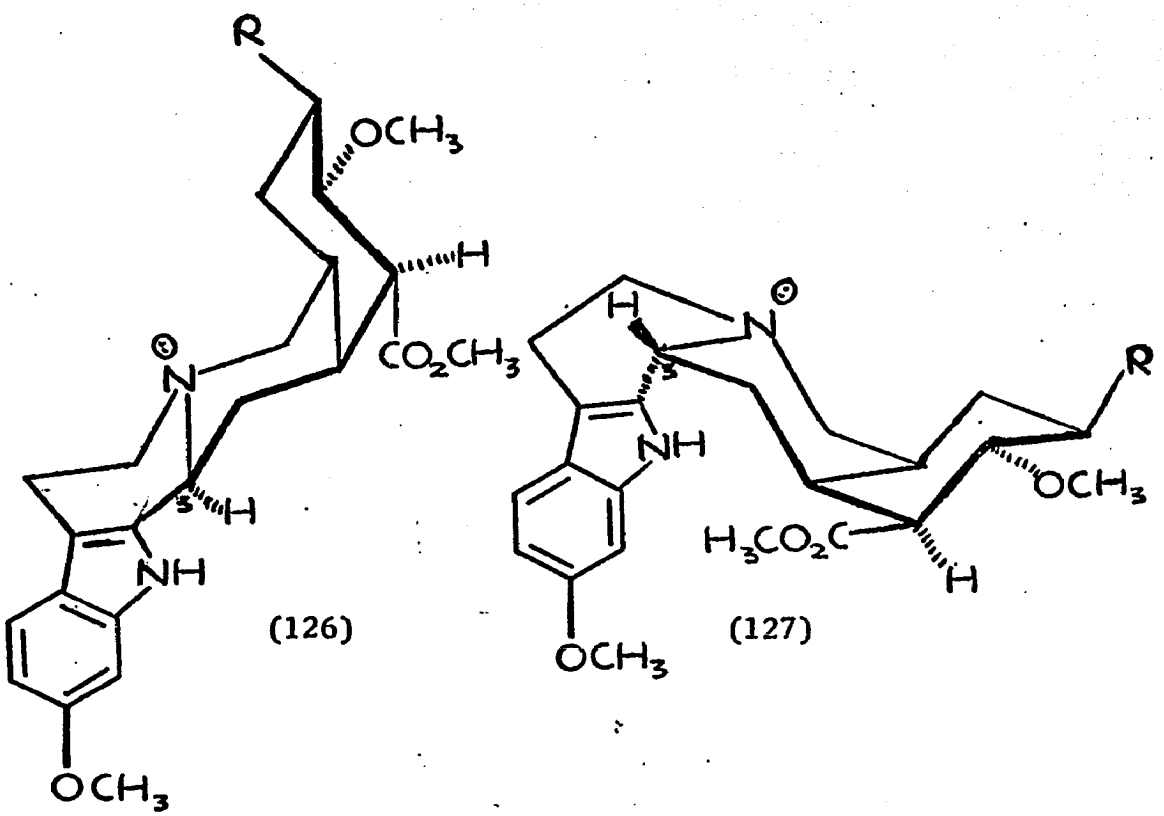

Figure 46. Conformations proposed for some reserpate derivatives (R = OH or 3',4',5'-trimethoxy benzoate)

in (126), the C-3 proton is in a diaxial antiparallel relation to the N-electrons the C-3 proton signal was always found above τ 6.2. On the other hand, when the C-3 proton is in an equatorial cis relationship with the N-electrons, as in (127), it resonates around τ 5.6. From these results we may expect in our case both C-3 protons to be of the latter type (τ 5.78 and 5.86). Also these authors[68] explain the lack of resolved fine structure in the C-3 proton signal in cases like (127) when N-electrons are in close proximity to it as, "...due to spin coupling to the nitrogen, which often smears the peak due to quadrapole relaxation of the nitrogen."

Wenkert et al.[69] have used the same argument in the stereochemical elucidation of the isomeric alkaloids ajmalicine (30) and tetrahydroalstonine. Again the equatorial and cis-oriented C-3 proton had a low field resonance

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(τ 5.55). Beckett et al.[70] during the structural elucidation of corynanth-eidine type alkaloids using IR, NMR, ORD and CD information tried to establish normal, pseudo, allo and epi-allo configurations. These authors have used extensively the already proposed argument for the C-3 proton and its environment. They also are discussing the relative effect of N-electrons on the methyl group in some quinolizidine compounds (Figure 47).

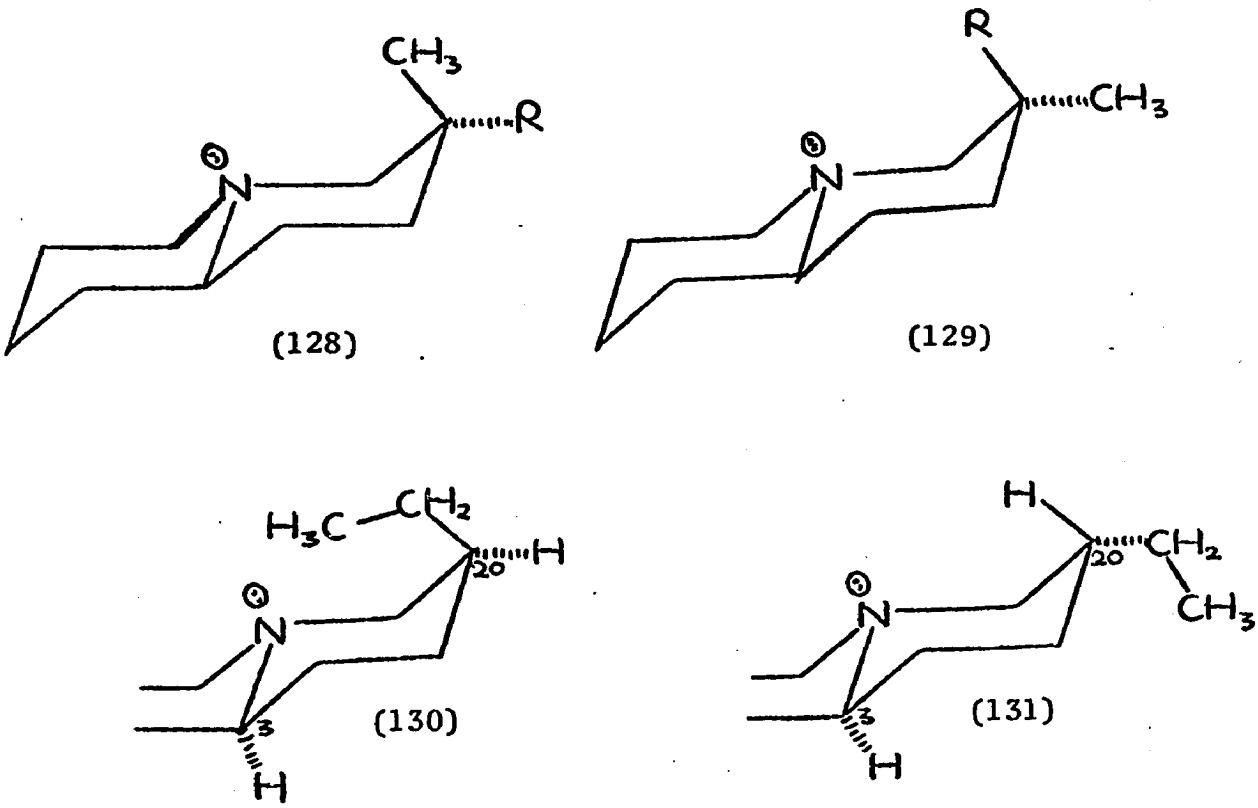

Figure 47. Stereochemical relations in some quinolizidine derivatives.

In (128) the methyl signal is at τ 8.9, whereas in (129) it is at τ 9.16. This means that the methyl signal shifted by 0.26 τ, because of the change from the cis 1:3-diaxial relationship to the trans 1:3-axial-equatorial one. Finally, Wenkert et al.[40] studied the conformational implication, revealed by NMR in several flavopereirine derivatives, pertinent to the C-3

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proton and methyl group of the ethyl side chain. Partial structures (130) and (131) are given for these alkaloids. These authors accept even larger limits between a "truly axial" and a "truly equatorial" C-3 proton anticipating a difference as large as 1.26 τ.

Another means of assigning the relative position of the C-3 proton and the N-electrons was by IR spectroscopy. Bohlmann[71] showed that in certain quinolizidine alkaloids, infrared bands in the C-H region appear when hydrogen atoms on a carbon atom adjacent to a nitrogen are trans, antiparallel to the unshared electrons of this hetero atom. This technique has proven to be a useful tool in the stereochemical assignments in numerous alkaloids.[72,73] In both of our alkaloids no Bohlmann bands between 2700-2800 cm^{-1} were apparent in the IR spectra, which is further support to the above suggestion that the C-3 proton is not in a co-planar and trans relation with the N-electrons. On the above basis I feel that alcohol-I is the "cis" dl-pair - best represented by (122) or (132) whereas alcohol-II is the "trans" dl-pair - best represented by (120) or (133) (Figure 48).

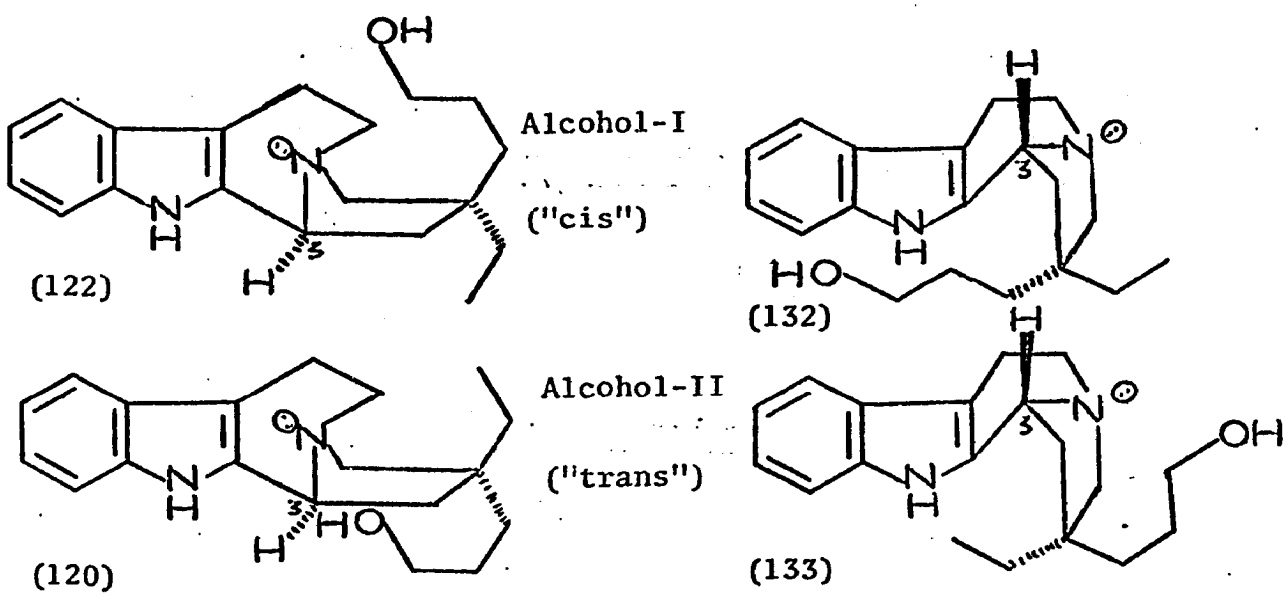

Figure 48. Conformation of the isomeric alcohols-I and II.

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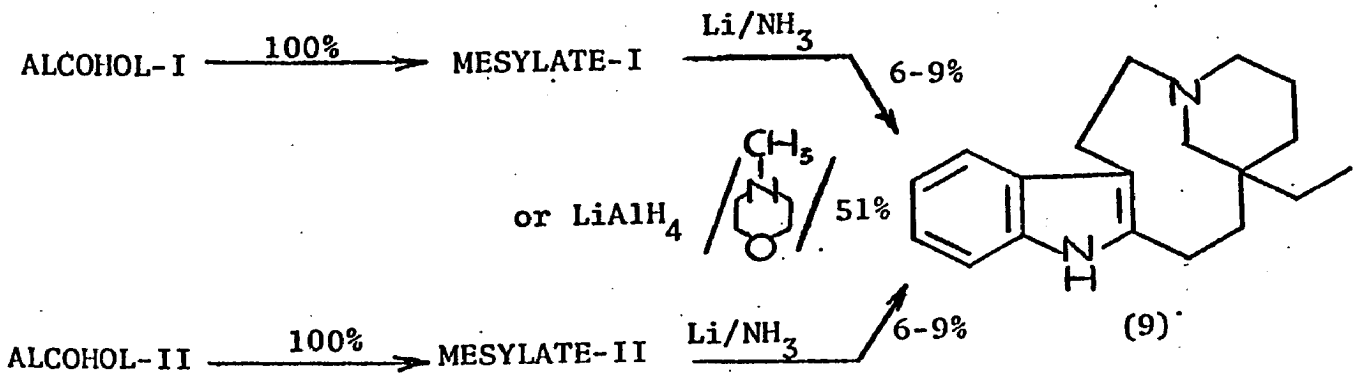
Treatment of each of these alcohols with methanesulfonyl chloride in triethylamine provided quantitative yields of the corresponding mesylates (95) (Figure 37). These compounds were obtained as a yellowish glass after purification by rapid column chromatography on alumina.

Each of these mesylates reacted with lithium in liquid ammonia[74] and the crude reaction products were purified by column chromatography on neutral alumina to give in both cases identical materials which crystallized upon standing. From TLC investigation and superimposable IR spectra in comparison with authentic samples this compound was identified as dl-quebrachamine (9). The overall yield of both reactions to provide dl-quebrachamine was 6-9% from the corresponding alcohols. In addition some starting material was recovered as well. When the above reaction was performed in N-methyl morpholine under reflux for 7 hours (≈115°)with lithium aluminum hydride,[75] followed by conventional work up and purification by chromatography and crystallization from methanol we were able to obtain dl-quebrachamine in 51% yield. The identity of this compound with authentic natural quebrachamine was established by its TLC properties, m.p., mixed m.p., superimposable IR, NMR and mass spectra. I believe that the latter reaction yield might be improved by using a stronger aprotic solvent, since the mesylates



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are insoluble in N-methyl morpholine.

The structural identity of alcohols-I and II was now established beyond doubt since both compounds yielded the same product, dl-quebrachamine. It was now clear as already discussed previously that these compounds must differ only in a stereochemical sense.

Having obtained dl-quebrachamine in excellent yield and having improved the whole sequence leading to the alcohols, it was now clear that a vastly improved total synthesis to that previously reported[53] was available. The application of this sequence to the Vinca series will be discussed later.

I would now like to return briefly to the mercuric acetate oxidative cyclization of amine (92) to the tetracyclic intermediates (93) and (96) since some of the results obtained in a reinvestigation of this reaction relate directly to the above discussion. It was noted that in the previous investigation[3] only three of the four theoretically possible cyclic products - two dl-pairs bearing the "desired" system as in (93) and two dl-pairs bearing the "undesired" system as in (96) - were recognized (Figure 24). Furthermore, due to the great difficulty encountered in the separation of these alcohols, the subsequent steps leading to dl-quebrachamine were performed at that time on mixtures of alcohols.

It was clearly desirable to make a more thorough study of this reaction and to relate some of these compounds to alcohols-I and II as mentioned above. For this purpose we performed the mercuric acetate oxidative cyclization followed by sodium borohydride reduction in a special reaction apparatus. The work up of the reaction mixture was carried out under highly purified nitrogen, and special care was exercised throughout the experiment. The reaction product, a brown gum, was chromatographed on neutral alumina

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(Shawinigan, activity II-III)to give in 38% yield the mixture of cyclized benzylamines (93) and (96) having the desired spectral data. These dl-epimers without any further separation were submitted to catalytic hydrogenolysis over palladium in glacial acetic acid. The resulting crude mixture of alcohols was chromatographed on neutral alumina (Shawinigan, activity II-III) to provide all four of the expected alcohols. The new alcohol not previously identified was named A' for the sake of convenience. In relation to previous results these alcohols were designated as A', A, B and C in order of increasing polarity on alumina chromatoplates when these were developed with a solvent mixture of 5% methanol in chloroform. All purified alcohols were isolated as transparent greenish solids. Alcohols A' and A were eluted with benzene/chloroform (50:50), alcohol B with chloroform and finally alcohol C with chloroform/methanol (99:1). The yields of alcohols A', A, B and C from the cyclized amines (93) and (96) were 10%, 11%, 17% and 14% respectively (total 52%). Now the problem was to identify by comparison with alcohols-I and II which two of these four alcohols possessed the "desired" (94) structure and which represented cyclization in the "undesired" manner (97). It was thought during the previous investigations[3] that alcohols B and C were most likely the ones which provided dl-quebrachamine although no definite conclusions could be reached at that time. We now find that in fact alcohols A and C possess the desired structures.

The new alcohol A' had a typical indole ultraviolet absorption with maxima at 291, 283, 275 and 230 mμ. The IR spectrum was almost identical with those of the other three alcohols with strong OH absorption at 3270 cm^{-1} and no Bohlmann bands were present.[71] In the NMR spectrum (Figure 49) an NH signal at τ 1.2, an envelope of four aromatic protons

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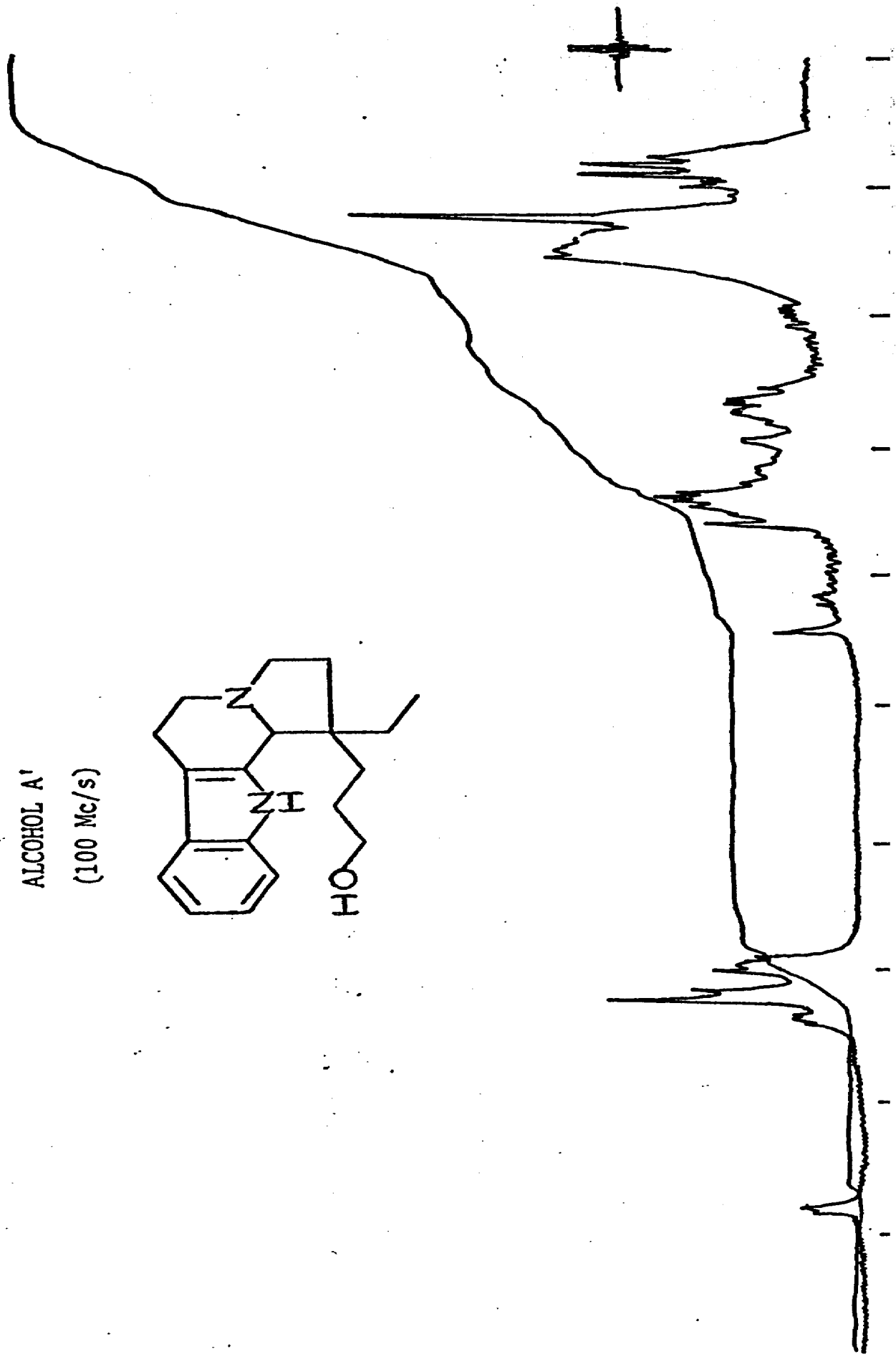

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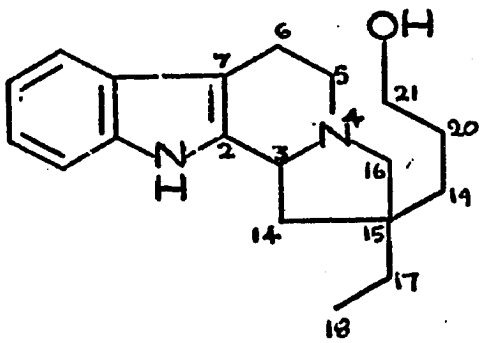
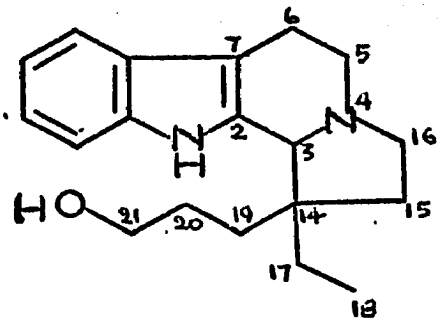


(94)



(97)

centered at τ 2.85 and a methyl triplet at τ 9.12 were apparent. A signal at τ 6.43 for one proton might be assigned to the C-3 proton. The mass spectrum of this compound (Figure 50) contained a molecular ion at m/e 298, and peaks at 297 (M-1), 184, 170 and 156, very characteristic of molecules like (94) or (97), which possess a substituted tetrahydro-β-carboline system[67] (Figure 51). High resolution mass spectrometry established the molecular formula $C_{19}H_{26}ON_2$ (Found: 298.204; Calc: 298.204). A further comparison of the mass spectra of alcohols A', A, B and C revealed that the intensity ratio of the molecular ion peak (m/e 298) to the one at m/e 184 as in a relation of 2:1 in both alcohols A and C[3], while in alcohols A' and B the ratios are 1:5 and 1:3 respectively. The mass spectra of alcohols A and C are reproduced for comparison (Figure 50). The above observation might be due to the contribution of a fragment like (134) which is the analog of the fragment at m/e 156 for the alcohols A and C. Finally we may note that the ratio of peaks at m/e 297 to m/e 298 (M^+) is 1:1 for alcohols A and C, but 1:2 for the alcohols A' and B. This indicates that the M-1 fragment in the latter alcohols does not contribute as much.

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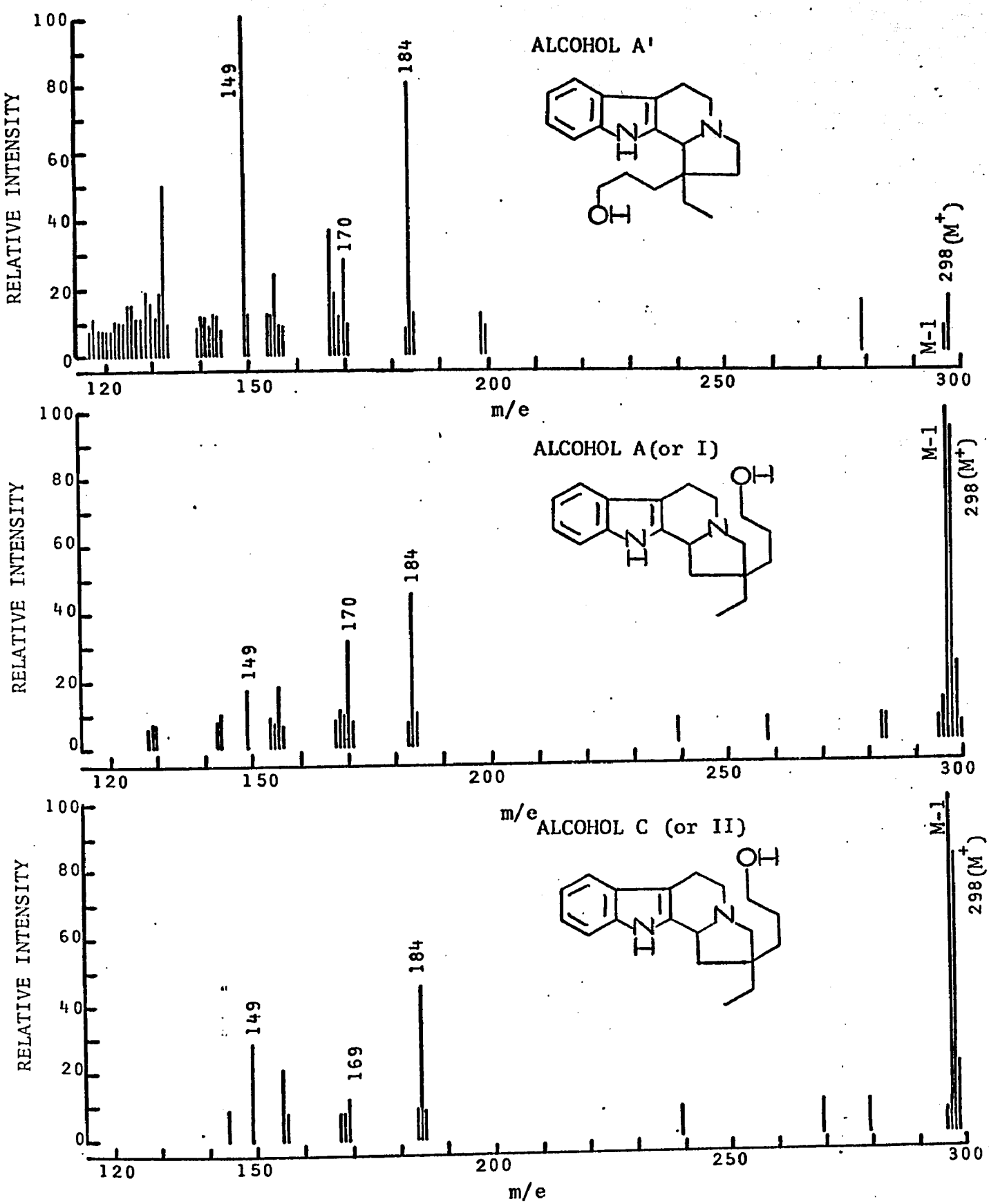

Figure 50. Mass spectra of alcohols A', A (or I) and C (or II).

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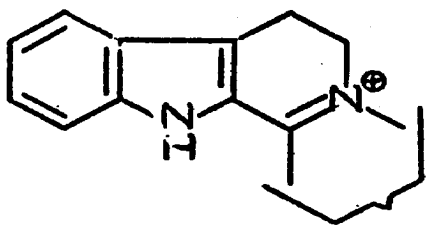
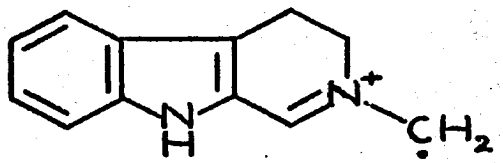
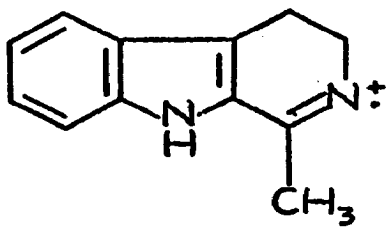


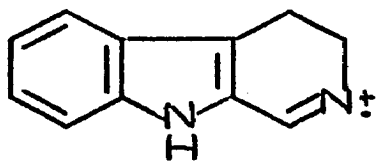
M-1



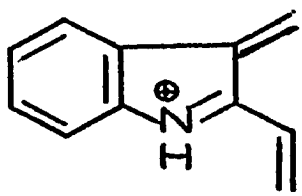
m/e 184



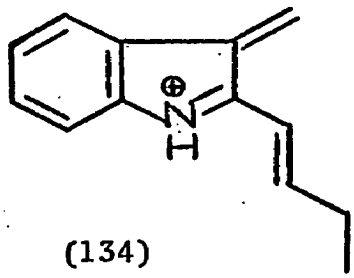
m/e 184



m/e 170



m/e 156



(134)

m/e 184

Figure 51. Common fragments in the mass spectrometer of a substituted tetrahydro-β-carboline system.

Alcohols A, B and C were shown to be identical with the ones prepared by the previous authors[53] (IR, NMR, TLC, Mass spectra and High Resolution mass spectra). Having obtained alcohol-I and alcohol-II by the sequence in Figure 37, we compared these two alcohols, known to be cyclized in the "desired" way, with alcohols A', A, B and C. TLC investigation and finally comparison of IR, NMR, and Mass spectra established the following:

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Alcohol-I ≡ Alcohol A ≡ "cis" dl-pair

Alcohol-II ≡ Alcohol C ≡ "trans" dl-pair

This means that alcohols A' and B represent cyclization in the undesired manner and possess the gross formula (97).

A comparison of the NMR spectra of alcohols A and C with those of the alcohols A' and B revealed that the C-3 proton in the first two was at τ 5.86 and 5.78 respectively while in the second pair no C-3 proton signal was seen below τ 6.4. This result when coupled with the IR spectra, indicated that in the first two compounds the N-electrons and the C-3 proton were in a cis relationship rather than in a trans one and therefore the C-3 proton was in a pseudo-equatorial orientation[68-73] (Figure 48). In the second pair - alcohols A' and B - the high resonance of the C-3 proton may lead to the conclusion that the N-electrons and C-3 protons are in a trans rather than a cis orientation and considering the absence of Bohlmann bands in the IR spectrum the C-3 proton must be also pseudo-equatorial as in (135) and (137). There was another alternative in the latter case; that is, the N-electrons and C-3 proton conformation was similar to that in alcohols A and C, but the shielding arising from the close proximity of this proton to the ethyl group or side chain may cause this C-3 proton to resonate at a higher field - see (136) and (138). Some possible structures for these two "undesired" alcohols A' and B are shown in Figure 52. Since the IR data suggested that the N-electrons and C-3 protons in this last pair are not co-planar and antiparallel we tend to support structures similar to (138) for alcohol A' and (136) for alcohol B, rather than (137) and (135) respectively. In these last structures the C-3 proton is close to an axial orientation. A slight shielding of the aromatic protons also was observed in alcohol A' and a weak

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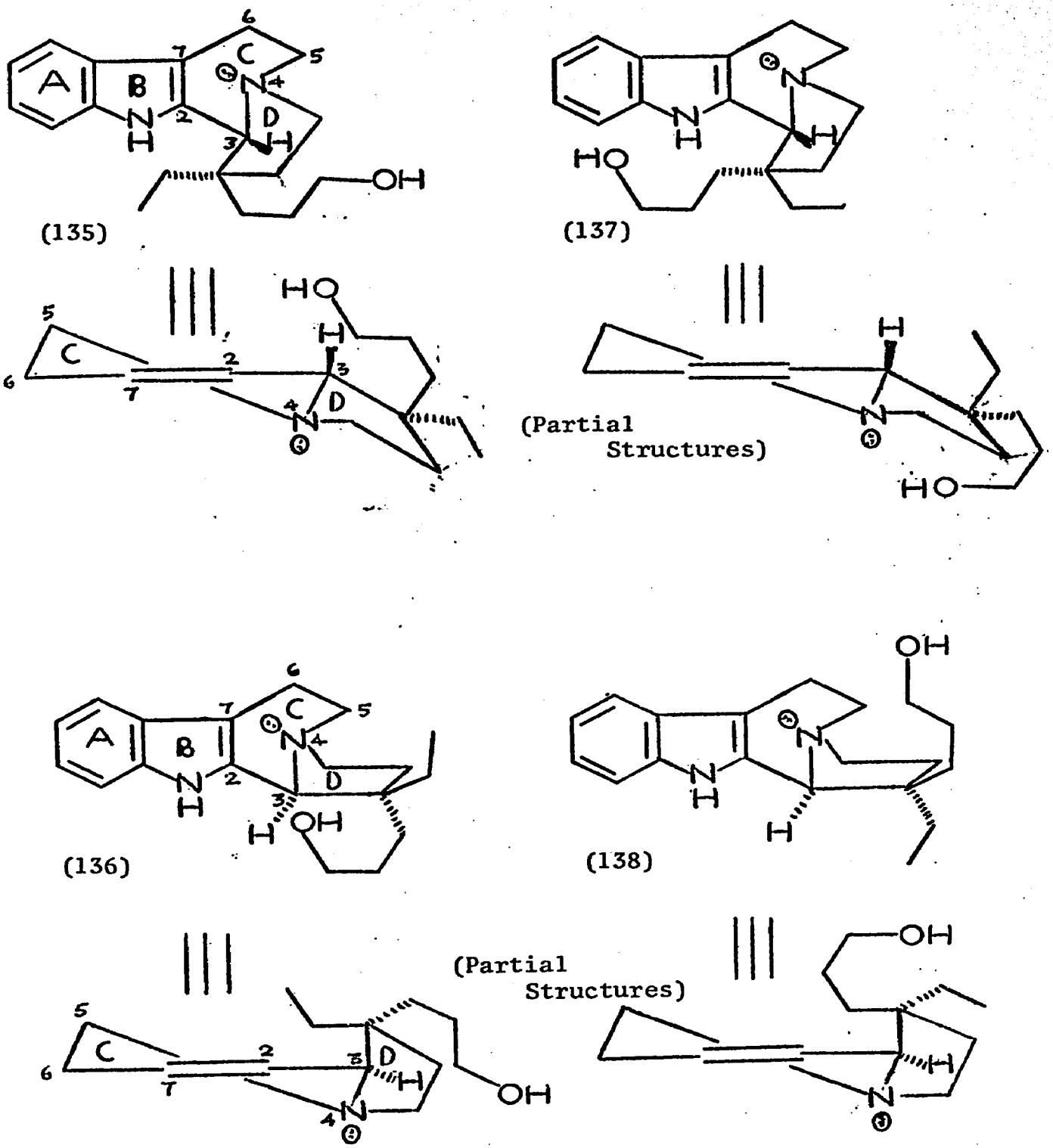

Figure 52. Possible conformations of alcohols A' and B.

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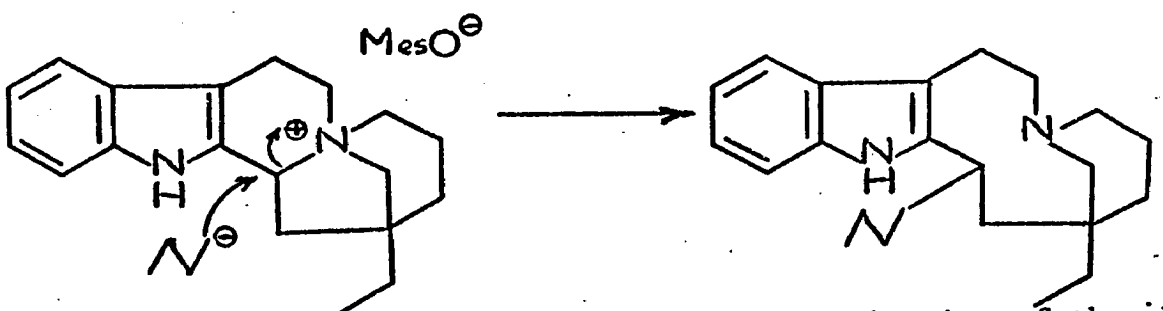
deshielding of the methyl group of the side chain was in agreement with structure (138) where, the side chain bearing the hydroxyl group lies over the indole nucleus and the ethyl chain is cis to the N-electrons. Exactly the reverse is true for alcohol B and as we can see structure (136) is in agreement.

Now that a greatly improved total synthesis of the quebrachamine system was at hand, the next aim was the development of a general versatile reaction for the introduction of appropriate functionality at C-3 of this system. Success in this direction would provide an entry into the total synthesis of a large number of Vinca alkaloids.

2) Introduction of functionalities at C-3 of quebrachamine.

For this purpose we had available from our previous work the previously mentioned alcohols and the very stable quarternary mesylates in gram quantities. We chose to utilize these latter intermediates in a manner such that the formation of the nine-membered ring would occur simultaneously with the introduction of the appropriate function at C-3. A general scheme for this conversion is outlined in which it is noted that attack by nucleophile ($N^{\ominus}$) takes place at a carbon site adjacent to the quarternary nitrogen



atom of the mesylate. In effect a successful application of the above was the synthesis of dl-quebrachamine from the mesylate as already mentioned,

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where the nucleophile was the hydride anion. In this instance we chose to study the reaction with cyanide ion as nucleophile. When either of the mesylates of alcohol-I or alcohol-II were reacted with potassium cyanide in dimethylformamide at 150° (bath temperature) for 4 1/2 hours followed by conventional work up of the reaction mixture a dark gummy product was obtained Investigation of the product mixture resulting from either mesylate by means of TLC showed them to be identical. Chromatography of this crude product gave the two desired isomeric cyanides possessing the gross formula (139) (Figure 53), another isomeric cyanide and some starting material (95). Initial attempts to prepare these desired cyanides (139) failed or gave other products when the reaction was carried out in diethylene glycol. In most

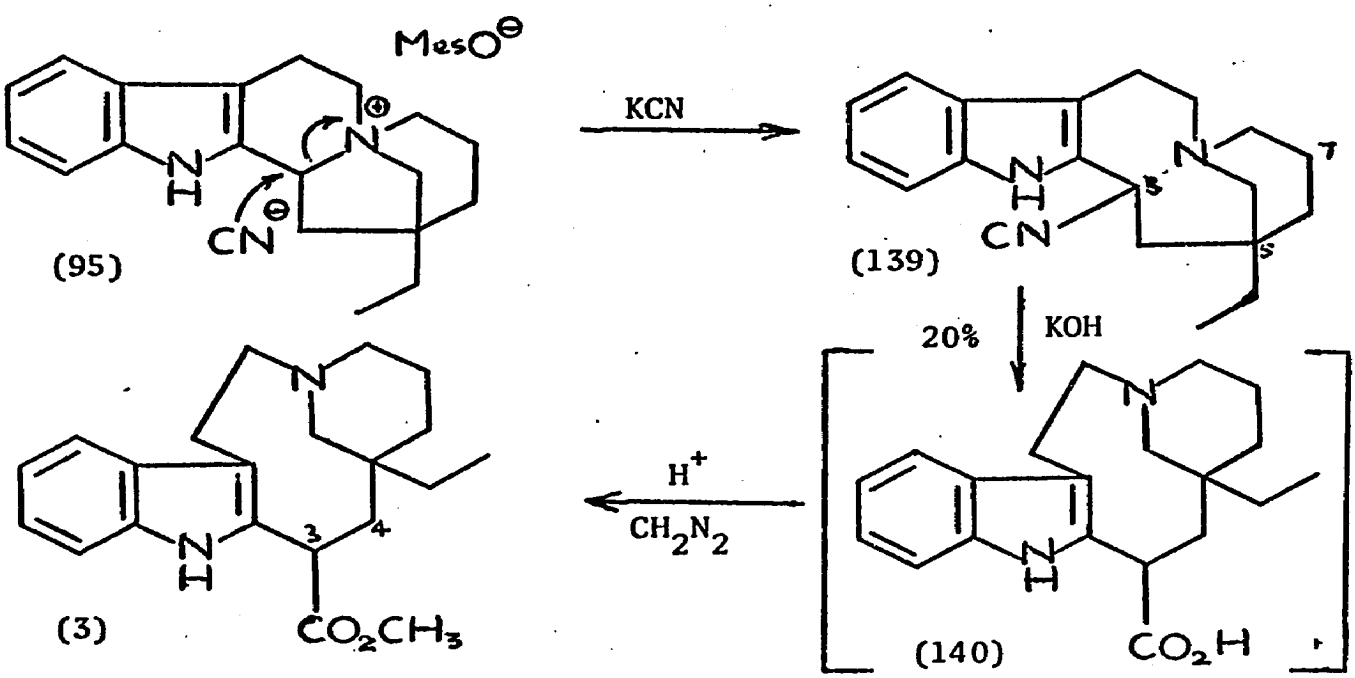

Figure 53. Introduction of functional groups in C-3 of the quebrachamine skeleton.

of the cases, starting material (95) was recovered unreacted. A wide variation of the reaction conditions (the temperature from 105° to 170°, the

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time from 4 to 70 hours and the concentration) was studied. In the recent literature there are some similar reactions reported. Harley-Mason[76a] succeeded in the preparation of compounds like (142) from the methiodide (141) and later, used the mesylate (143) to prepare dl-cyano-dihydrocleavamine (144)[76b] (Figure 54). In both cases he used diethylene glycol and

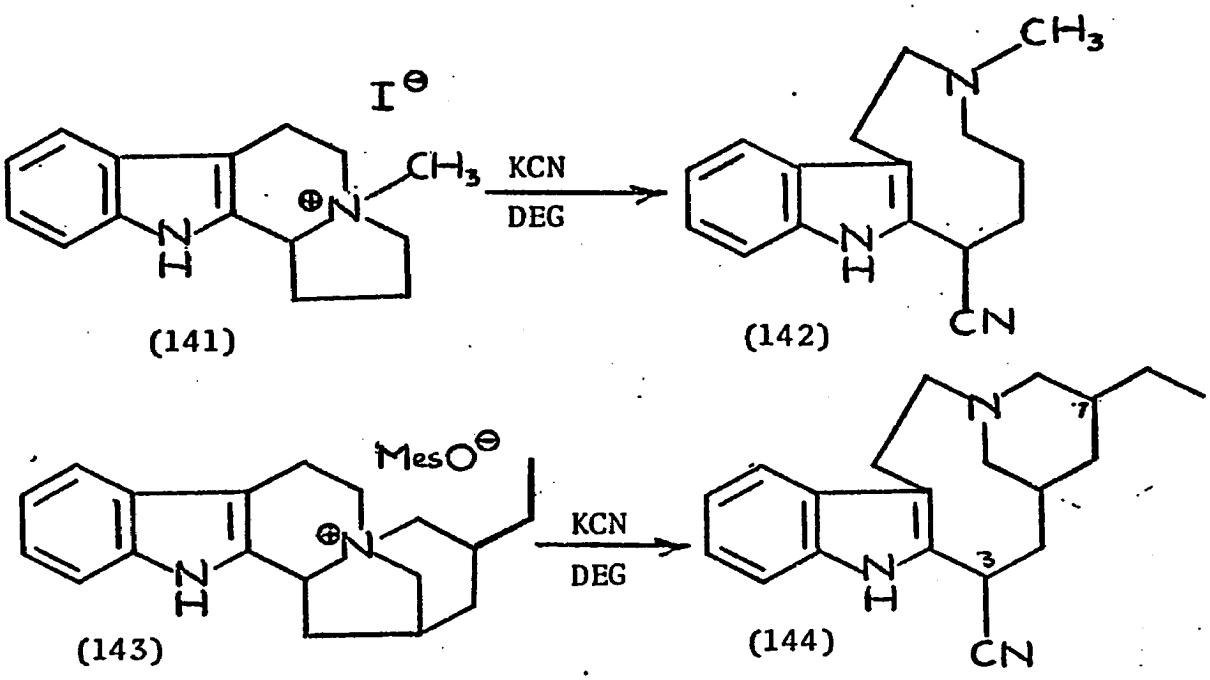

Figure 54. Introduction of cyanide in C-3 by other workers.[76a,b]

potassium cyanide. The reason that we failed to obtain the corresponding cyanides using this procedure might be due partially to the same reasons that the reaction failed to go through the chloroindolenine sequence to yield quebrachamine (see below). In other words the steric interference of the C-5 ethyl in the quebrachamine series is much more serious than the C-7 ethyl group in the cleavamine series. However it is obvious that the solvent effect plays a decisive part in making this reaction go even in low yield.

Using dimethylformamide cyanide-I, cyanide-II and the other isomeric cyanide-III (in order of increasing polarity on alumina chromatoplates when

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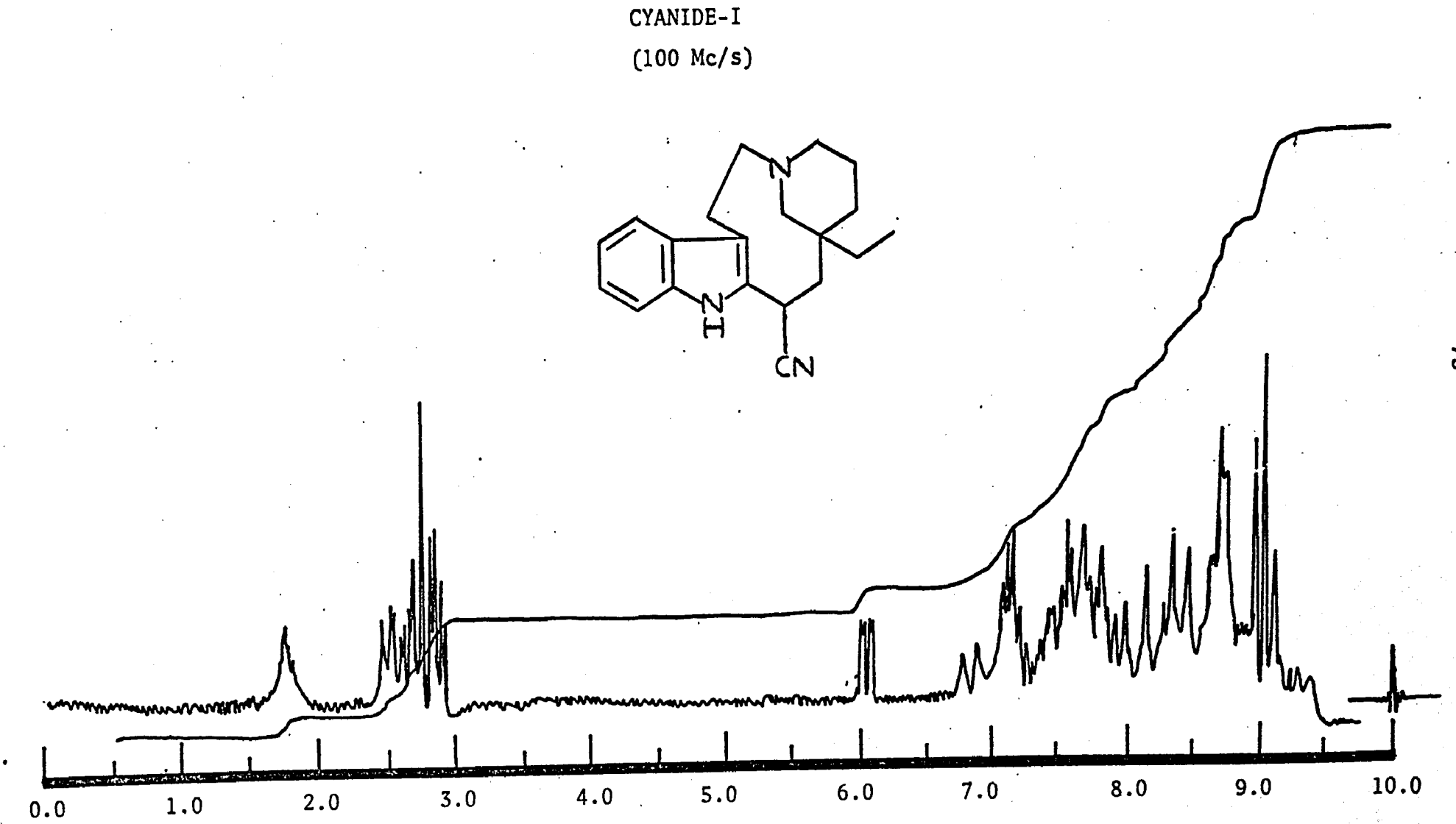

Figure 55. NMR spectrum of cyanide-I (139).

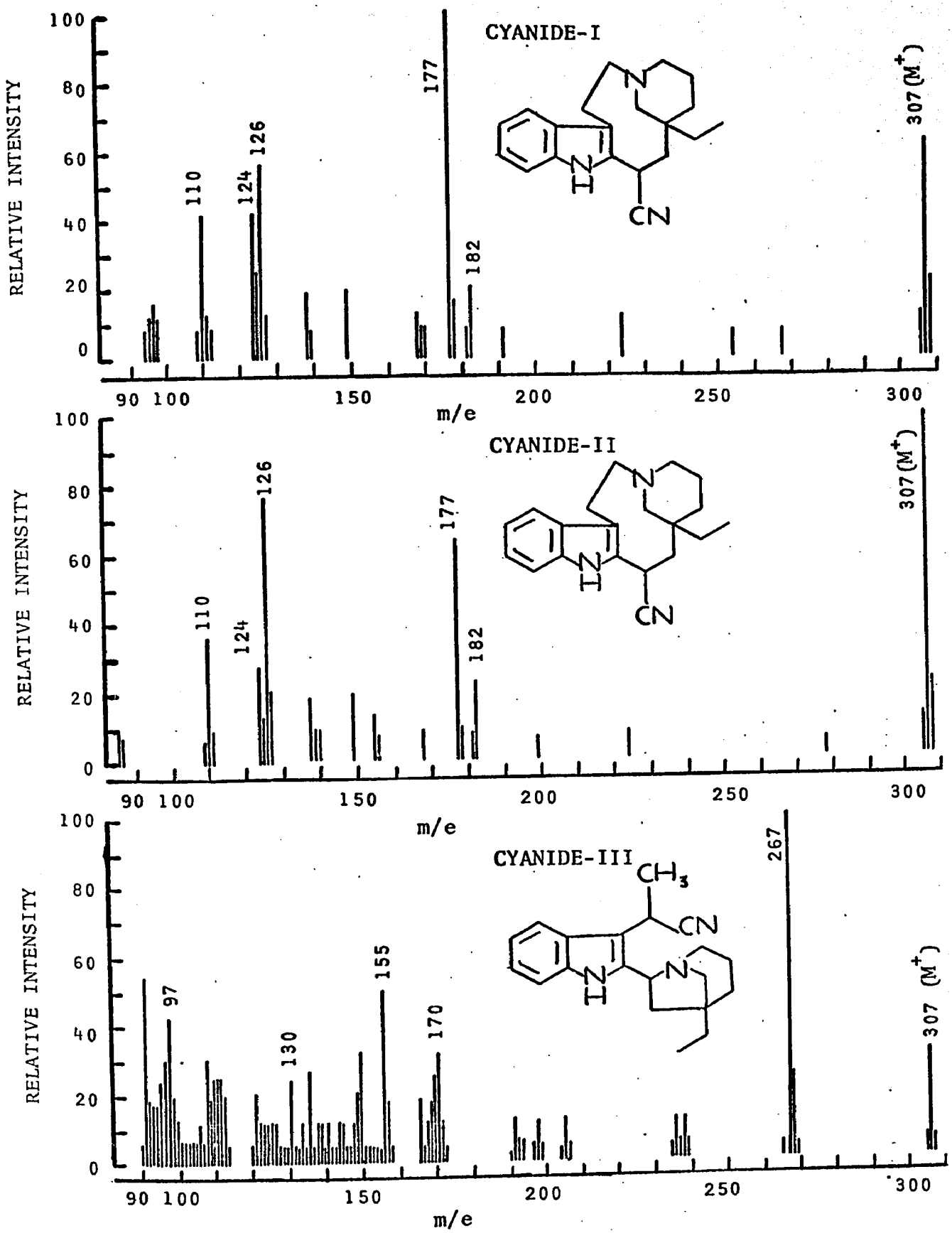

Figure 56. Mass spectra of cyanide-I, II and III.

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developed by chloroform), were obtained in 6%, 8%, and 26% yield from either of the alcohols. Some starting material was also recovered.

Cyanide-I, crystallized from ethyl ether had a m.p. 208-210° and exhibited a normal indole ultraviolet spectrum with maxima at 292.5, 285, 278 and 225 mμ. The infrared spectrum showed the nitrile absorption at 2230 cm^{-1} and the sharp NH vibration at 3360 cm^{-1}. The NMR spectrum (Figure 55) possessed a one-proton quartet at τ 6.08 (-CH CN) and a methyl triplet at τ 9.07. The coupling constants of this proton at τ 6.08 are J_{AB} = 5 and J_{AC} = 2 cps. The mass spectrum of this compound (Figure 56) has a base peak at m/e 177 and other significant peaks at 124, 126 and 182. These fragments are depicted in Figure 57 and are in accord with expectation.[67,77]

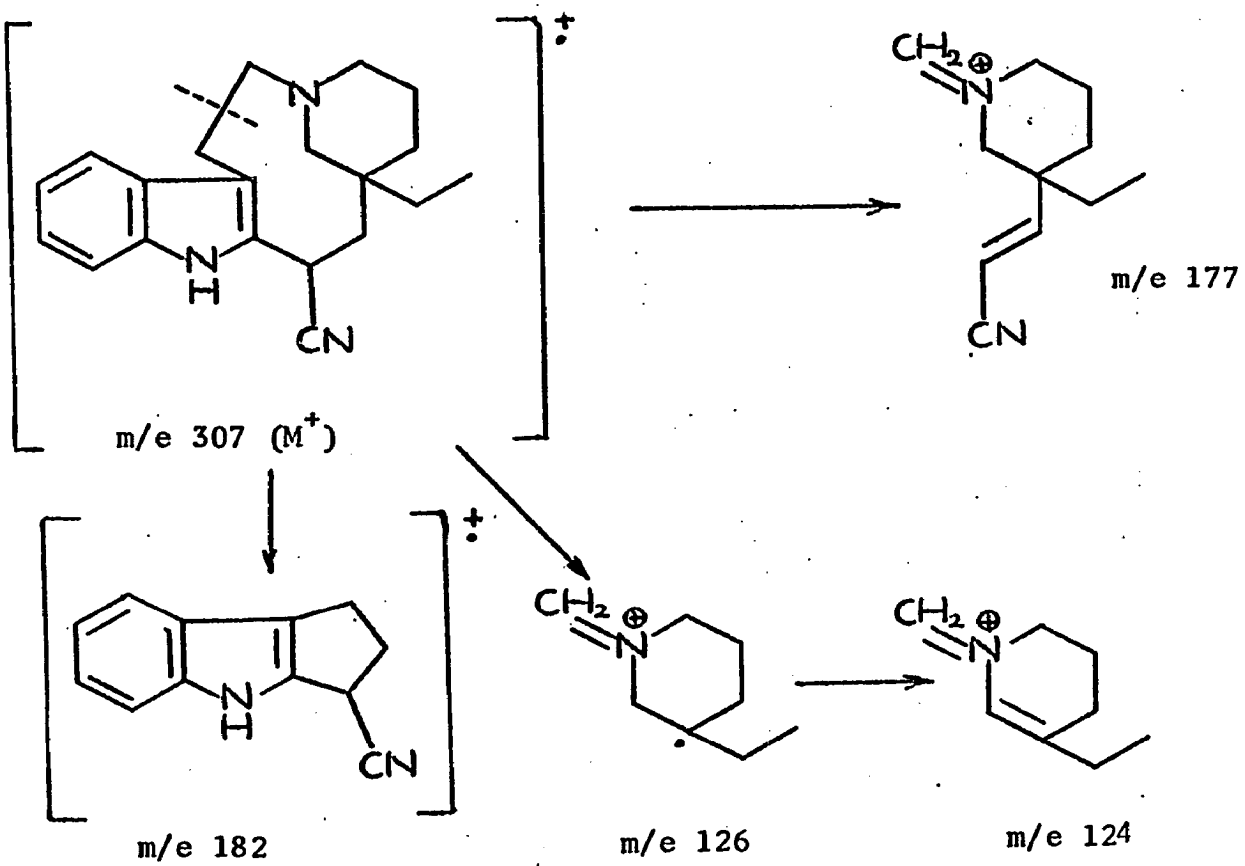

Figure 57. Postulated fragmentation of cyanide-I and cyanide-II.

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High resolution mass spectroscopy established the molecular formula $C_{20}H_{25}N_3$, for this compound (found: 307.204; calc: 307.204).

Cyanide-II, crystallized from n-hexane, had a m.p. 164-168°. Its ultraviolet spectrum revealed a typical indole chromophore (293, 284, 278 and 225 mμ). The infrared spectrum showed a nitrile peak at 2225 cm^{-1} and the sharp NH vibration at 3360 cm^{-1}. The NMR spectrum (Figure 58) exhibited a low field one-proton quartet at τ 3.99 (-CHCN) with J_{AB} = 10 and J_{AC} = 4 cps and a methyl triplet at τ 9.34. High resolution mass spectrometry agreed with the molecular formula, $C_{20}H_{25}N_3$ (found: 307.204; calc: 307.204). The fragmentation of this molecule was the same as for cyanide-I (see Figures 56 and 57).

Cyanide-III was more polar than cyanide-I and cyanide-II and resisted crystallization. It was characterized as an amorphous solid. The infrared spectrum showed a pronounced nitrile peak at 2220 cm^{-1}, a strong NH vibration at 3280 cm^{-1}. The ultraviolet spectrum indicated a typical indole chromophore (290, 283, 275 and 226). The NMR spectrum (Figure 59) was most informative. Two one-proton multiplets at τ 5.50 and 5.88, a methyl triplet at τ 9.17 and the typical indole proton signals were present. Finally a singlet of two protons at τ 7.42 was apparent. The mass spectrum (Figure 56) had a molecular peak at m/e 307 which revealed the isomeric nature of this cyanide to the other two. However a completely different fragmentation than the other two cyanides was shown. The main fragments of this molecule to which we have assigned structure (145) are shown in Figure 60. The formation of cyanide-III can be explained as taking place via a Hofmann-type elimination and through a β-vinyl indole intermediate like (146), as shown in Figure 61. Dolby and Gribble[78] during some recent

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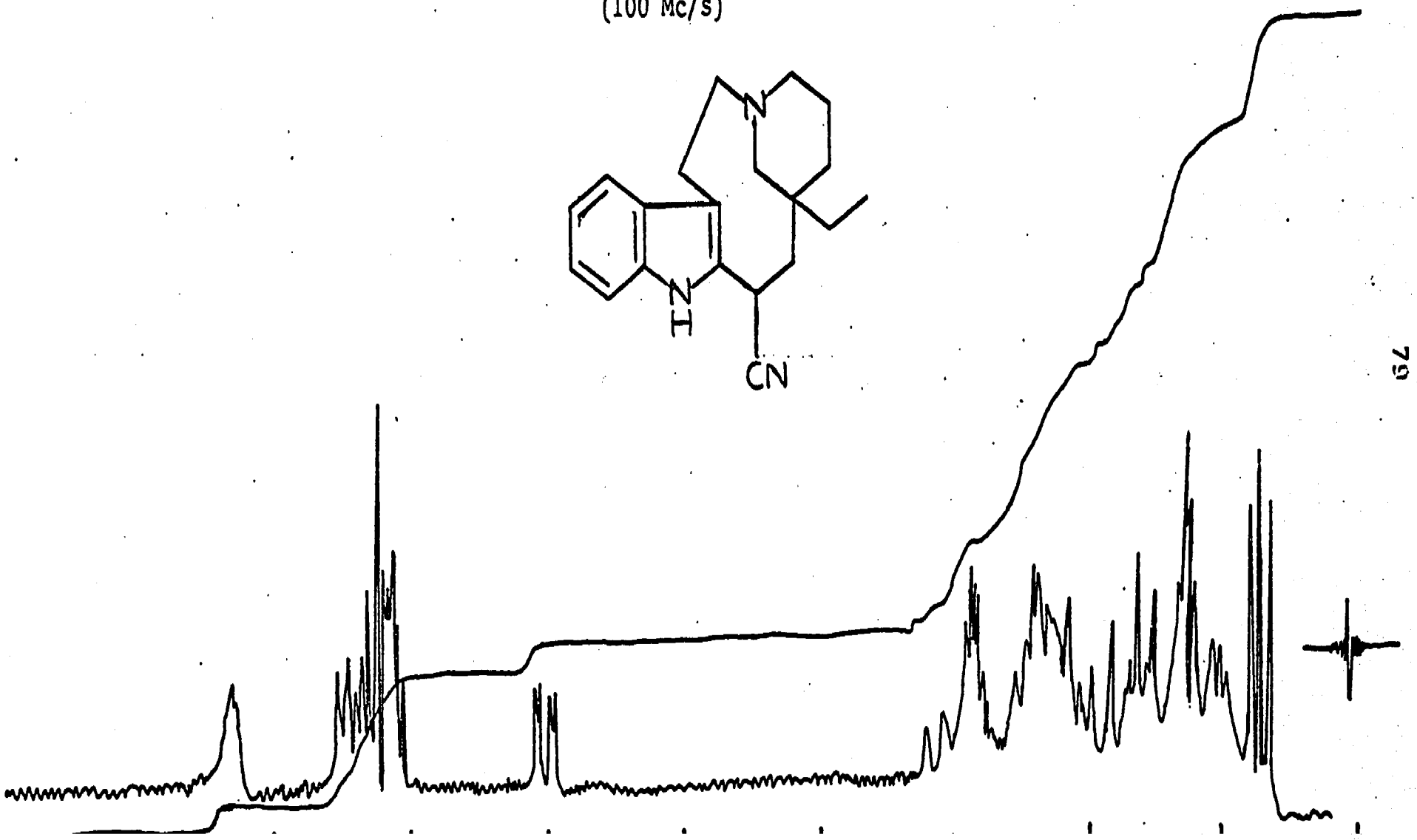
CYANIDE-II

(100 Mc/s)



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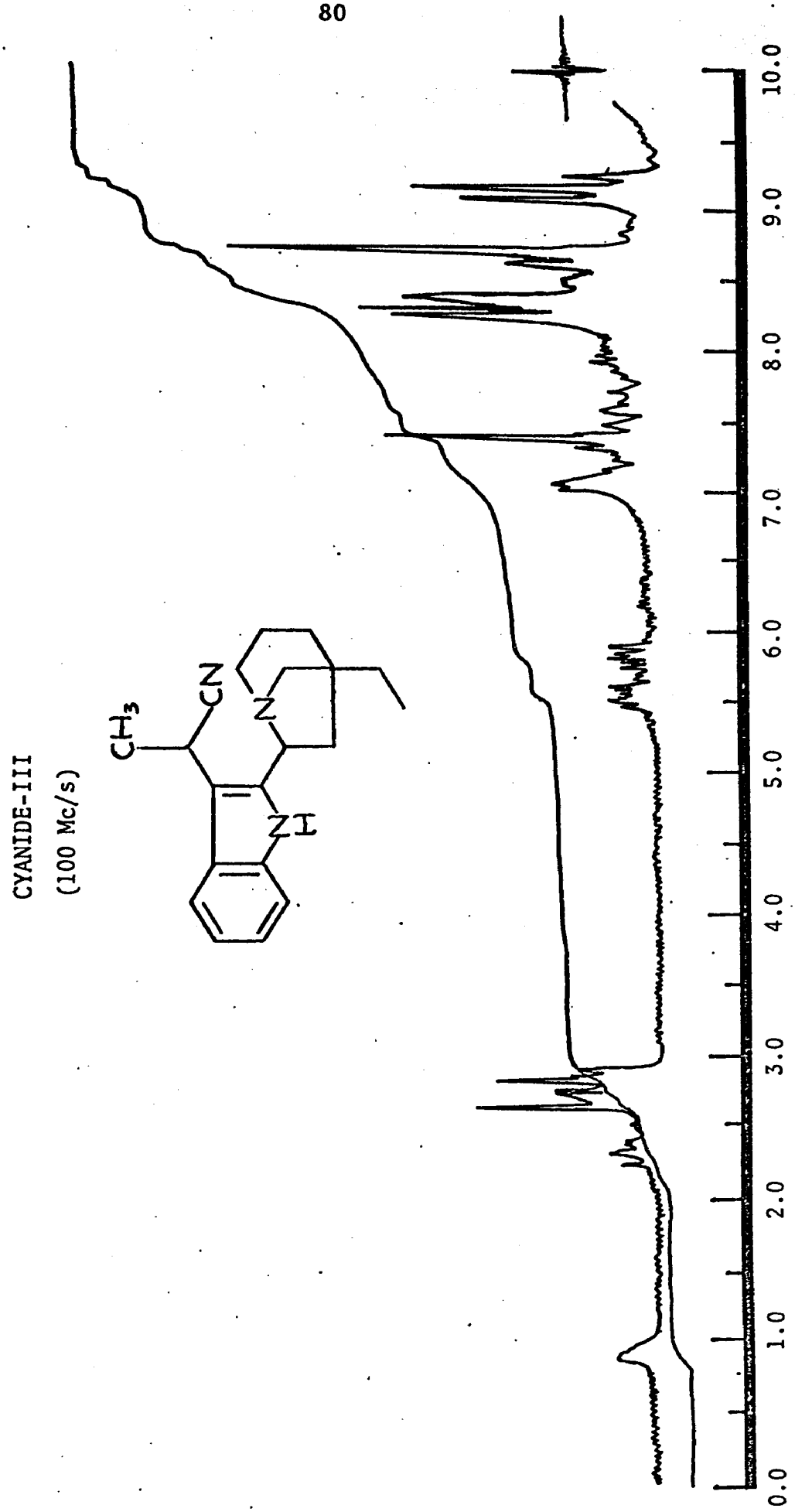

Figure 59. NMR spectrum of cyanide-III (145).

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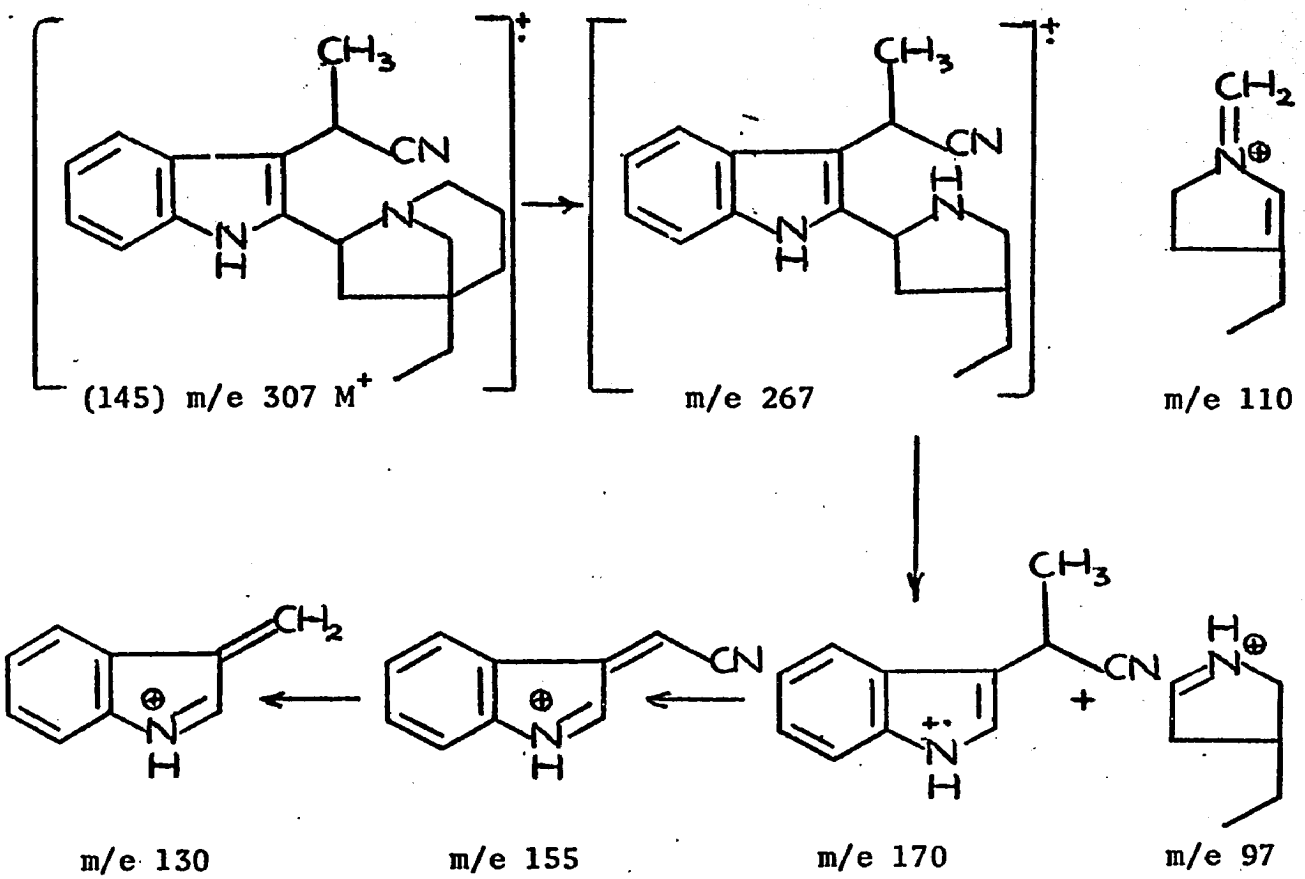

Figure 60. Fragmentation of cyanide-III upon electron impact.

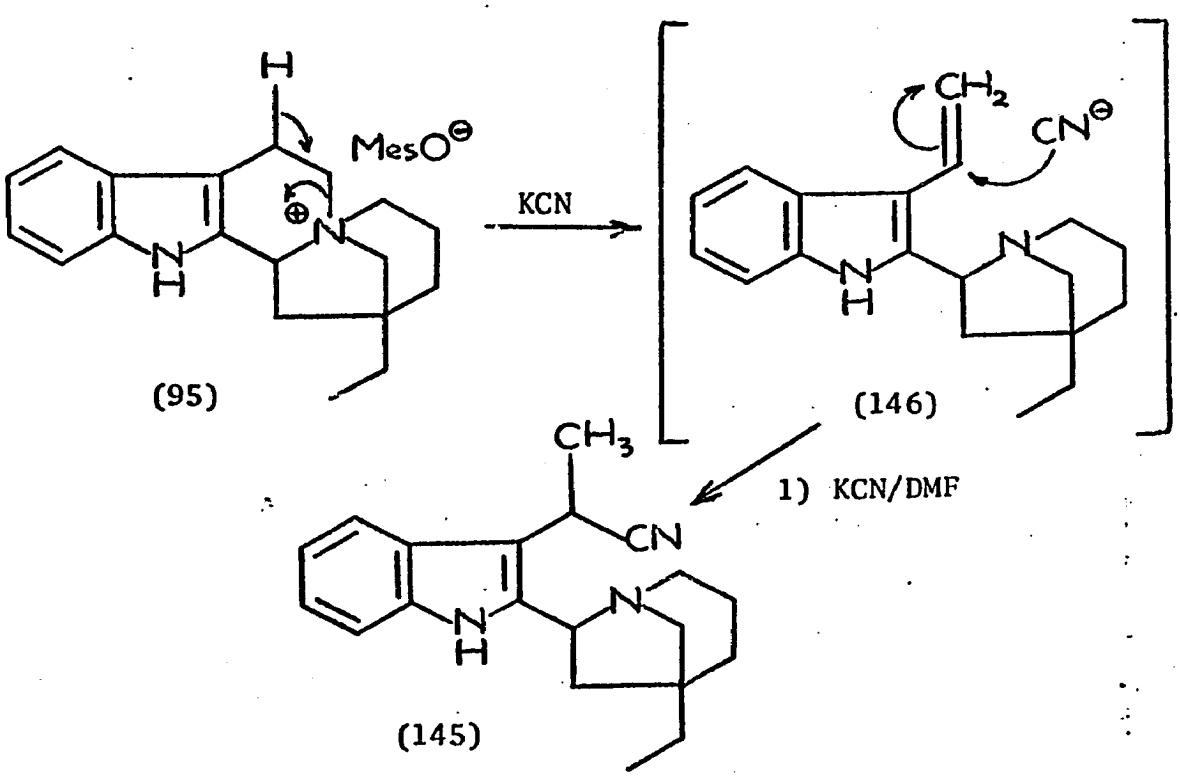

Figure 61. Possible mechanism for the formation of cyanide-III.

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reactions on 3-vinylindoles came across a very similar case to ours and they explained their results by the same mechanism (Figure 62). It seems that potassium cyanide is basic enough to promote such a type of reaction, especially at high temperatures (150°).

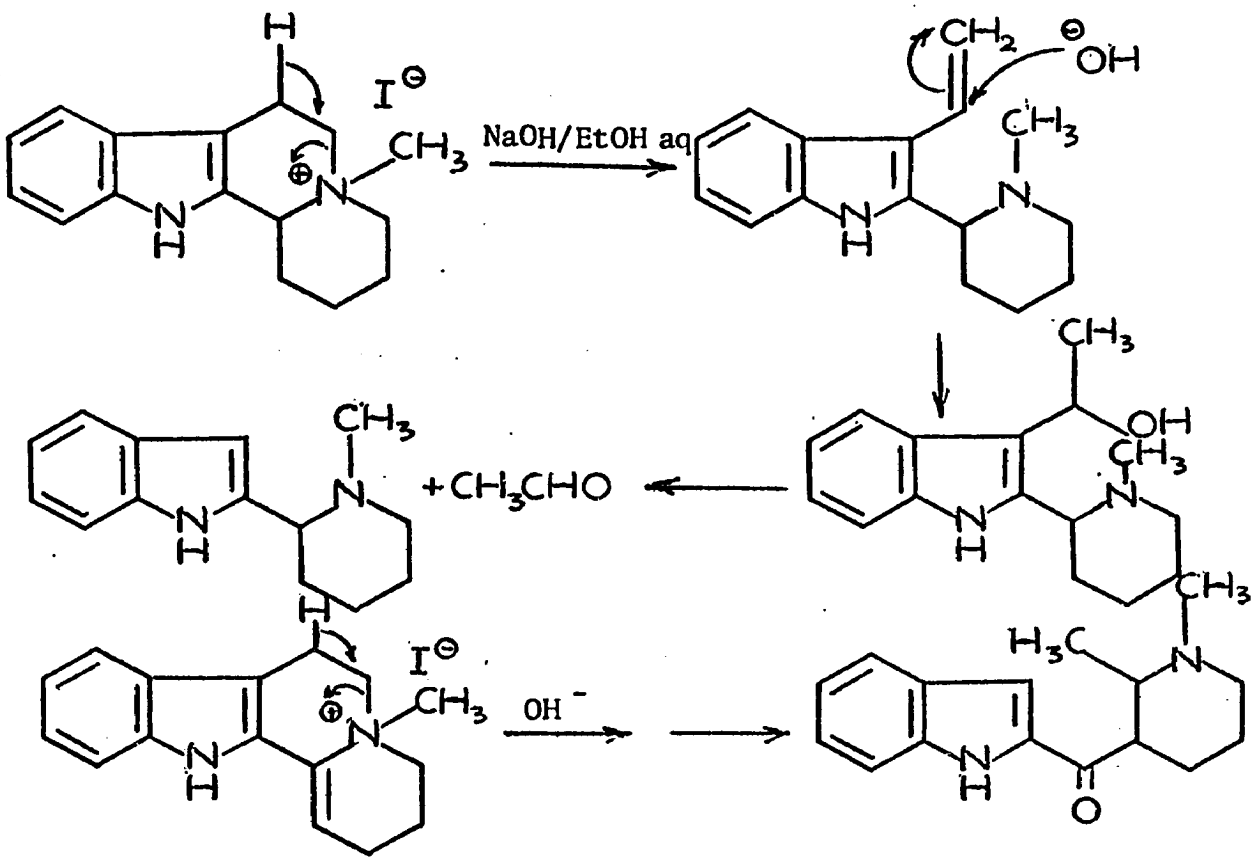

Figure 62. Mechanistic aspects of some 3-vinylindole chemistry.[78]

The introduction of a function at C-3 of a quebrachamine-type skeleton can be achieved also indirectly. For example, carbomethoxydihydrocleavamine (72) was prepared in our laboratory from dihydrocleavamine (70) by this approach.[79] This sequence is outlined in Figure 63.

In spite of the fact that this second approach has been used successfully on several occasions[80] and that it also seems straightforward - quebrachamine being commercially available - attempts to obtain the

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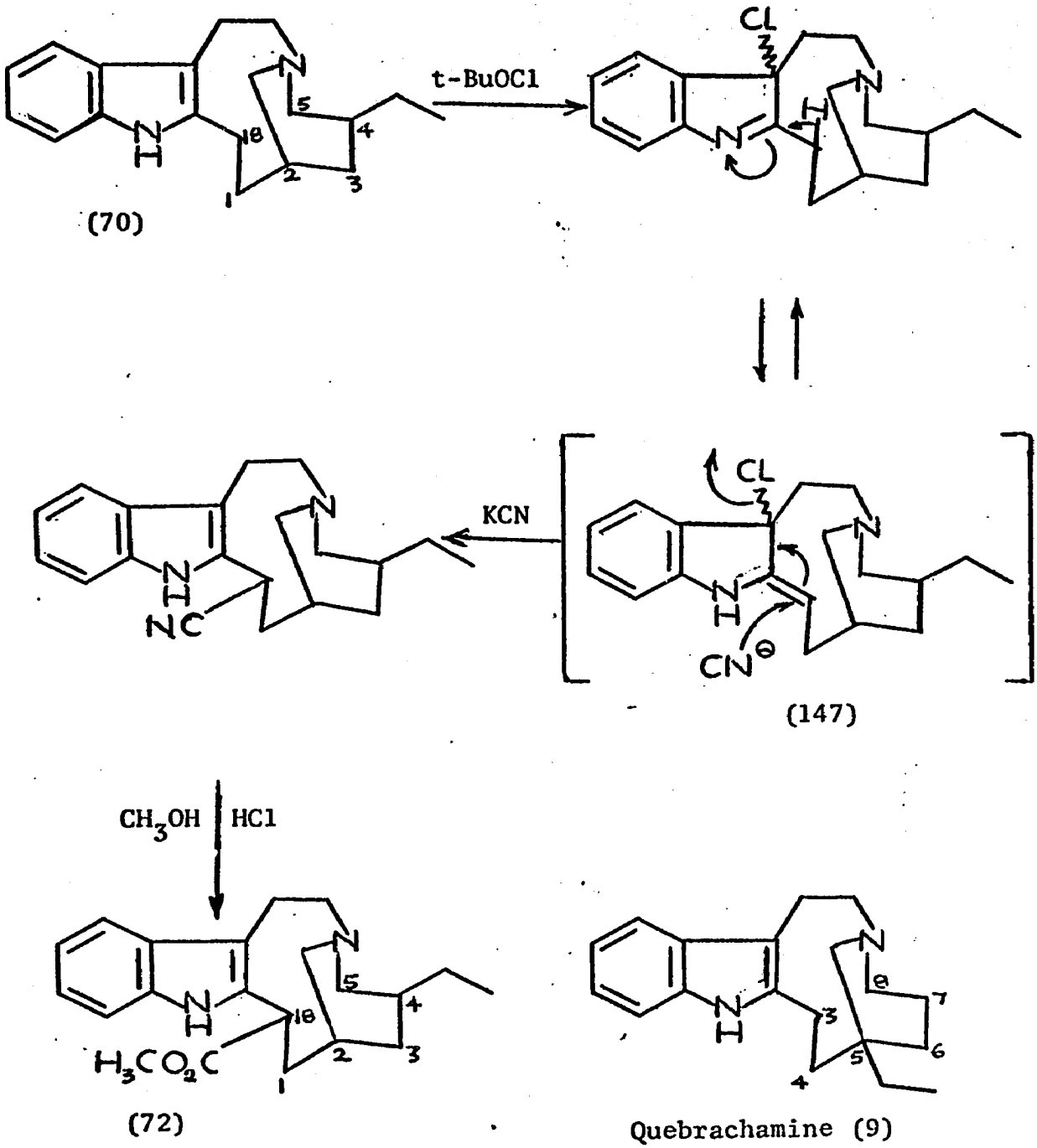

Figure 63. Synthesis of carbomethoxydihydrocleavamine (72).

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corresponding carbomethoxy quebrachamine failed.[81] The reason for this failure might be due to the fact that the close proximity of the ethyl group at C-5 in the corresponding quebrachamine skeleton inhibits the attack by the nucleophile. It also undoubtedly introduces stereochemical strain in the reaction site of the molecule forbidding the formation of the corresponding crucial reaction intermediate chloroindolenine (147) which eventually would lead to the desired product.

However in spite of the above side reactions enhanced by steric factors we tried to improve the reaction leading to the desired nitriles. In order to check the effect of solvent polarity on the reaction site, methanol, ethylene glycol, dioxane and even benzene were used with an excess of potassium cyanide (usually four-fold excess). The reaction time was also extended up to 9 hours. The reactions were checked every half an hour, but usually unreacted starting material was recovered or other minor products were formed. None of the desired cyanides was found, the only exception being the reaction with ethylene glycol, when small amounts were noticed (TLC information only). If we compare these results with the successfully applied reaction (although in low yield) it seems that DMF is a unique solvent for this purpose. We also noticed during numerous attempts that depending on reaction conditions employed varying amounts of the cyanides were obtained. For example by maintaining dry conditions, the amount of cyanide-III decreased, while the total yield of cyanides-I and II did not increase. In this instance more starting material was recovered from the aqueous layer. At this time we did not consider it worthwhile to spend more time trying to improve this reaction.

For the cyanides-I and II the chemical shift of the C-3 proton can be easily explained by considering several conformations similar to those

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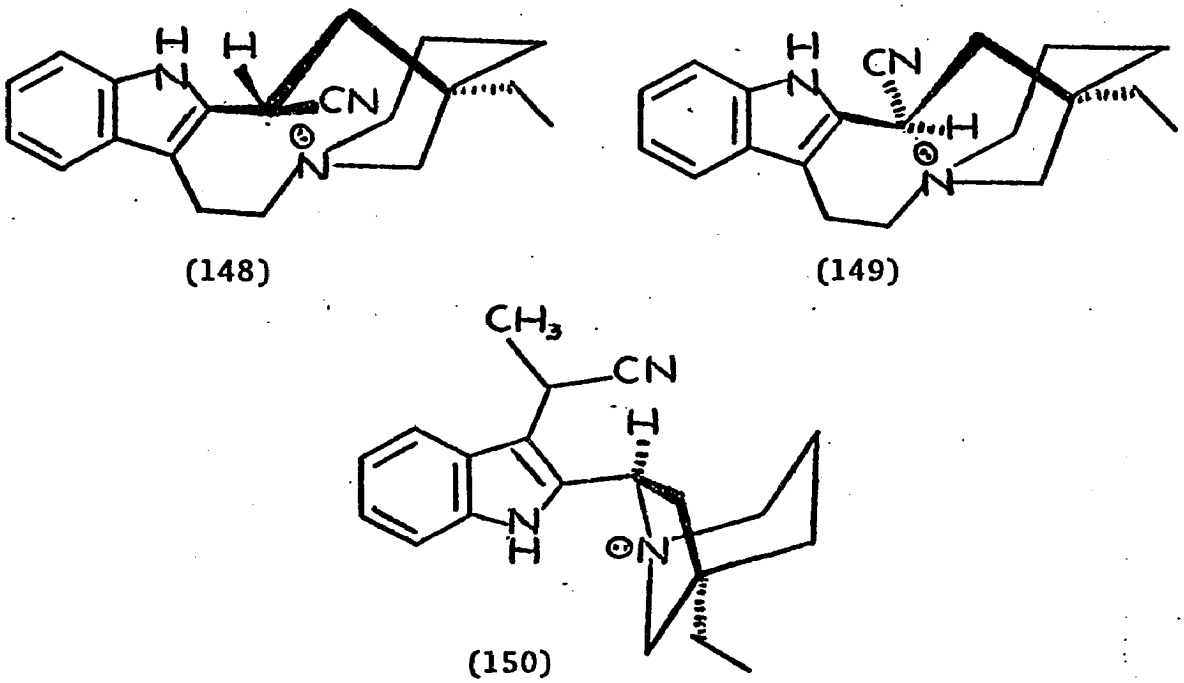
proposed by Kompis.[4] According to this proposal, the C-3 proton is away from (case of cyanide-I) or close to (case of cyanide-II) the lone pair of electrons on nitrogen, resulting in magnetic shielding or deshielding of this proton. These molecules are drawn out in Figure 64 to illustrate this



(148) (149)

(150)

Figure 64. Prospective formulae showing the relative shielding of the C-3 proton due to its spacial orientation.

situation. In these terms structures (148), (149) and (150) are assigned to cyanides-I, II and III respectively.

Alkaline hydrolysis of a mixture of these cyanides-I and II or either of them separately followed by esterification gave the same reaction products. Rapid filtration of the crude product on an alumina column using benzene–chloroform (1:1) as eluant gave the esters in a crude yield of 81%. Further purification of this material by column chromatography on silica gel afforded

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a mixture of two epimers (47%) in a 2:3 ratio (TLC and NMR information). The more abundant material had the same TLC properties as an authentic sample of naturally occurring vincadine, kindly provided by Dr. I. Kompis. Separation of these two epimers by preparative TLC gave colourless semi-crystalline materials, which turned dark quickly during the usual handling. For example, when we tried to crystallize or sublime them extensive decomposition was apparent in spite of extensive precautions. However both epimers were reasonably stable in the dark and at low temperature (refrigeration).

The major component had a normal indole ultraviolet absorption (292, 286 and 227 mμ) which compared well with the values reported for vincadine itself.[82] The infrared spectrum, showing a strong carbonyl absorption at 1725 cm^{-1} and an NH peak at 3380 cm^{-1}, was also in agreement. The most important features of the NMR spectrum (Figure 65) were a strong methyl singlet at τ 6.28 ($COOCH_3$), a one-proton quartet at τ 6.20 (C-3 H, J_{AB}=6 and J_{AC} = 2 cps) and a methyl triplet at τ 9.16. In addition, an envelope of four aromatic protons centered at τ 2.8 and a broad singlet for the proton on the indole nitrogen at τ 1.04 were present. High resolution mass spectrometry established the formula $C_{21}H_{28}O_2N_2$ (found: 340.215; calc: 340.215). The mass spectrum (Figure 66) had significant peaks at m/e 124, 138, 210, 215, 281 and 340 (M^+), and it was superimposable with the one of naturally occurring vincadine. A rationalization for some of the fragments is presented in Figure 67.

The isomeric nature of the minor component was established by high resolution mass spectrometry, revealing the formula $C_{21}H_{28}O_2N_2$ (found: 340.215; calc: 340.215). The indole chromophoric system was present in this epimer (293, 287 and 227 mμ), while the infrared spectrum had a strong carbonyl absorption at 1720 cm^{-1} and a NH absorption at 3380 cm^{-1}. The NMR spectrum (Figure 68) was similar to that of the major vincadine and was

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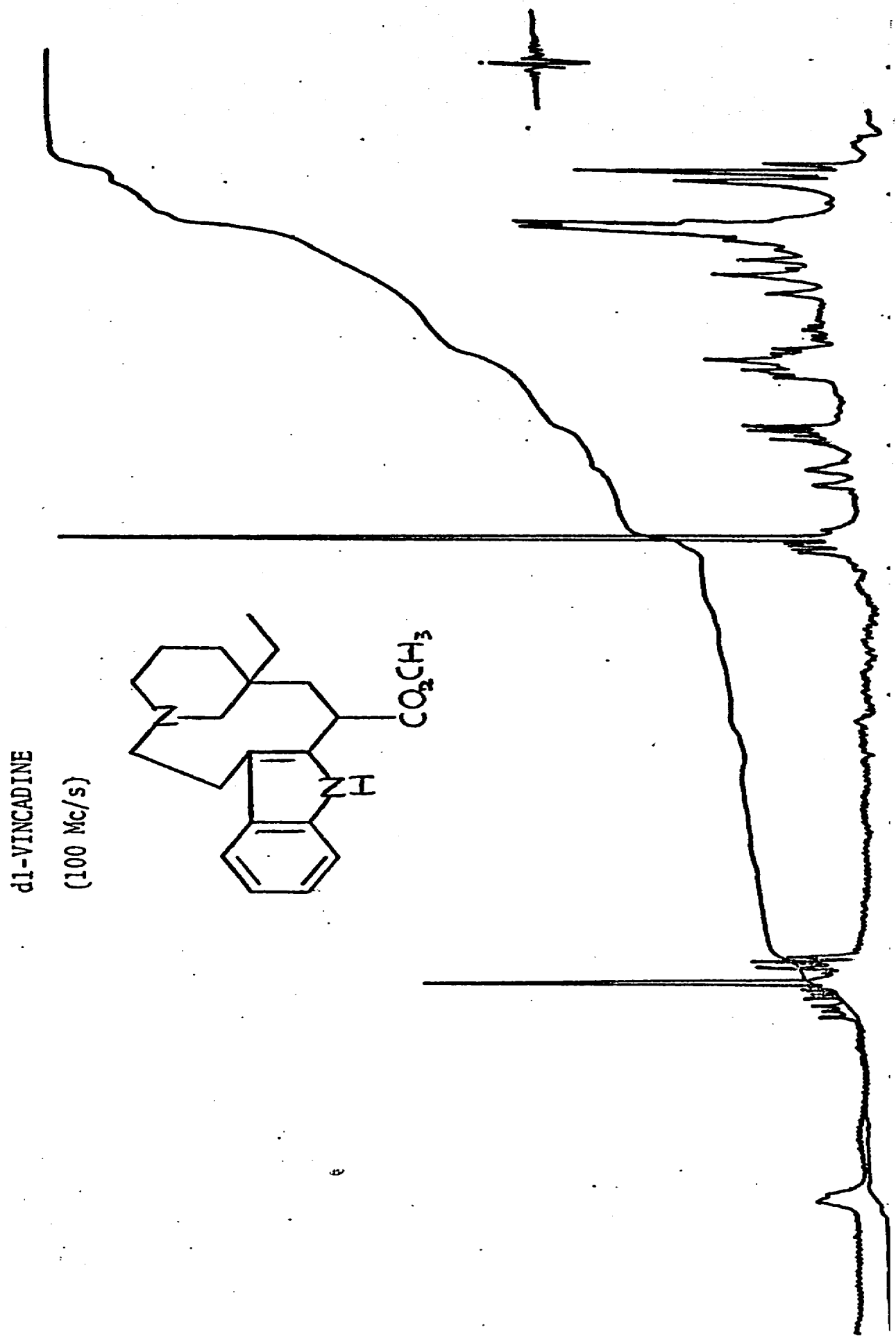

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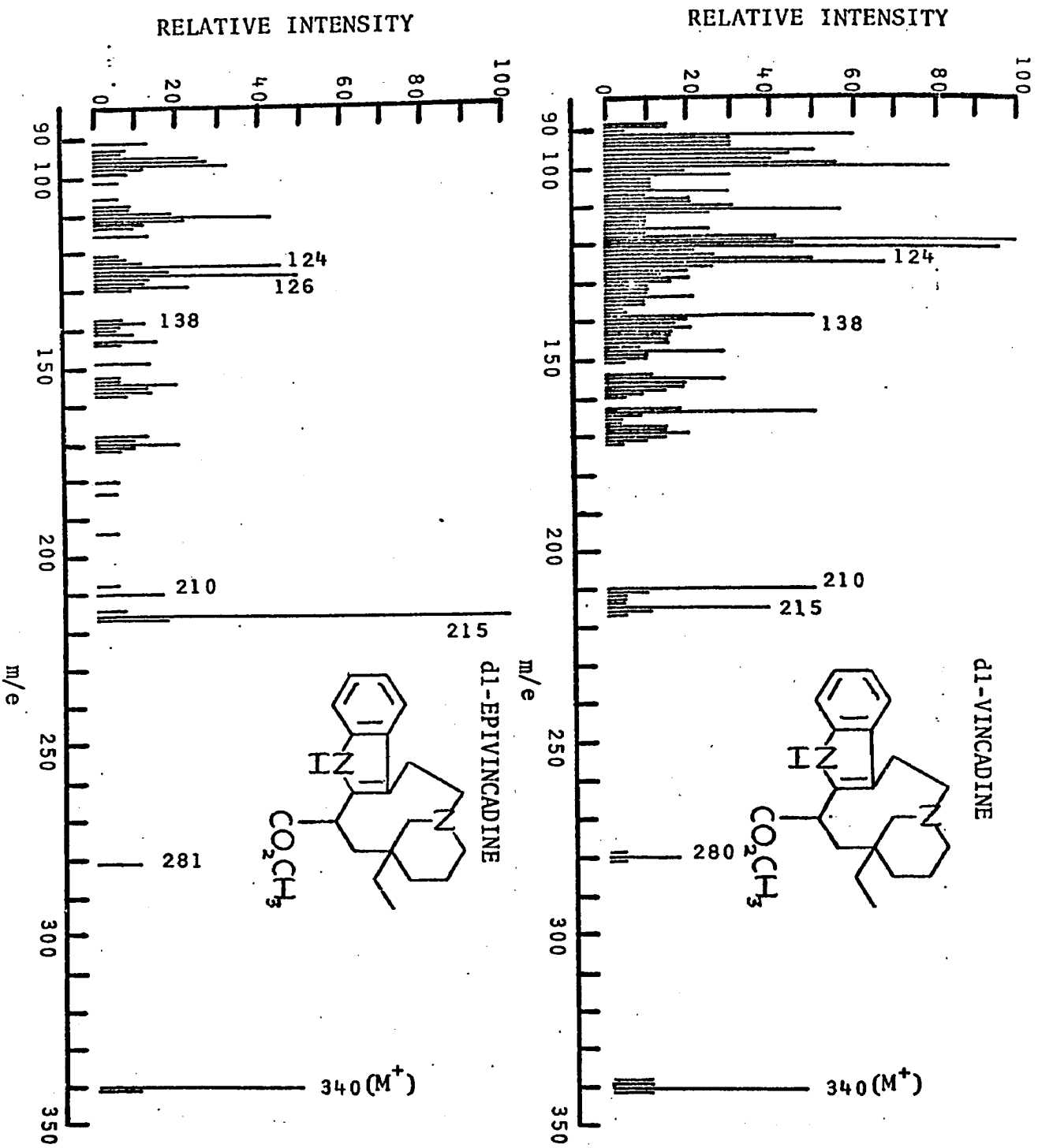

Figure 66. Mass spectra of dl-vincadine (3) and its epimer.

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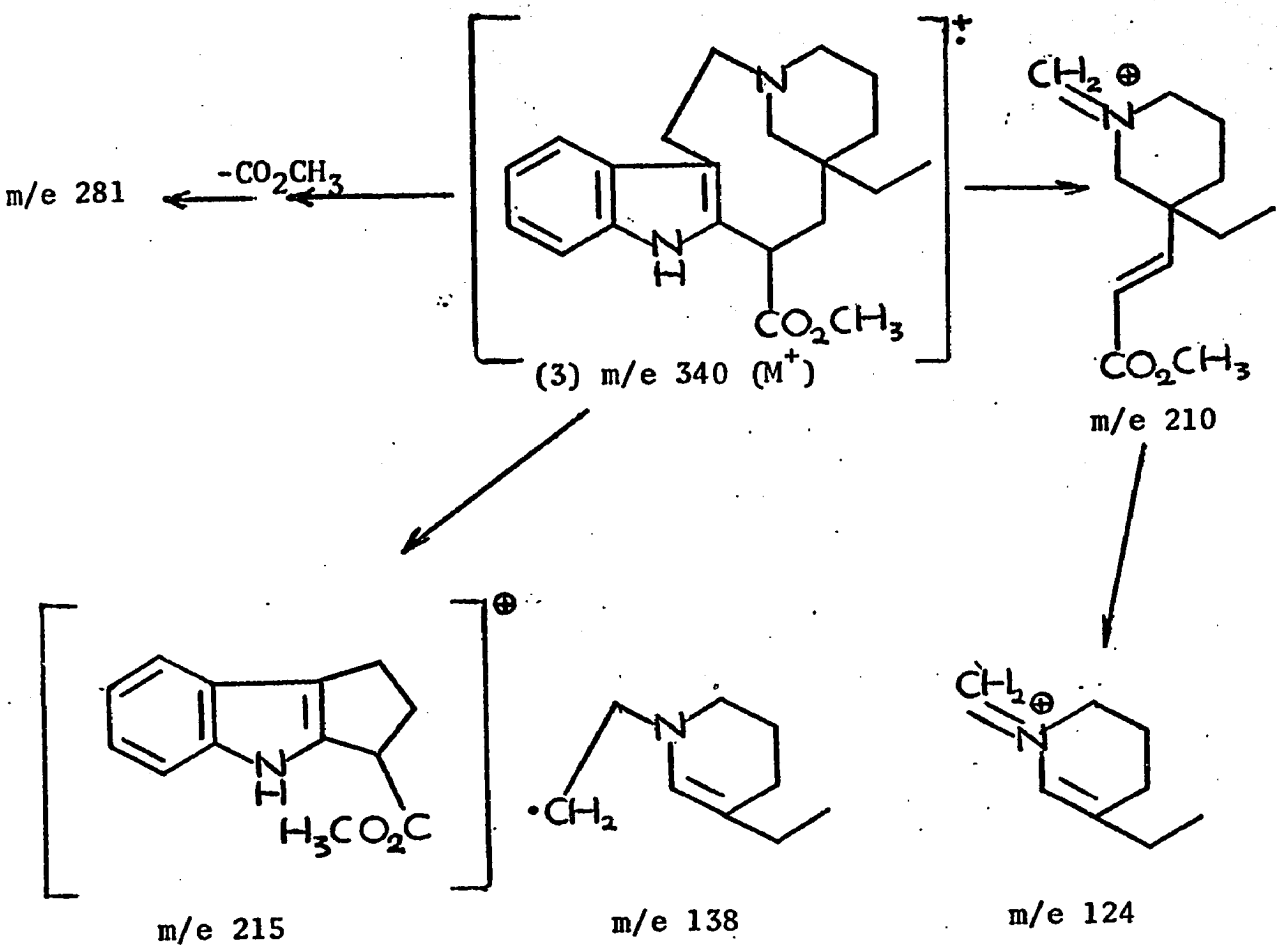

Figure 67. Plausible fragmentation of the epimeric vincadines upon electron impact.

very informative. First of all the C-3 proton signal had shifted from τ 6.20 to 4.41, with coupling constants of 10 and 3 cps. The simultaneous upfield shift of both methyl groups of the carbomethoxy and ethyl functions to 6.35 (singlet) and τ 9.33 (triplet) respectively was evident. These results are in agreement with expectation in view of factors similar to those previously explained for the case of the epimer cyanides (Figure 64).

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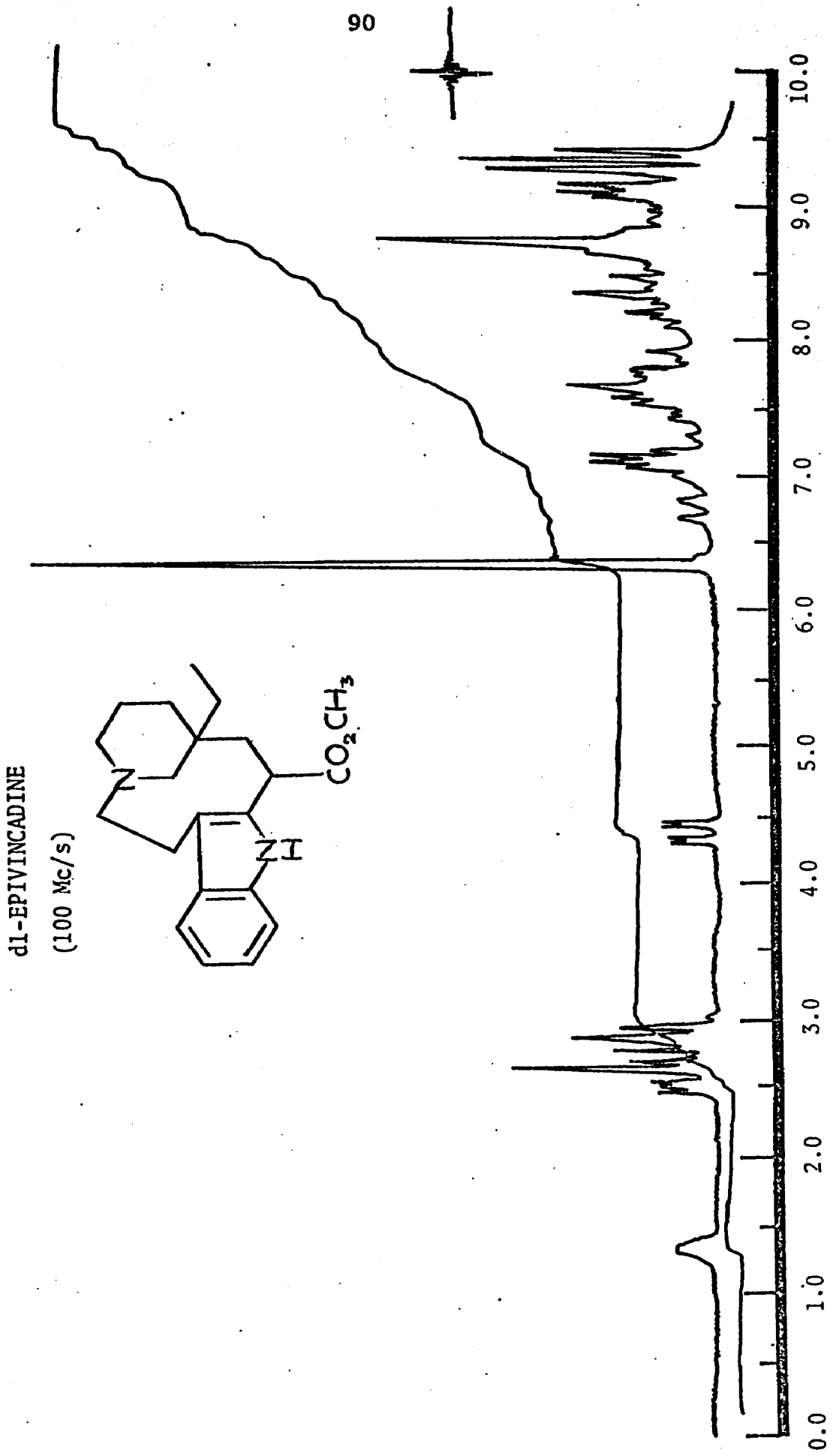

Figure 68. NMR spectrum of dl-epivincadine.

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Finally, the mass spectrum of this epimer (Figure 66) showed the same fragmentation as that of the major isomer, bearing significant peaks at m/e 124, 138, 210, 215, 281 and 340 (M^+). The preferable fragmentation due to the differences in the stereochemistry of these epimers, especially the peak at m/e 215, correlates excellently with the case of vincaminoreine and vincaminorine.[77] According to the data presented above and further experimental evidence given below, the major synthetic component was clearly dl-vincadine while the minor isomer was dl-epivincadine.

It is pertinent to comment at this point about the stereochemical differences at C-3 already proposed above for the cyanides and esters obtained in the synthetic sequence and to corroborate these proposals with further experimental evidence. First of all, since each cyanide-I or II reacted separately under the same conditions and gave the same two dl-pairs of methyl esters it was clear that they were structurally identical except in terms of stereochemistry at C-3. Furthermore it was obvious that epimerisation took place at C-3 during the basic hydrolysis of the cyanides (20% KOH/150°). When naturally occurring vincadine was treated with sodium methoxide in methanol for 1/2 hour, it also gave a mixture of epimers which was identical with the one obtained from the hydrolysis and esterification of either of the cyanides (TLC investigation, superimposable IR). This result established that the natural system behaved in an analogous manner to the synthetic material.

It has been proven that acidic hydrolysis of natural vincadine gives (+)-quebrachamine (155) (Figure 69). Also, vincadine upon N-methylation with methyl iodide in liquid ammonia gives vincaminoreine (151).[83] In the same manner vincaminoreine (151) and its epimer vincaminorine (152) by acid hydrolysis (5 N HCl/heat) are converted to N-methyl (+)-quebrachamine

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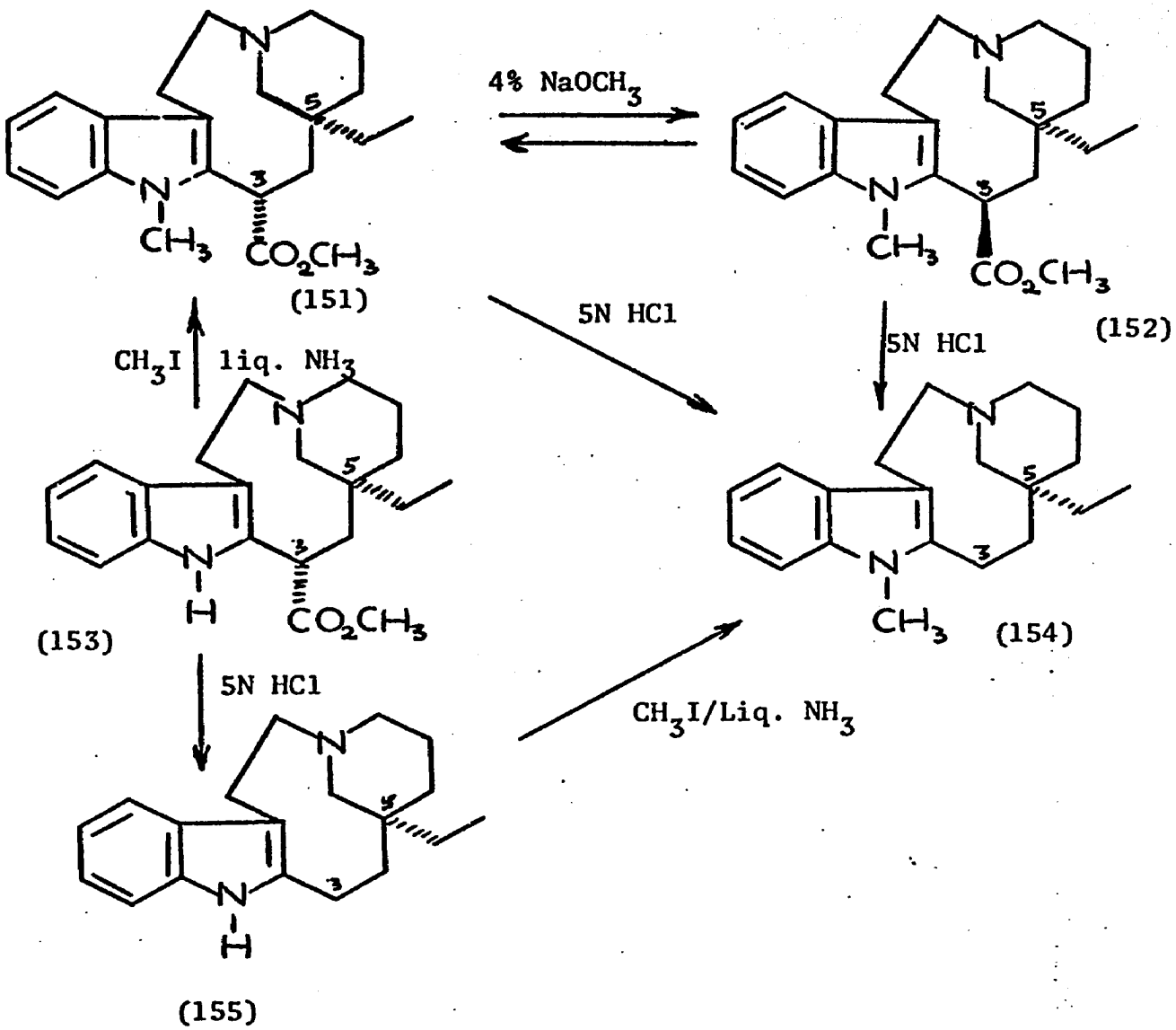

Figure 69. Chemical interrelations of some natural alkaloids.

(154).[77] Finally, vincaminorine was equilibrated in the presence of sodium methoxide to vincaminoreine. These results indicate that vincadine, vincaminoreine and vincaminorine have the same stereochemistry at C-5. Therefore they must differ in the stereochemistry at the only other asymmetric center, namely C-3. The absolute configuration of (+)-quebrachamine is known from the work of Schmid et al.[84] and its relative configuration is as indicated. Since the relative configuration of vincaminoreine and

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vincaminorine is as shown in Figure 69 vincadine must also possess the above indicated relative configuration (153). On this base the synthetic dl-vincadine and dl-epivincadine can be represented as in Figure 70.

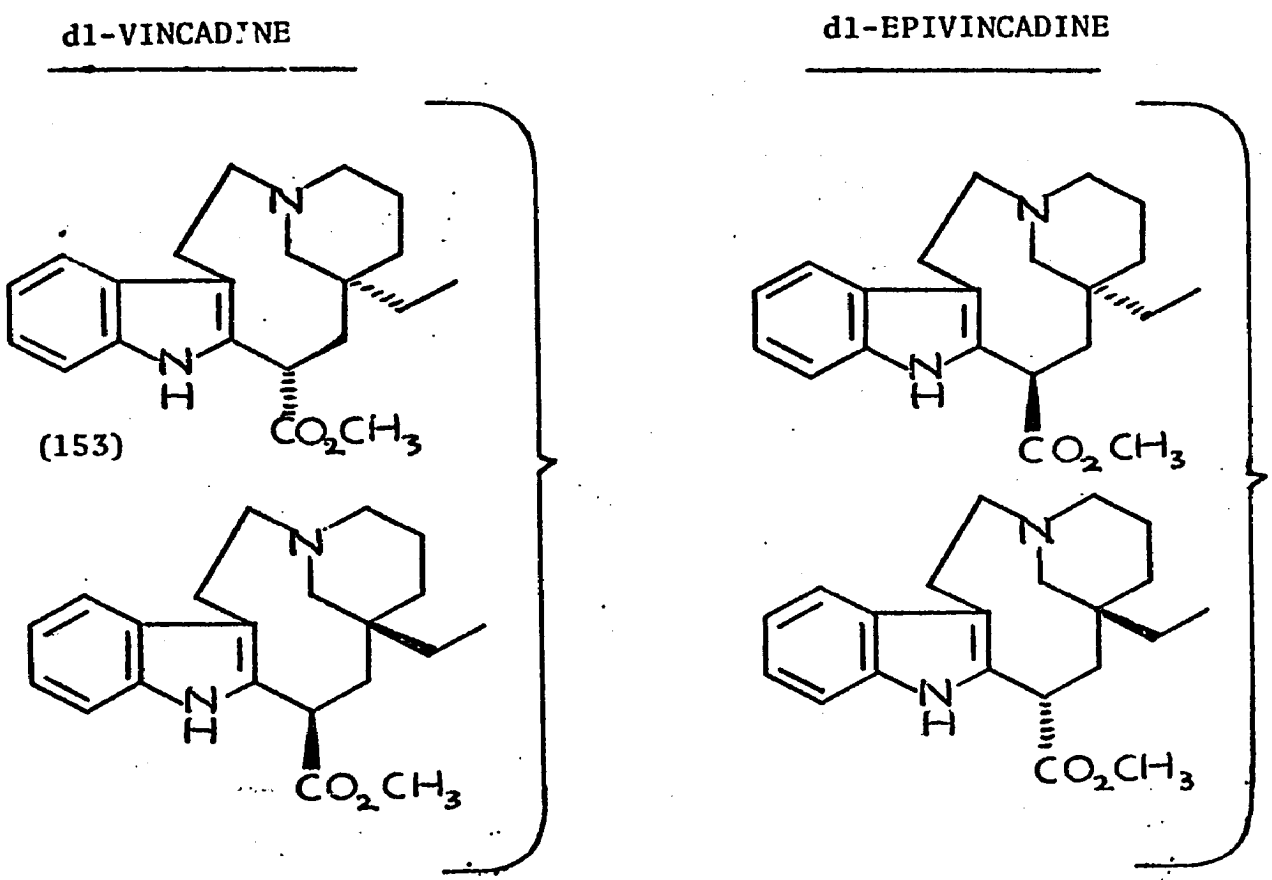

Figure 70. Relative configurations of dl-vincadine and dl-epivincadine.

Having completed the total synthesis of dl-vincadine (3), the total synthesis of dl-vincaminoreine (4) and dl-vincaminorine (5) was also in hand, as well as of N-methyl-dl-quebrachamine (8) in view of the previously mentioned interconversions, as given in Figure 69.[77,83]

An entry into the pentacyclic series exemplified by vincadifformine[85,86] and minovine[4,82] was now possible by means of the transannular cyclization approach.[42] When vincadine (156, R = H) and vincaminoreine (156, R = CH_3)

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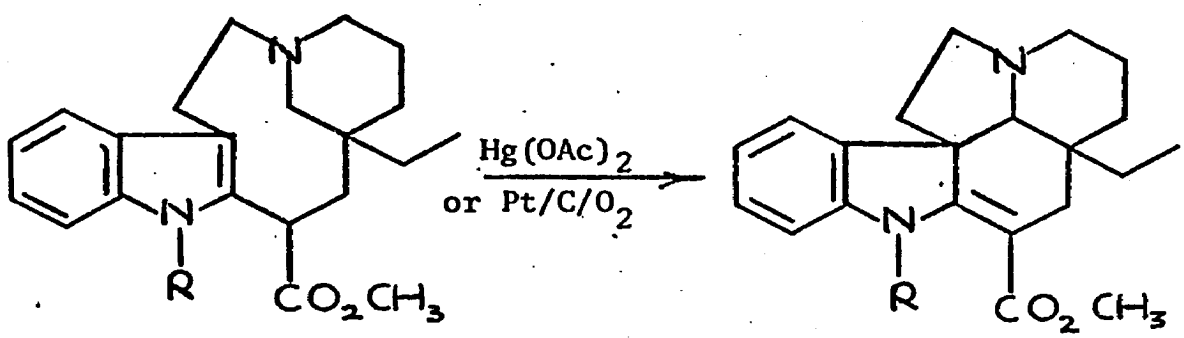
were reacted with either mercuric acetate, as before, or oxygen in the presence of a catalyst (5% platinum on charcoal)[39] they provided vincadifformine (157, R = H) and minovine (157, R = CH_3) (Figure 71) identical in every



(156) (157)

Figure 71. Transannular cyclization of vincadine and vincaminoreine to vincadifformine and minovine respectively.

respect (infrared, ultraviolet, TLC) with authentic samples.[87]

In order to check the versatility of these approaches to the total synthesis of various indole alkaloids it was desirable to try other substrates, to see the effect of any other functional groups might have. It was also attractive and wise to choose such substrates that might eventually lead to naturally occurring alkaloids.

3) Extension of the approach to alkaloids bearing an oxygen function in the aromatic ring.

For this purpose we thought that a sequence analogous to the one previously employed (Figures 24 and 72) would be sufficient. The diethyl ester (90) was available from our previous experiments. We prepared

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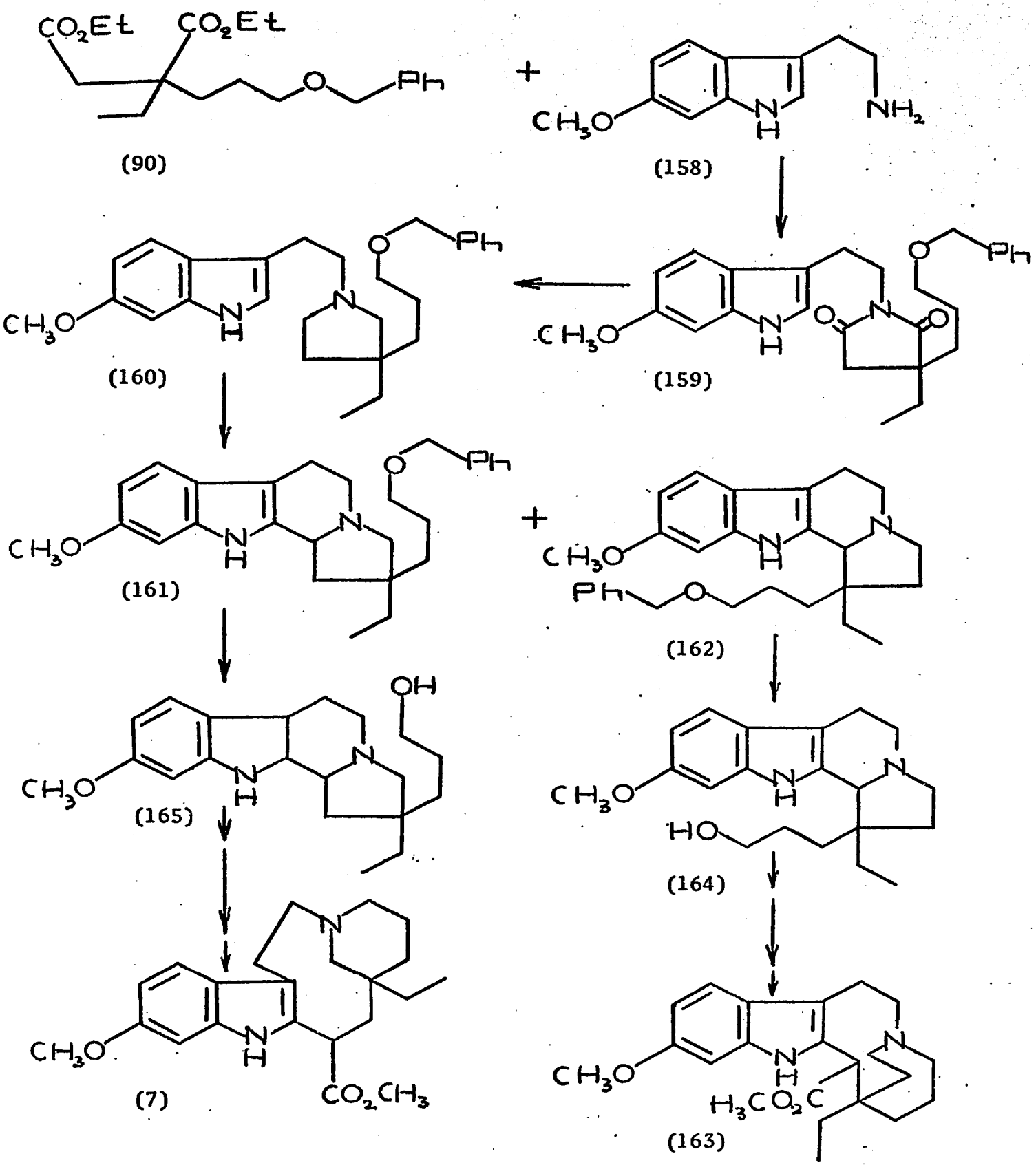

Figure 72. Reaction sequence leading to total synthesis of dl-vincaminoridine (7).

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6-methoxytryptamine (158) by a sequence shown in Figure 73, starting from

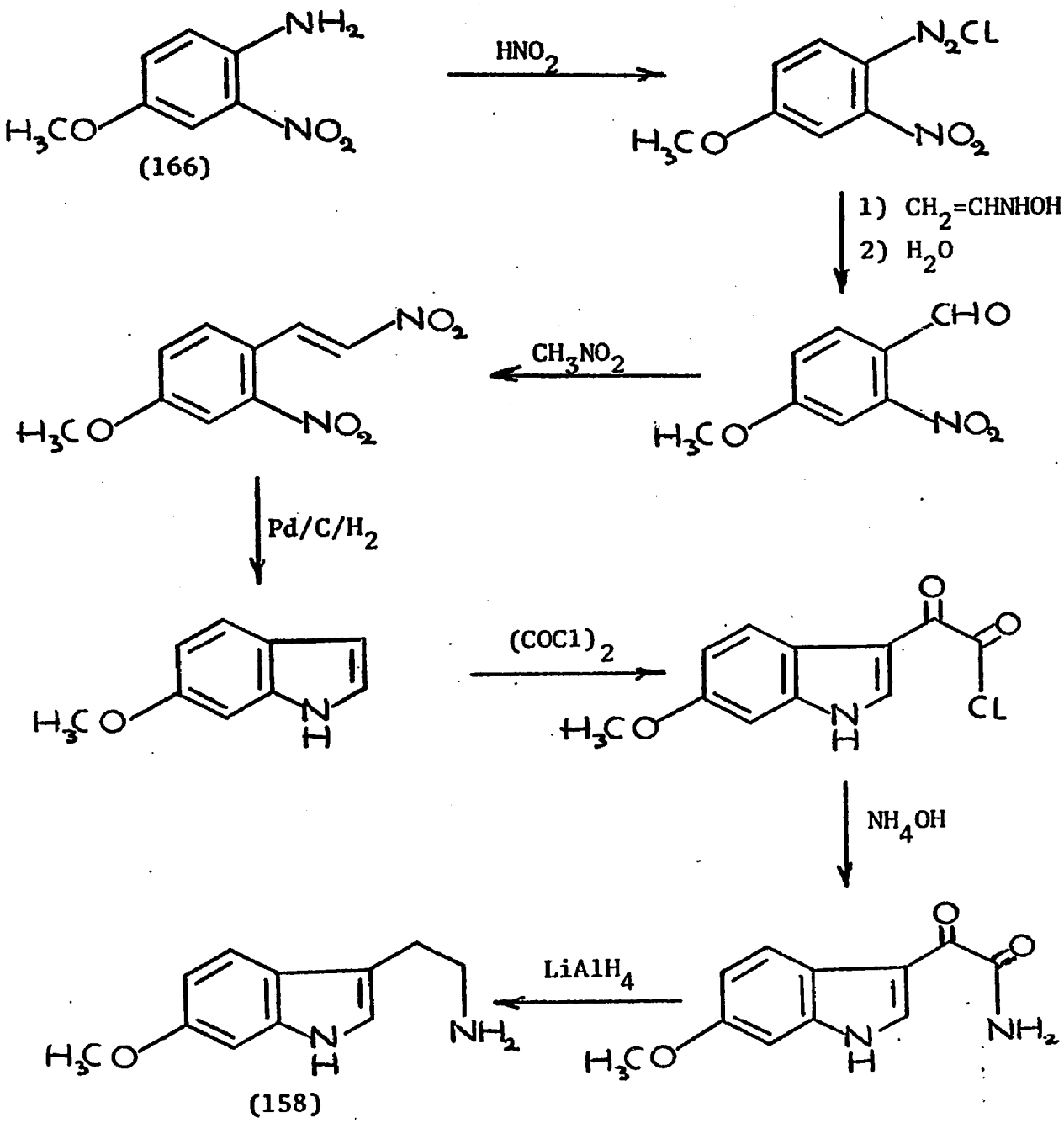

Figure 73. Preparation of 6-methoxytryptamine.[88]

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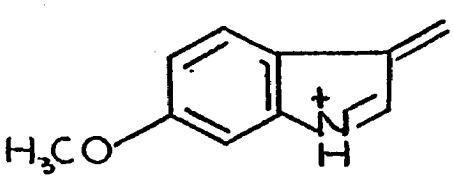
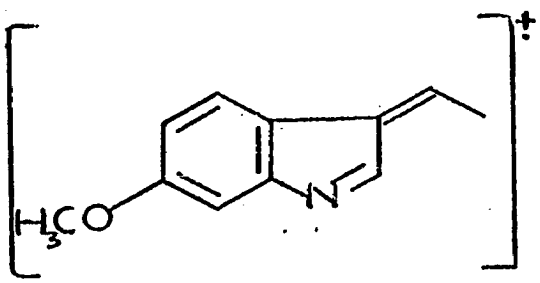
2-nitroanisidine (166), a commercially available compound.[88]

Condensation of the diethyl ester (90) with 6-methoxytryptamine (158) (molar ratio 3:1) under reflux in 2-(2-ethoxyethoxy)ethanol for 56 hours afforded a dark gum. Chromatography on neutral alumina (Shawinigan, activity III) gave the desired pure product (159) in 63% yield. A fair amount of unreacted diester as well as some unreacted amine (158) was recovered from the aqueous layer. The desired product (159), a yellow gum, had a methoxy indole chromophore in the ultraviolet spectrum with maxima at 292.5, 273, and 277.5 mμ. Its infrared spectrum showed a lactam absorption at 1680 cm^{-1} (very strong) and 1760 cm^{-1} (medium), also the presence of NH absorption at 3380 cm^{-1}. The NMR spectrum was most informative (Figure 74). The 1,2,4,-trisubstituted benzene system of the indole portion was apparent by a doublet at τ 2.48 (J_{ortho} = 10 cps) a quartet at τ 3.16 (J_{ortho} = 8 cps, J_{meta} = 2cps) and a doublet at τ 3.25 (J_{meta} = 2 cps). The proton at C-2 of the indole ring was overlapping with the doublet at τ 3.25, while a singlet at τ 6.21 was assigned to the methoxy protons. Distillation of this material gave a yellowish glass which analysed for $C_{27}H_{32}O_4N_2$, and high resolution mass spectrometry agreed with this formula (found: 448.236; calc: 448.236). In the mass spectrum (Figure 75) significant peaks at m/e 91, 160, 173 and 448 (M^+) were present:



m/e 160



m/e 173

m/e 91

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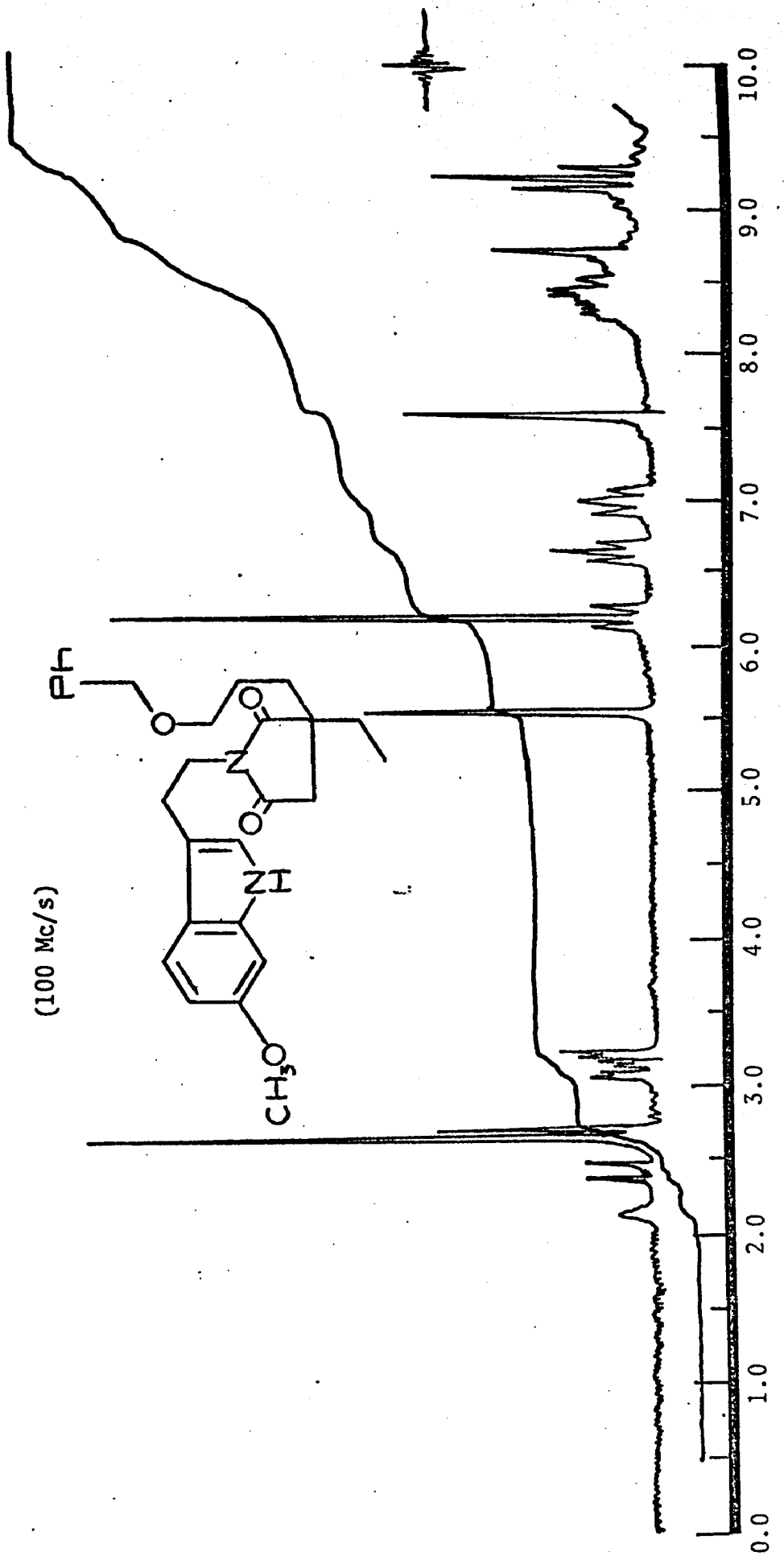

Figure 74. NMR spectrum of 6-methoxy imide (159).

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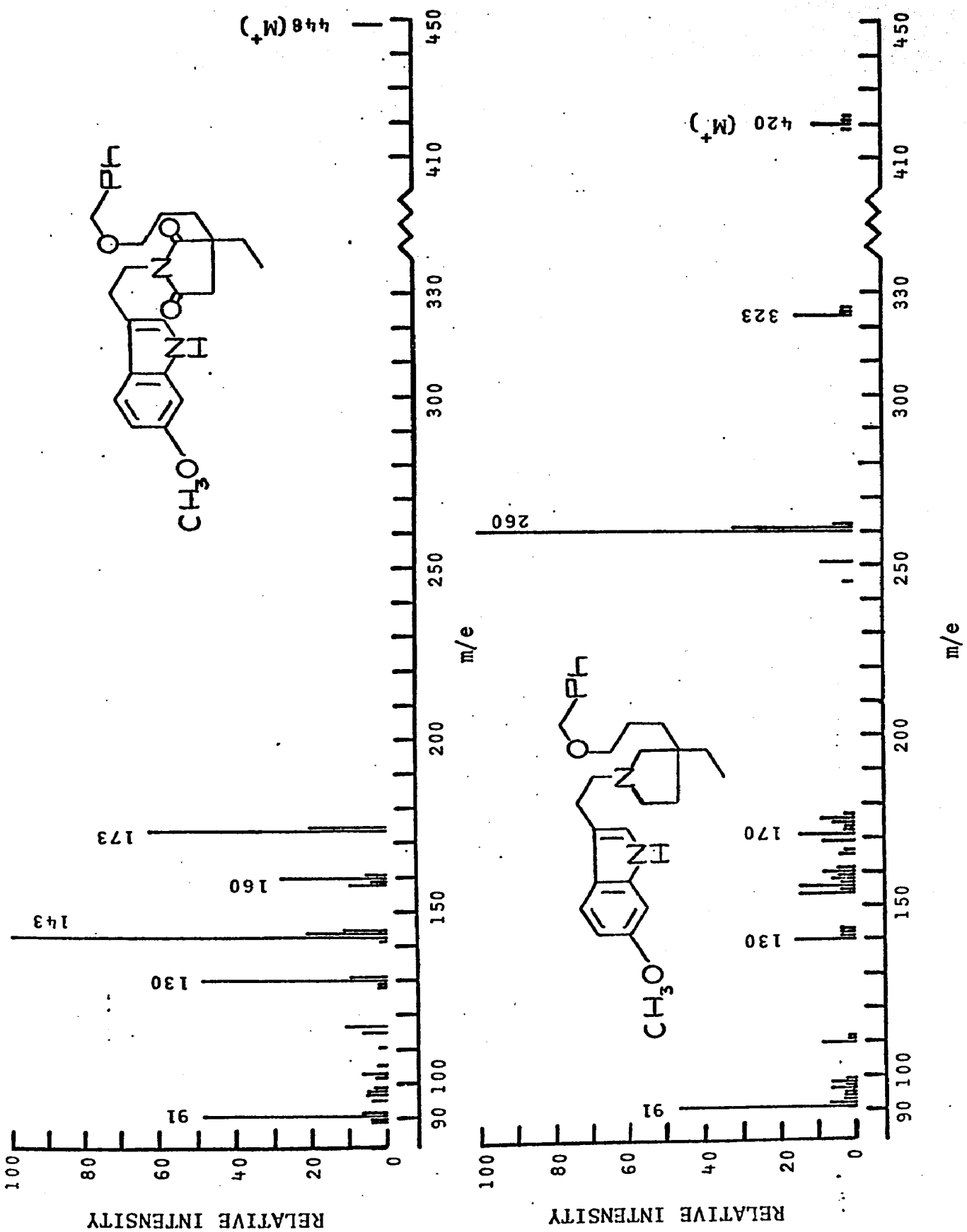

Figure 75. Mass spectra of 6-methoxy imide (159) and amine (160).

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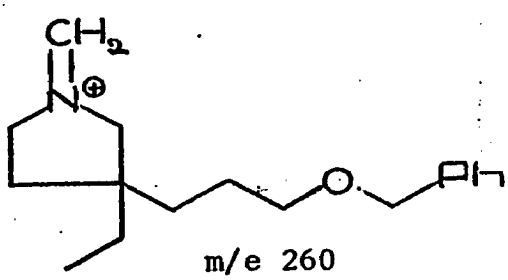
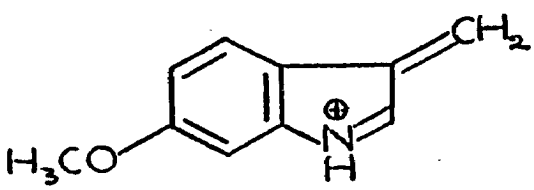
The imide (159) was submitted to lithium aluminum hydride reduction in refluxing tetrahydrofuran (10 hours) to give a brown gum. Column chromatography on alumina (Woelm) and elution with benzene-ethyl ether (4:1) gave the pure amine (160). This amine could also be purified by vacuum distillation (260°/0.03 mm.). Mass spectrometry and elemental analysis of this material revealed the formula $C_{27}H_{36}O_2N_2$ for this compound. The ultraviolet spectrum again showed a normal 7-methoxy indole chromophore, while in the infrared spectrum complete removal of the characteristic succinimide carbonyl absorption was evident. In the NMR spectrum besides the expected small shifts, the upfield of the triplet at τ 6.23 ($-CCH_2CH_2N-$) and also the appearance of a new triplet at τ 7.38 ($-CCH_2\underline{CH_2}N$) were evident (Figure 76). The mass spectrum (Figure 75) of this compound had the expected peaks at m/e 91, 160, 170, 260 (base peak) and 420 (M^+) presumably due to the following fragments:

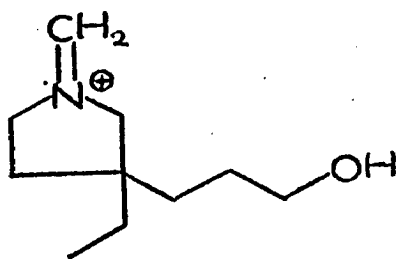
m/e 91



m/e 260



m/e 160



m/e 170

The next step was the Pictet-Spengler type cyclization at the α-position of the indole ring. The mercuric acetate reaction again seemed convenient since we had ample previous experience with it. When the amine (160) was

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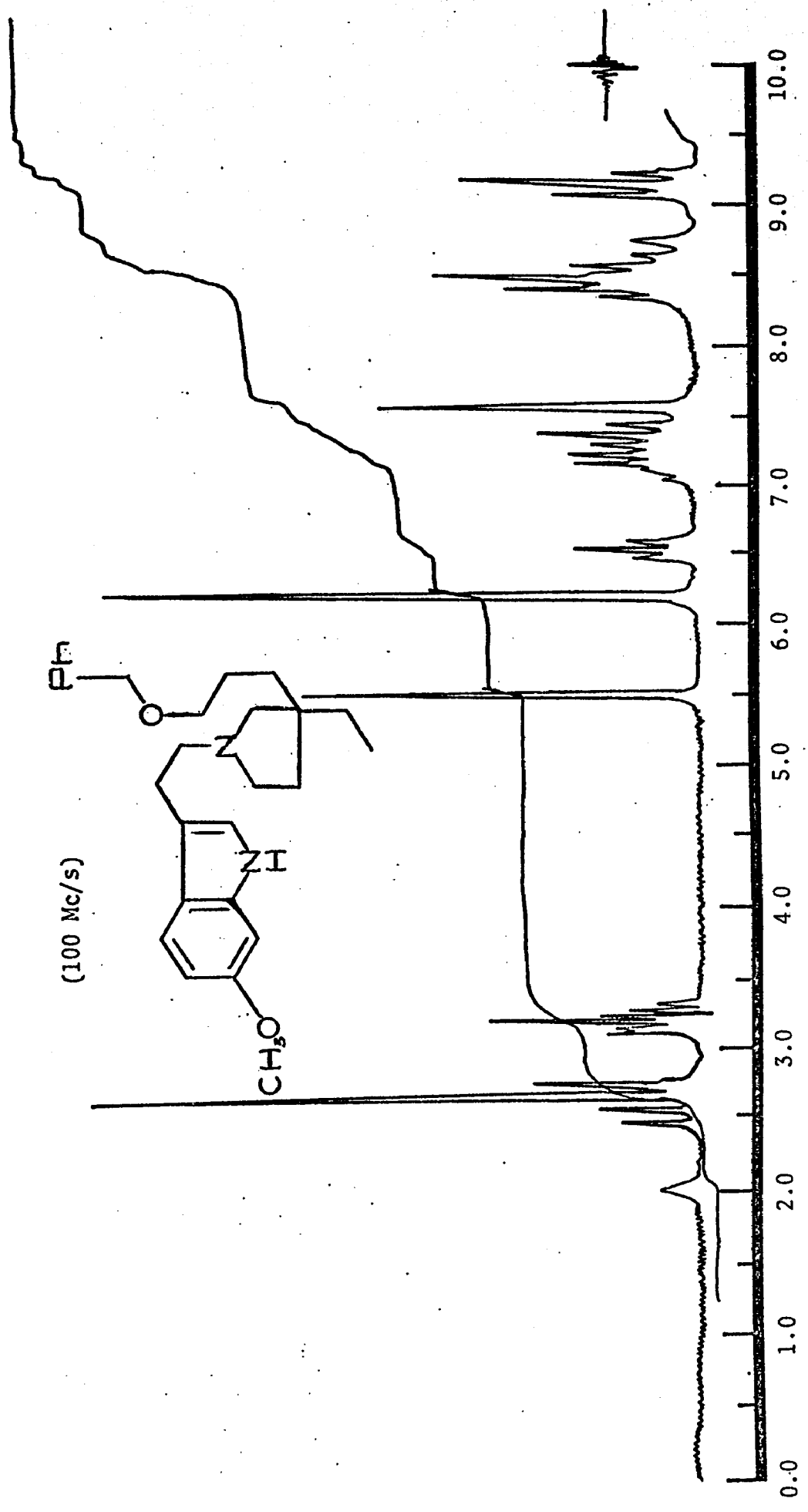

Figure 76. NMR spectrum of 6-methoxy amine (160).

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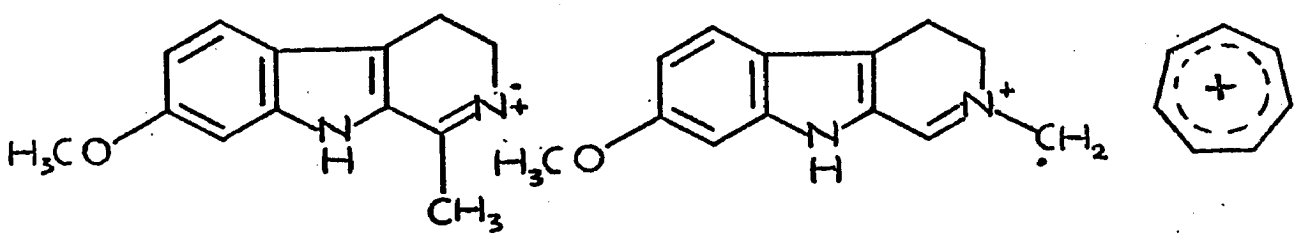
heated at 105° for 2 hours with a ten-fold excess of mercuric acetate in aqueous acetic acid, the crude reaction product was a dark gum. Column chromatography of this material gave several products. The major component (25%) was a very polar material which did not move from the base line of the chromatoplate (alumina/chloroform). Consequently it was felt that this material may result from air oxidation or was perhaps a mercuric salt.[40] Starting material (14%) was also recovered from this reaction. Two less polar spots on the chromatoplate seemed to be the epimers of the cyclized product. Separation and purification of the more polar component by preparative TLC, gave a pure product (2%) which had a normal indole ultraviolet spectrum (297, 270 and 227). The mass spectrum had a strong molecular peak at m/e 418 which showed that the cyclization took place and in addition to the base peak at m/e 214 and the one at m/e 91, other familiar peaks previously mentioned were also present. This material was not in sufficient quantity to establish its complete structure. Due to the poor yield we attempted to improve the conditions in this reaction. The reaction was



m/e 214 m/e 214 m/e 91

carried out as before except that we changed the solvent to methanol and the reflux period (at 65°) continued for 12 hours. At this time less starting material was present and the least polar component was the major compound (TLC information). While we were in the process of identifying these two

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reaction products the application of aldehyde (118) became apparent (see Figure 29). The high yields of the subsequent condensation-cyclization reaction applied in a previous series, (Figure 37) and the very low yields of this mercuric acetate cyclization forced us to abandon this route. This change in the sequence is depicted in Figure 77.

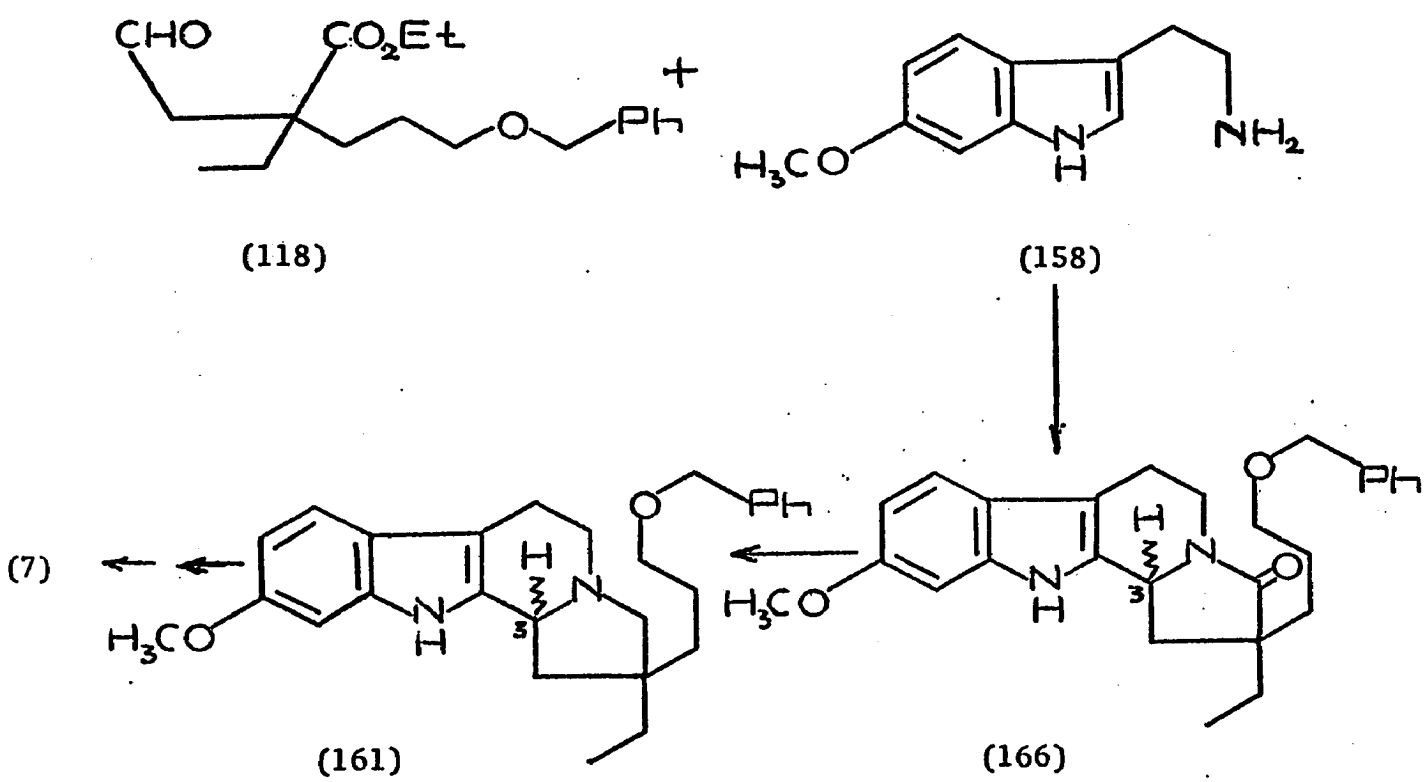

Figure 77. The modified sequence to tetracyclic amine (161).

When 6-methoxytryptamine (158) was condensed with aldehyde (118) under reflux for 2 hours in glacial acetic acid, it afforded after purification on a silica column, the cyclized lactam (166) in 75% yield. This product was a mixture of the expected two diastereoisomers (two asymmetric

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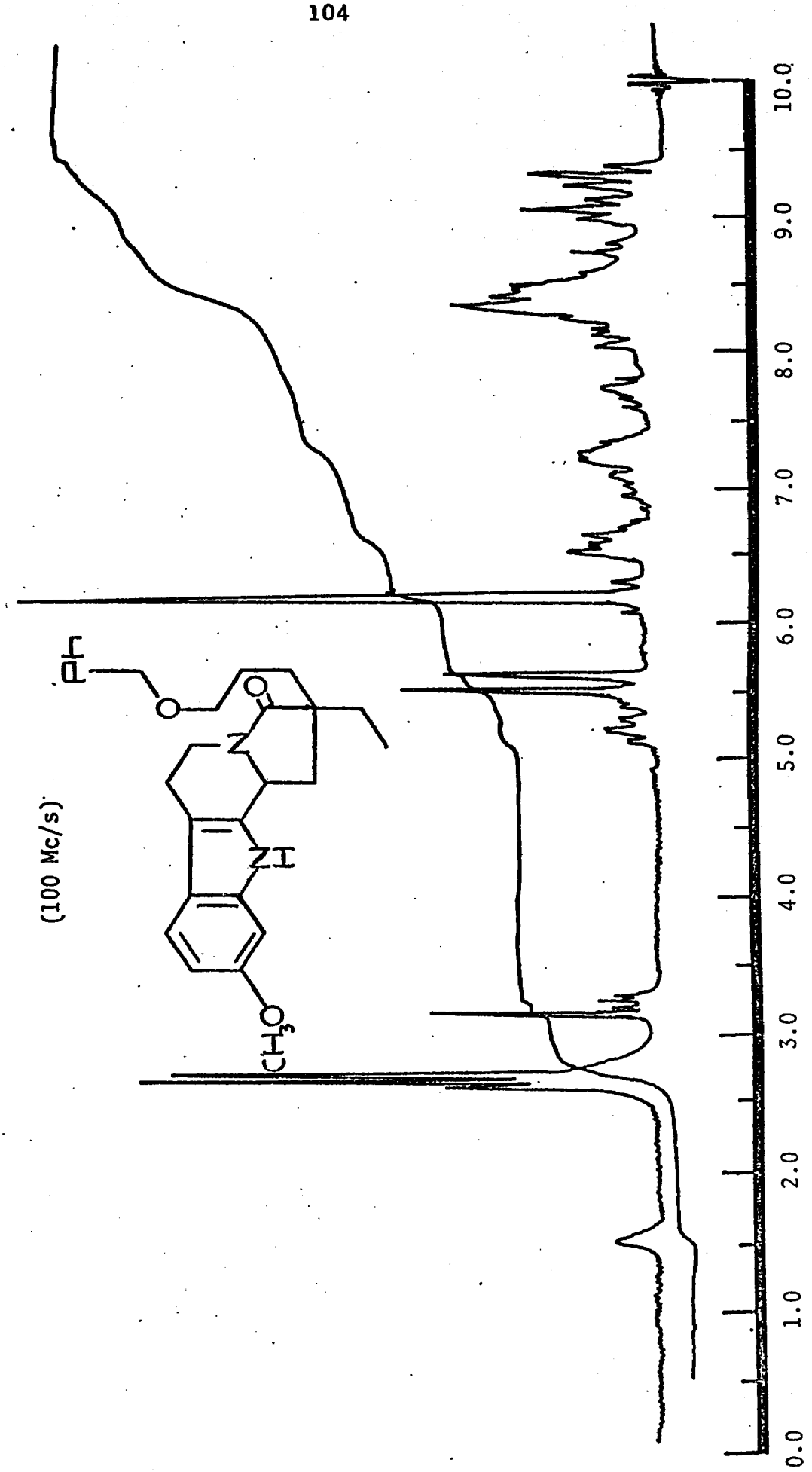

Figure 78. NMR spectrum of 11-methoxy amide (166).

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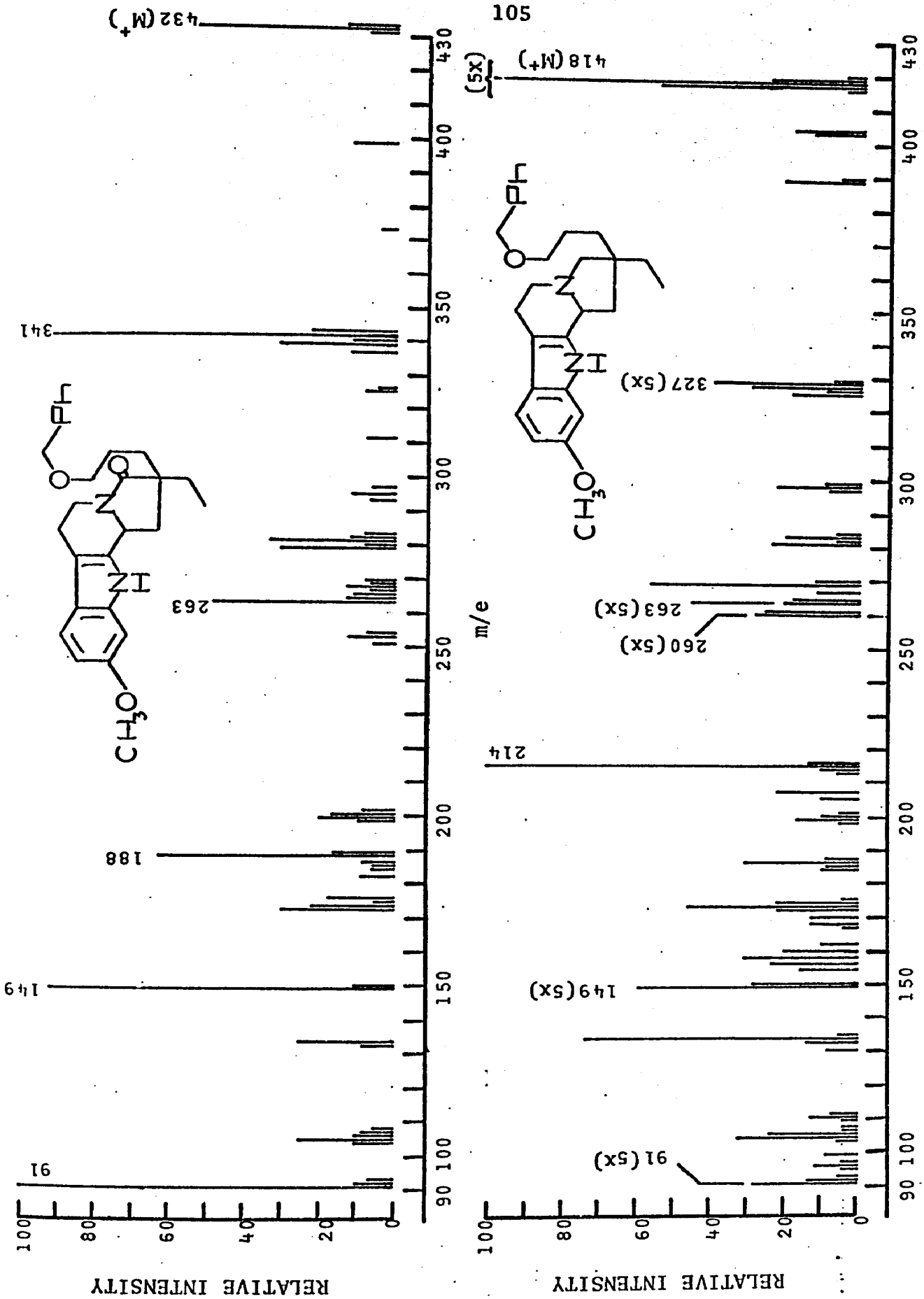

Figure 79. Mass spectra of 11-methoxy amide (166) and amine (161).

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centers are present) but no attempts to separate them at this stage were necessary foı our purpose. The presence of the methoxy indole and the lactam absorption was evident in the ultraviolet spectrum (336, 321, 297, 272, 264 and 227 mμ). In the infrared spectrum, the presence of a typical lactam absorption at 1670 cm^{-1} (very strong), a band at 3250 cm^{-1} (NH) and no Bohlmann bands were apparent.[68,71] The NMR spectrum (Figure 78) revealed the nature of this mixture. The most characteristic signals were a one-proton distorted triplet at τ 5.25 which was assigned to the C-3 proton, and the presence of only two aromatic protons between τ 3.0-3.5. This latter result revealed that the cyclization at the α-position of the indole ring had occurred. Elemental analysis and high resolution mass spectrometry suggested the formula, $C_{27}H_{32}O_3N_2$, for this material. In the mass spectrum (Figure 79) in addition to the molecular peak at m/e 432 and the tropylium ion fragment at m/e 91, other important peaks were at m/e 341, 281, 263 and 149 (presumably due to the fragments shown in Figure 80).

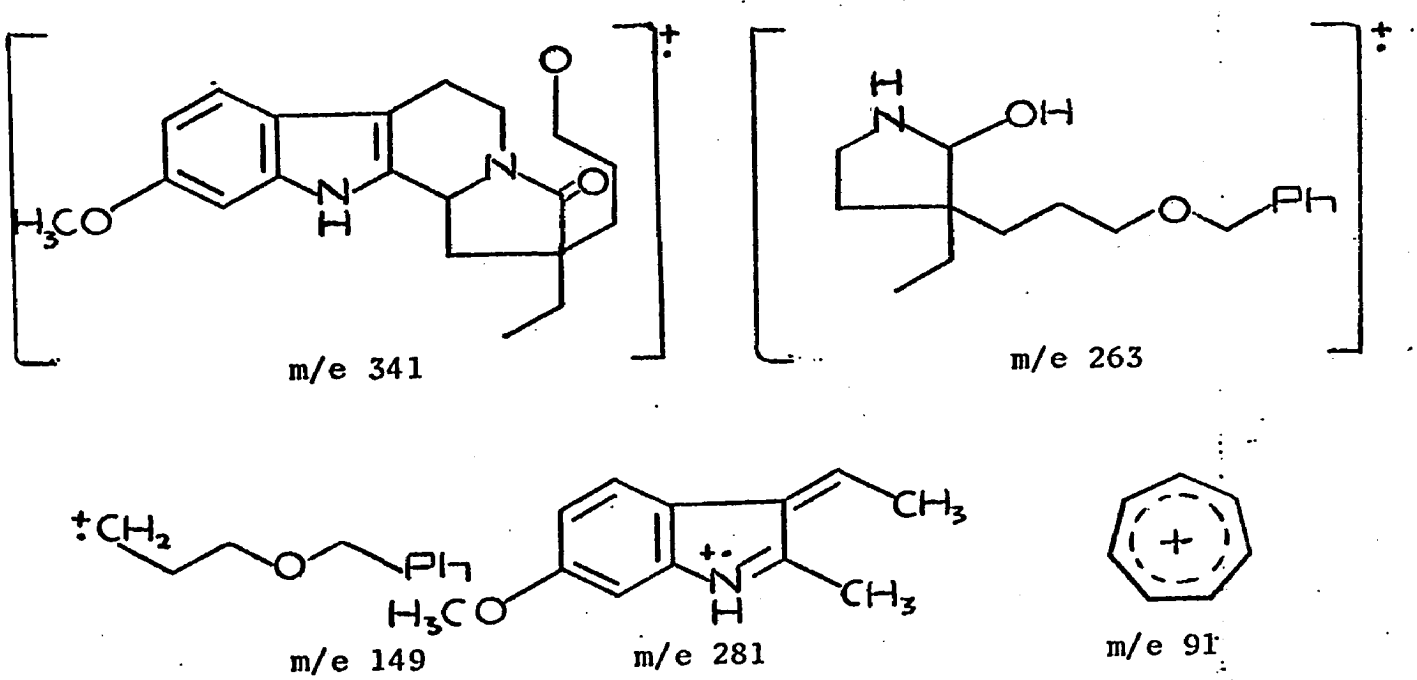

Figure 80. Some important fragments of the lactam (166).

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The next step was the removal of the carbonyl group and this was achieved by lithium aluminum hydride reduction in tetrahydrofuran. The isolated crude product after column chromatography on neutral alumina gave a mixture of diastereoisomers as a yellow amorphous material in a very good yield (83%). For analytical purposes, distillation (245°/0.1 mm.) afforded a yellowish glass. Elemental analysis and high resolution mass spectrometry revealed the formula, $C_{27}H_{34}O_2N_2$, for this compound (161). The ultraviolet spectrum still showed the typical methoxy indole absorptions (300, 270, 263 and 230 mμ), while the carbonyl absorption in the infrared spectrum was now absent. The NMR spectrum (Figure 81) demonstrated an upfield shift of the distorted triplet due to the C-3 proton now located at τ 5.93. All other signals were also in agreement with the assigned structure. The mass spectrum (Figure 79) had significant fragments at m/e 418(M^+) 327 (M-91), 260, 149 and 91 all in accord with expectations.

Catalytic debenzylation of the aminoether (161) was performed in glacial acetic acid, with palladium as catalyst. Large amounts of catalyst was used (extensive poisoning) and the time required for this hydrogenolysis to be completed was found to vary from experiment to experiment (usually 10 hours). Conventional work up and purification of the reaction product by chromatography on alumina gave several products. The less polar components (25% of the starting material) had a very strong carbonyl absorption at 1725 cm^{-1} and showed no conjugation. The NMR spectrum of this compound had a one-proton signal at τ 1.50 (NH of indole), a normal aromatic region for the methoxylated indole at τ 2.5-3.5. Also a sharp singlet at τ 6.18 (probably the CH_3O of the aromatic ring), a very strong singlet at τ 7.92 (probably the three protons of an acyl group) and finally a collapsed methyl triplet τ 9.15 were present. Time did not permit a further study of this

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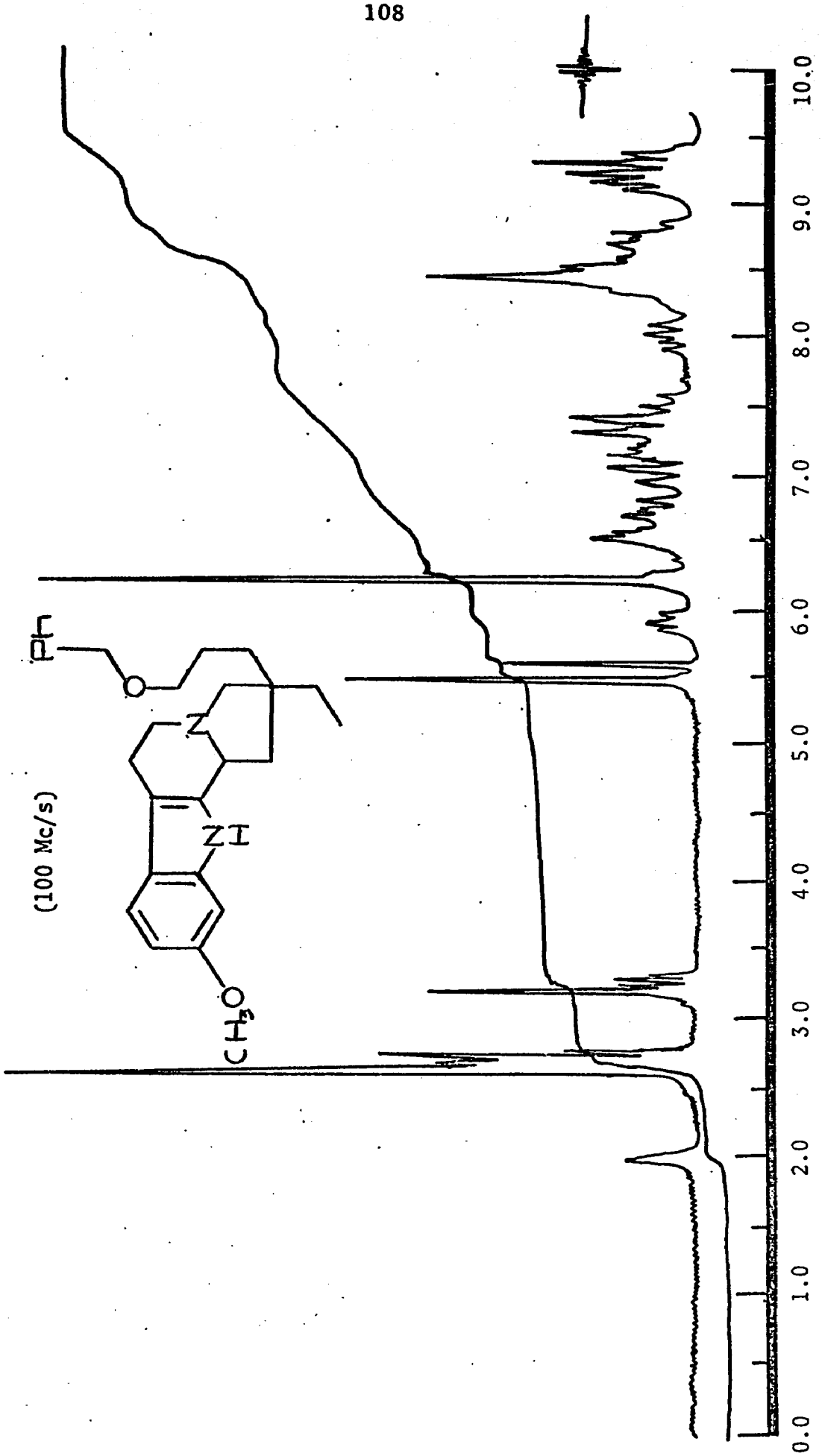

Figure 81. NMR spectrum of 11-methoxy amine (161).

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product.

Elution with chloroform afforded the less polar alcohol-I (27%) while the other alcohol-II (24%) was eluted with chloroform-methanol (98:2). A more polar, strongly fluorescent minor product was finally eluted but it was never isolated in pure form.

Alcohol-I was crystallized from methylene chloride-hexane (3:1) and recrystallized once more from wet methanol or acetone to give a pure sample m.p. 154-155°. The infrared spectrum showed a broad absorption at 3210 cm^{-1} (OH) and a sharp peak at 3360 (NH) cm^{-1}. The ultraviolet spectrum had maxima at 297, 268 and 227.5 mμ. The NMR spectrum (Figure 82) of this compound was in agreement with the expected structure and has a multiplet at τ 6.00 for the C-3 proton while the methyl protons of the side chain resonated as a triplet at τ 9.18 (J = 6 cps). In addition, the aromatic region showed only three protons instead of eight as noted in the starting material. Elemental analysis and high resolution mass spectrometry established the molecular formula, $C_{20}H_{28}O_2N_2$, for this compound. The mass spectrum (Figure 83) of this alcohol-I had fragments at m/e 328 (M^+), 214, 199, 186 and 149 as expected.

The other, more polar alcohol-II after several crystallizations from methylene chloride and acetone was also obtained pure, m.p. 168-169°. The fact that this alcohol-II, was isomeric with alcohol-I, was established by elemental analysis as well as mass spectrometry. The infrared spectrum of this compound was almost superimposable with that of alcohol-I. The NMR spectrum (Figure 84) was consistent with that of alcohol-I but now the C-3 proton was seen as a poorly resolved triplet at τ 5.65 and the methyl protons of the ethyl chain resonated at higher field (τ 9.27). Finally the mass spectrum (Figure 83) had again the same main fragments as in alcohol-I.

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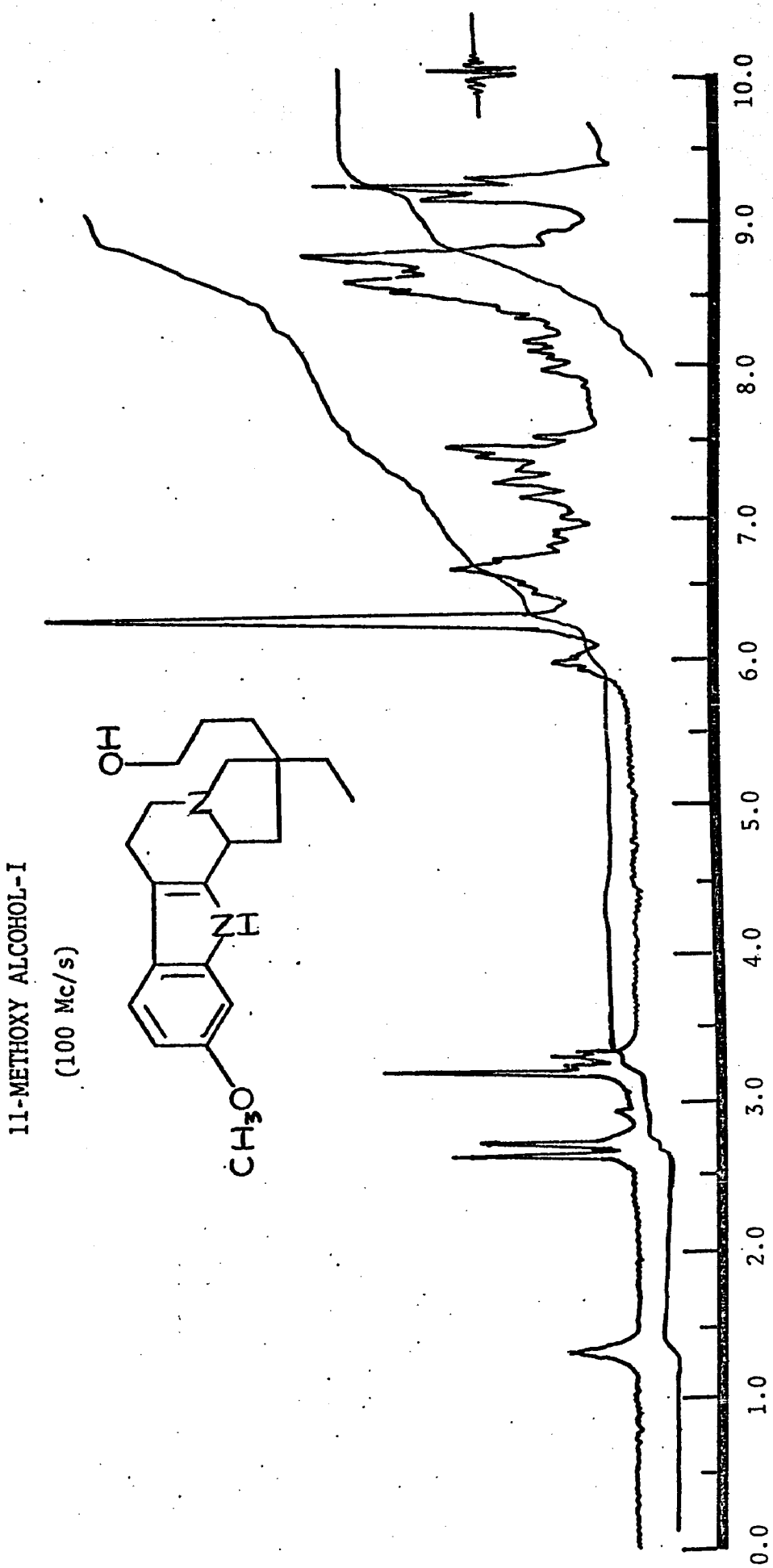

Figure 82. NMR spectrum of 11-methoxy alcohol-I (165).

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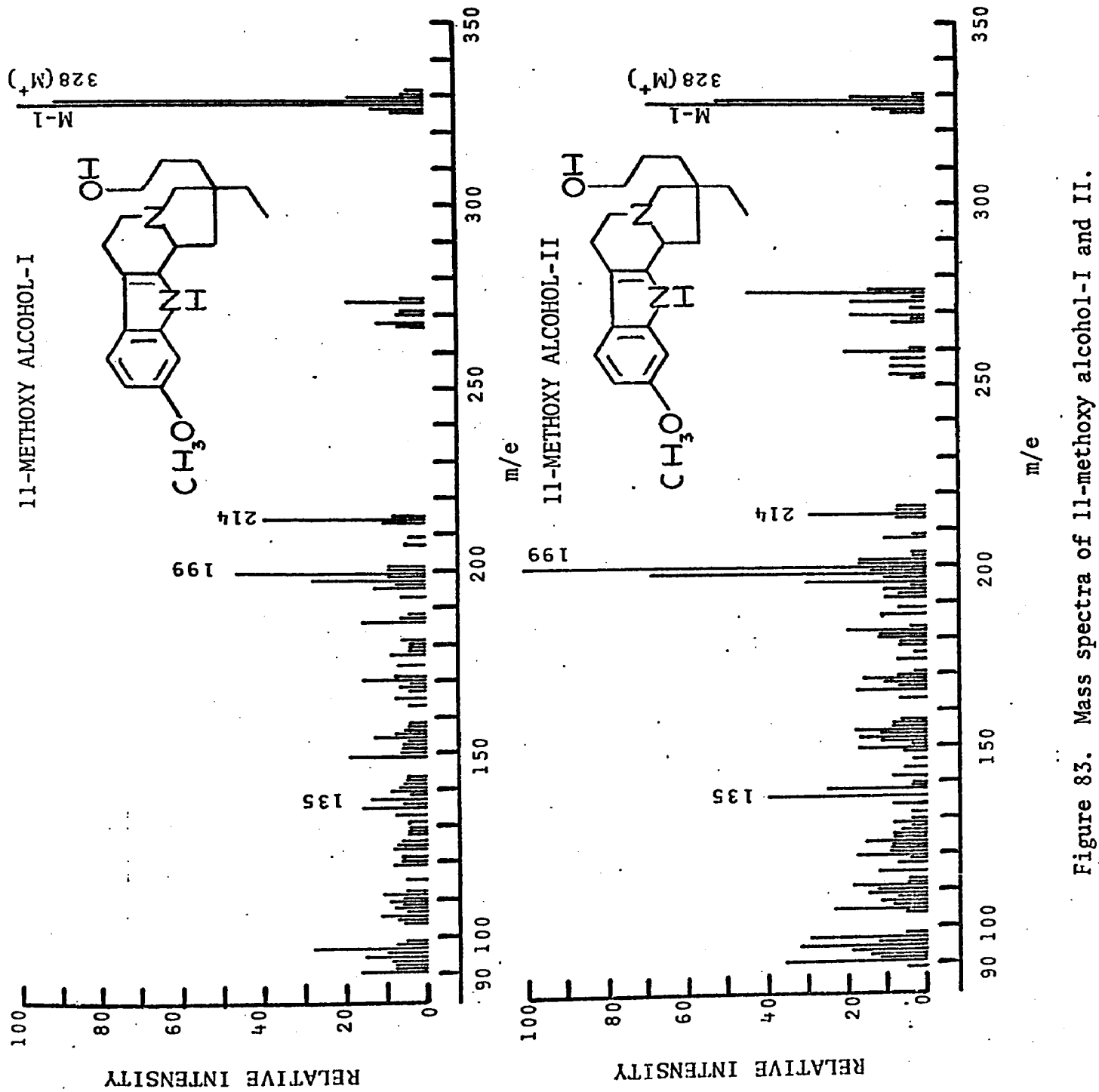

Figure 83. Mass spectra of 11-methoxy alcohol-I and II.

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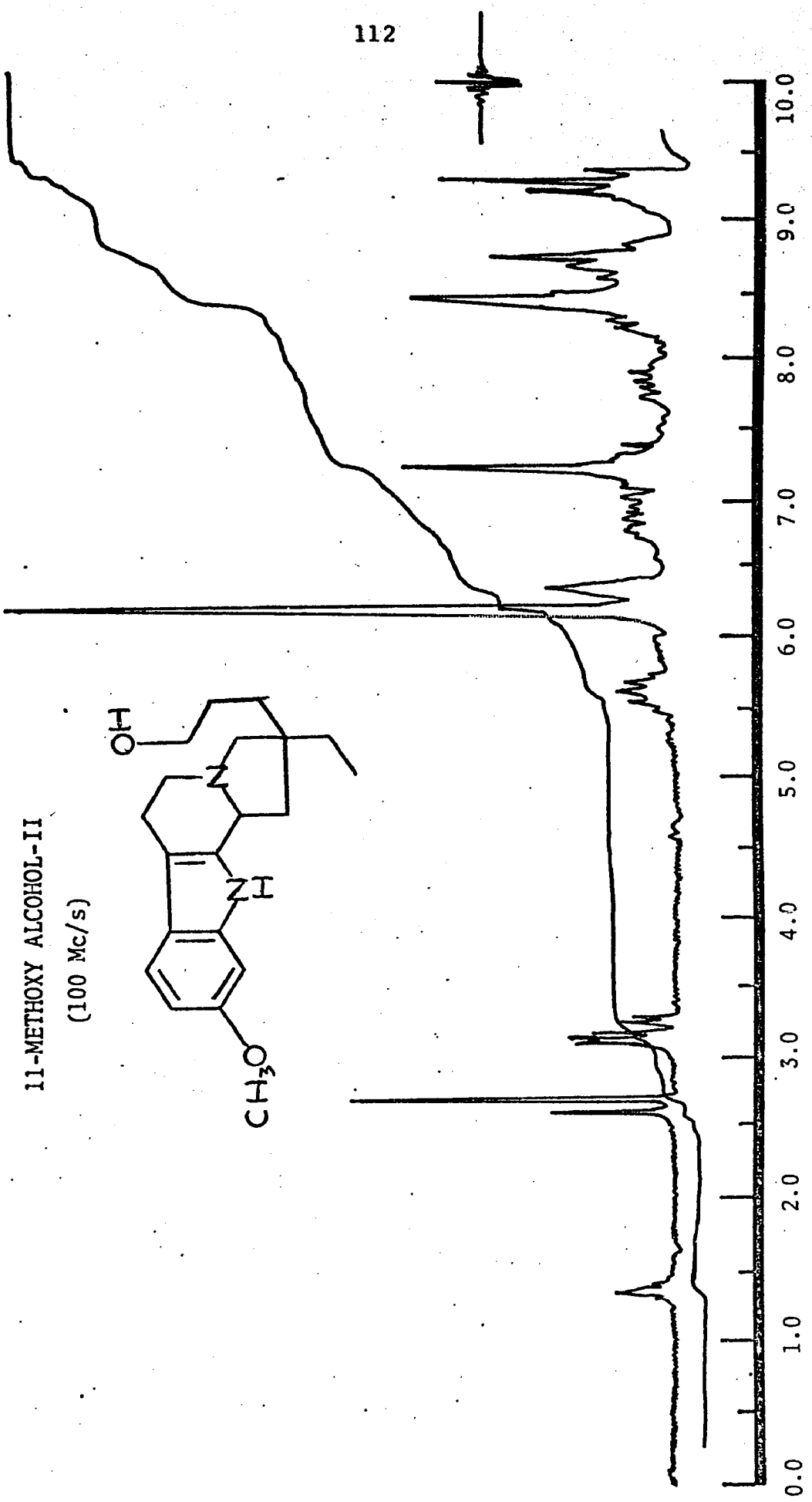

Figure 84. NMR spectrum of 11-methoxy alcohol-II (165).

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From spectral data presented above we could assign on the basis of arguments discussed in the earlier portion of this thesis, alcohol-I as being the "cis" and alcohol-II as the "trans" dl-pair (see Figure 48). These two epimers differ only in the stereochemistry on the one asymmetric center.

Conversion of both alcohols to the mesylates (167) (Figure 85) with

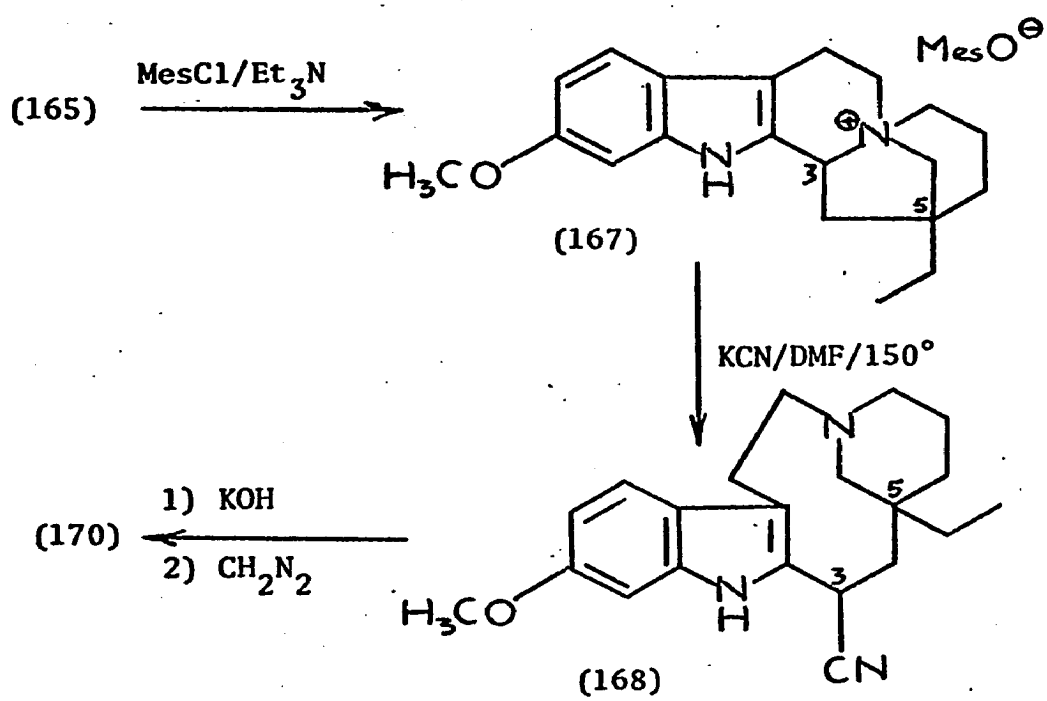

Figure 85. Preparation of 16-methoxyvincadine and its epimer.

methane sulfonyl chloride in triethylamine at room temperature gave the pure mesylates in 90-100% yields after rapid filtration through a short alumina column. These compound were not completely characterized.

When we applied the cyanide reaction as before (potassium cyanide, dimethylformamide, 150°) to each of these mesylates, we got identical

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mixture of products (TLC, IR, UV and NMR comparison). This was expected of course, since each of the mesylates was a dl-pair and during this reaction the asymmetric center at C-3 was first destroyed and then regenerated. In this manner, as before, three cyanides were isolated after column chromatography. Two of these compounds were epimers and the other one was of the same nature as the one described before (see Figure 64).

The isomeric nature of these cyanides was established by elemental analysis and high resolution mass spectrometry which indicated the formula $C_{21}H_{27}ON_3$.

Cyanide-I (the less polar from alumina chromatoplates, developed by chloroform) was crystallized from acetone-hexane, then methylene chloride-hexane and/or methanol, m.p. 186-187°. The infrared spectrum of the latter showed the nitrile band at 2225 cm^{-1} while the ultraviolet had maxima at 300, 275 and 225 μ. The NMR spectrum (Figure 86) showed a deformed quartet at 6.12 for the C-3 proton and a triplet at τ 9.07 ($CH_2\underline{CH}_3$). The mass spectrum (Figure 87) exhibited the expected fragmentation with shift of the fragments due to the indole part of the molecule by 30 mass units due to the presence of the methoxyl group cf. Figure 57. In this case fragments at m/e 337 (M^+), 212, 177, 126 and 124 were present.

The other cyanide-II was crystallized from methylene chloride-hexane and recrystallized from methanol, m.p. 191-192°. The infrared spectrum was almost superimposable with that of cyanide-I. The NMR spectrum (Figure 88) indicated the C-3 proton as a quartet at τ 4.04, while the methyl protons of the ethyl chain appeared as a triplet at τ 9.35. The mass spectrum (Figure 87) of this compound also showed the same fragmentation as the less polar cyanide. The yields of cyanide-I, cyanide-II and cyanide-III were 9%, 15% and 13% respectively. In comparison with the other sequence (in which

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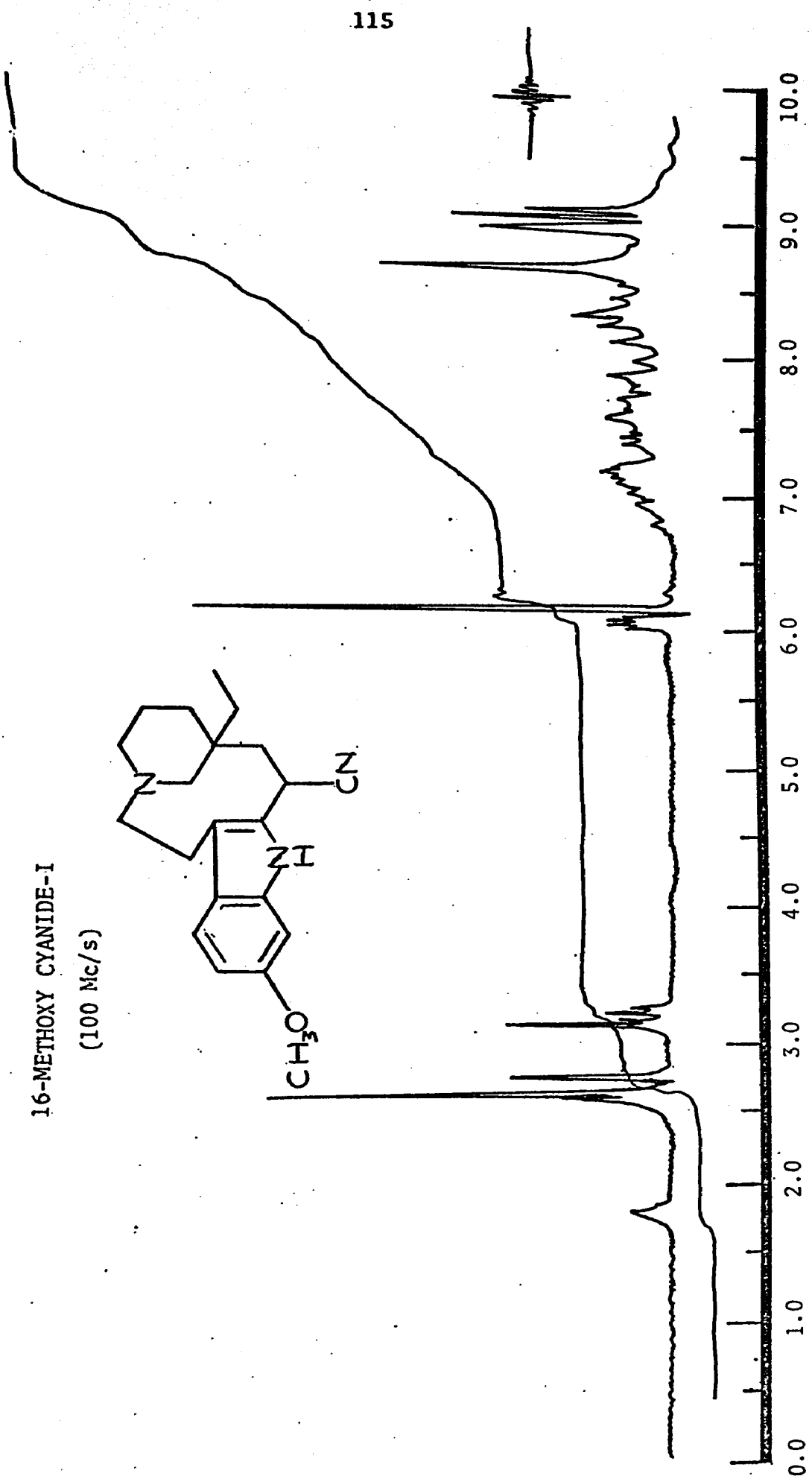

Figure 86. NMR spectrum of 16-methoxy cyanide-I (168).

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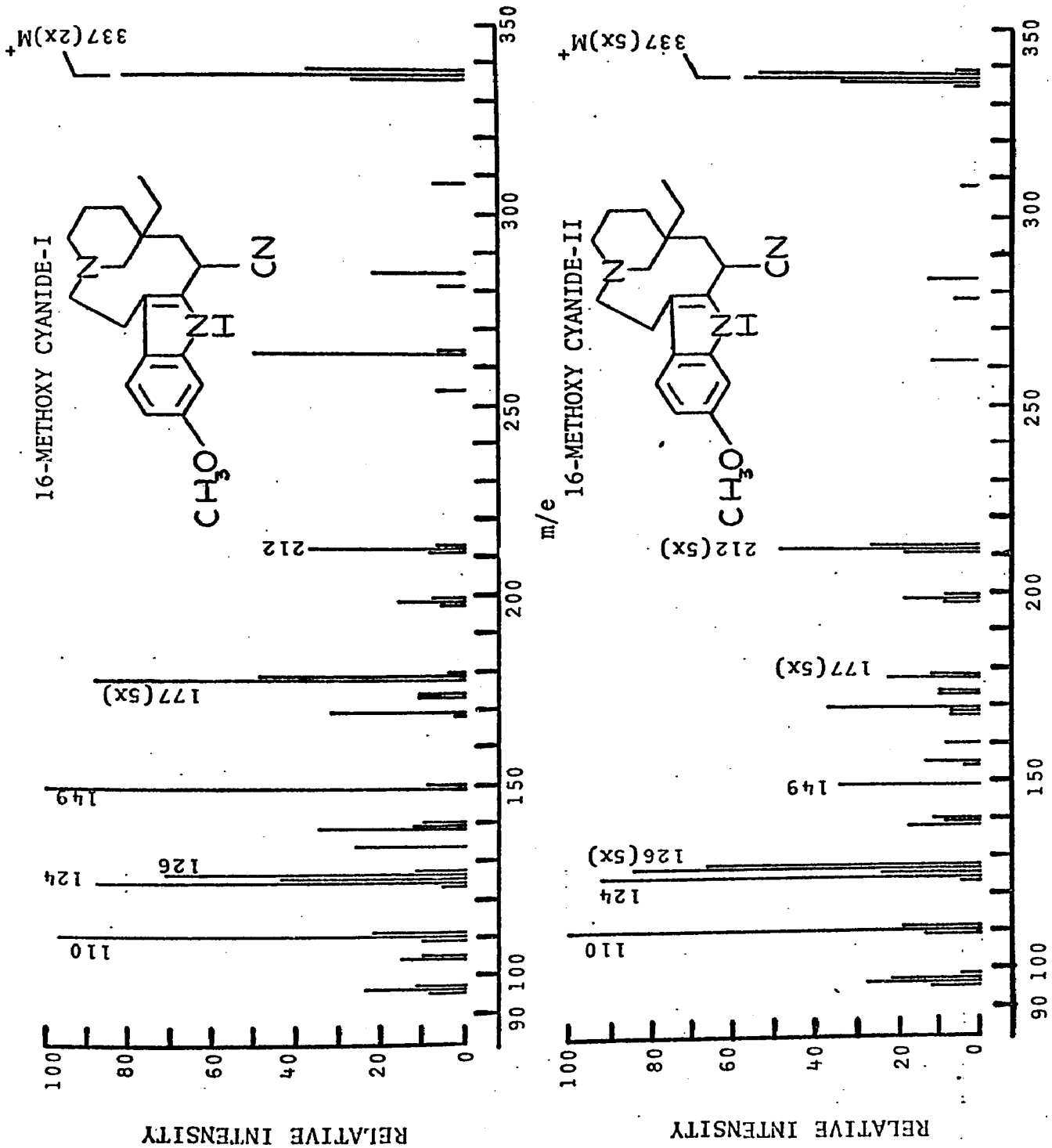

Figure 87. Mass spectra of 16-methoxy cyanide-I and II.

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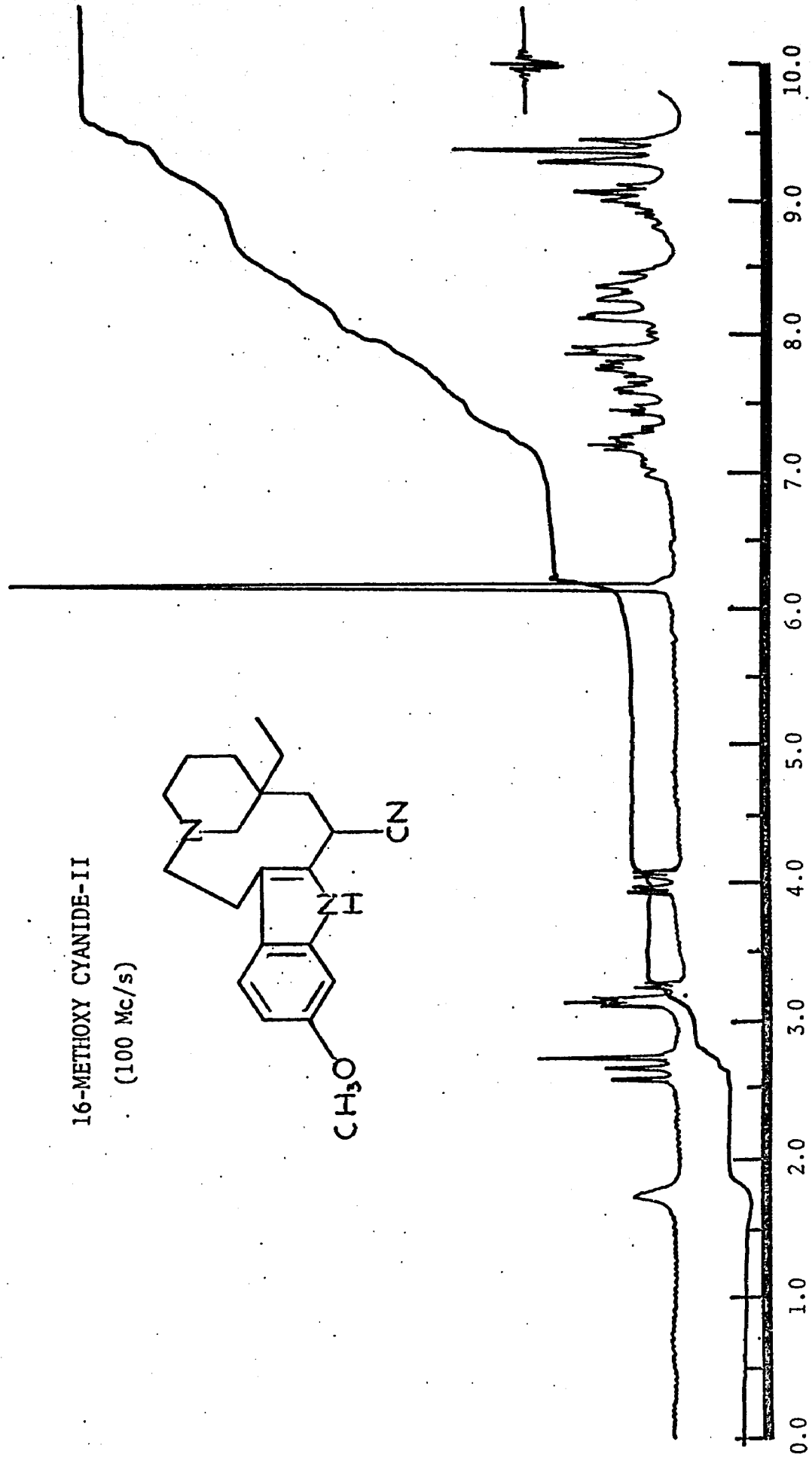

Figure 88. NMR spectrum of 16-methoxy cyanide-II (168).

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6%, 8% and 26% yields were realized) the yields of the desired cyanides (I and II) were a little higher while that of cyanide-III was lower. We thought it was worthwhile to try and improve this reaction in spite of the disappointments which we had experienced in the previous sequence.

Nagata et al. introduced cyanide into sterically hindered steroidal positions using potassium cyanide in DMF/H_2O mixtures and ammonium chloride. Yields of 40-65% were reported following 8 hour heating at 100°.[89a] Later, the same author reported an improvement of this reaction, by using trialkyl aluminum cyanides like AlR_3CN (R = Me, Et, i-Pr) and THF as a solvent.[89b] When we tried their conditions on our system we found no reaction taking place at 110-120° but under reflux the maximum amount of cyanides was formed after 14 1/2 hours, although starting material was still present in the mixture. Chromatography on alumina of this reaction product showed that the yield of mixture of two desired cyanides (I and II) was approximately the same as previously mentioned. Therefore this alteration was not a real improvement of the cyanide reaction. Next we thought that by using a strong base we might obtain possibly through an indolenine intermediate (169), a more desirable result (Figure 89). Sodium hydride was used in excess in dry DMF and the reaction product after purification as before gave a mixture of cyanides (I and II) in 35% yield (as compared to 25% obtained previously). This was an improvement of the reaction although it was not very impressive.

As in the previous sequence these cyanides (I or II), when subjected to alkaline hydrolysis followed by esterification provided identical reaction mixtures. The intermediate acids were again not isolated but were esterified directly with diazomethane (Figure 90) to provide the crude methyl esters in a 76% yield. After purification by chromatography on

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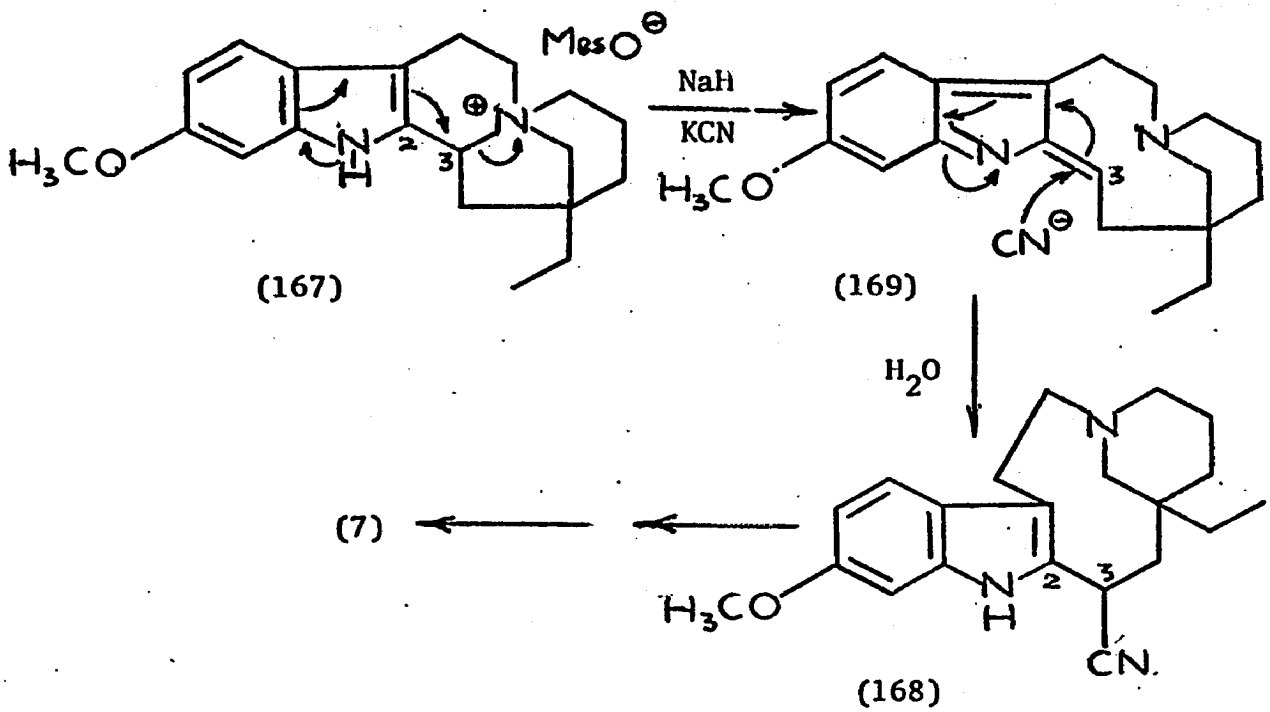

Figure 89. Base induced introduction of cyanide ion.

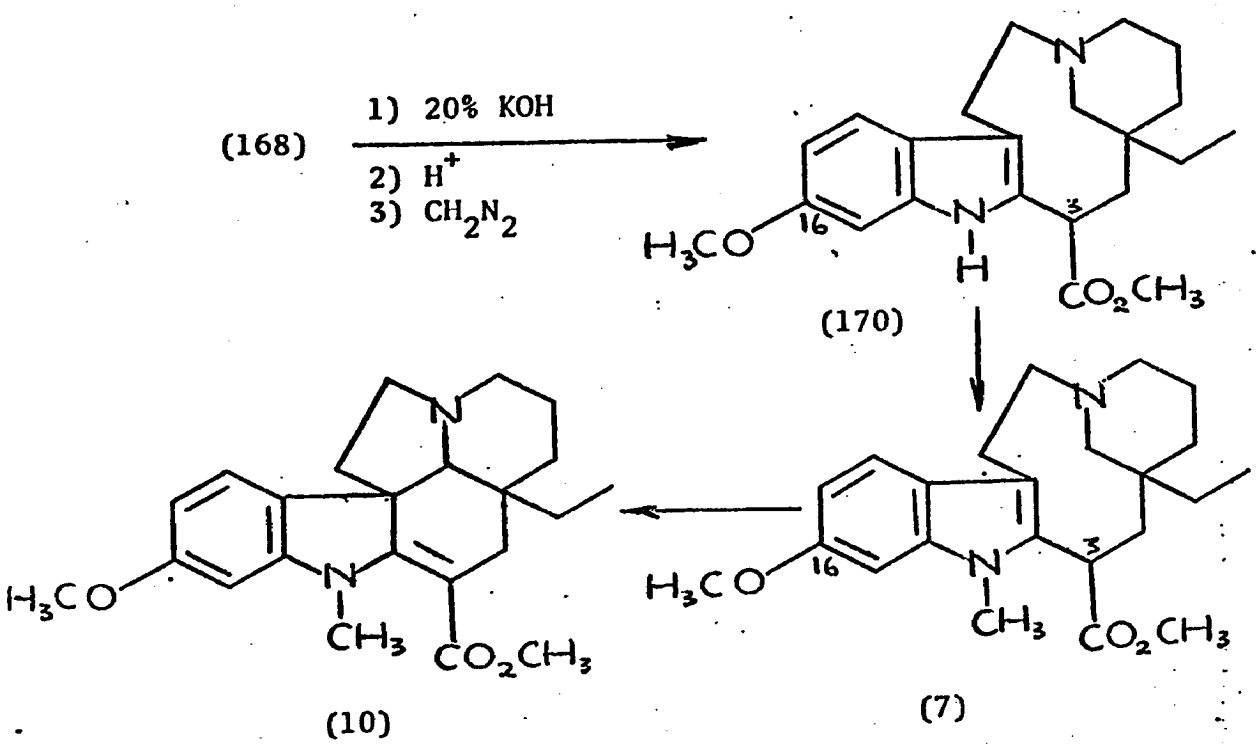

Figure 90. Conversion of cyanides to carboxylic acid esters.

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alumina (Woelm) 16-methoxy-dl-vincadine and its C-3 epimer were obtained in 18% and 12% yields respectively. We noticed during subsequent purifications that chromatography on alumina, silica gel or florosil resulted in poor recovery of the desired esters. The yields obtained in this series compared well with those in the previous series (14.5% and 11.5% respectively).

The major isomer (18%) isolated by preparative TLC had a methoxy indole type ultraviolet spectrum (301, 278, and 228 mμ) while its infrared spectrum showed an unconjugated carbonyl absorption (CO_2CH_3) at 1725 cm^{-1}. The NMR spectrum (Figure 91) had an unresolved quartet at τ 6.35 ($C\underline{H}COOCH_3$) while a new three-proton singlet at τ 6.31 was assigned to the protons of the ester methyl group. A triplet at τ 9.18 due to the methyl group of the ethyl side chain was also present. These values compare well with those of dl-vincadine itself. The mass spectrum (Figure 92) was similar to the corresponding one of dl-vincadine (Figure 67) with the exception that the fragments resulting from the indole part of the molecule had shifted up by 30 mass units to the presence of the the methoxyl group. Consequently, fragments at m/e 370 (M^+), 245, 210, 138 and 124 were present. By analogy with the previous series, this compound was named 16-methoxy-dl-vincadine.

The minor isomer (12%) isolated by preparative TLC had also a methoxy indole chromophore and an infrared spectrum which was almost superimposable with the one of above compound. The NMR spectrum (Figure 93) now had the C-3 proton quartet (J_{AB} = 12, J_{AC} = 2 cps) at τ 4.49, the ester methyl protons as a singlet at τ 6.38 and the methyl of the side chain was a triplet at τ9.36. These peaks were in close agreement with those recorded for dl-epi-vincadine. The mass spectrum (Figure 92) was similar to the one of 16-methoxy-dl-vincadine with common fragments at m/e 370 (M^+), 245, 210, 126 and 124. Finally high resolution mass spectrometry confirmed the isomeric nature of these two diastereoisomers, and established the formula $C_{22}H_{30}O_3N_2$

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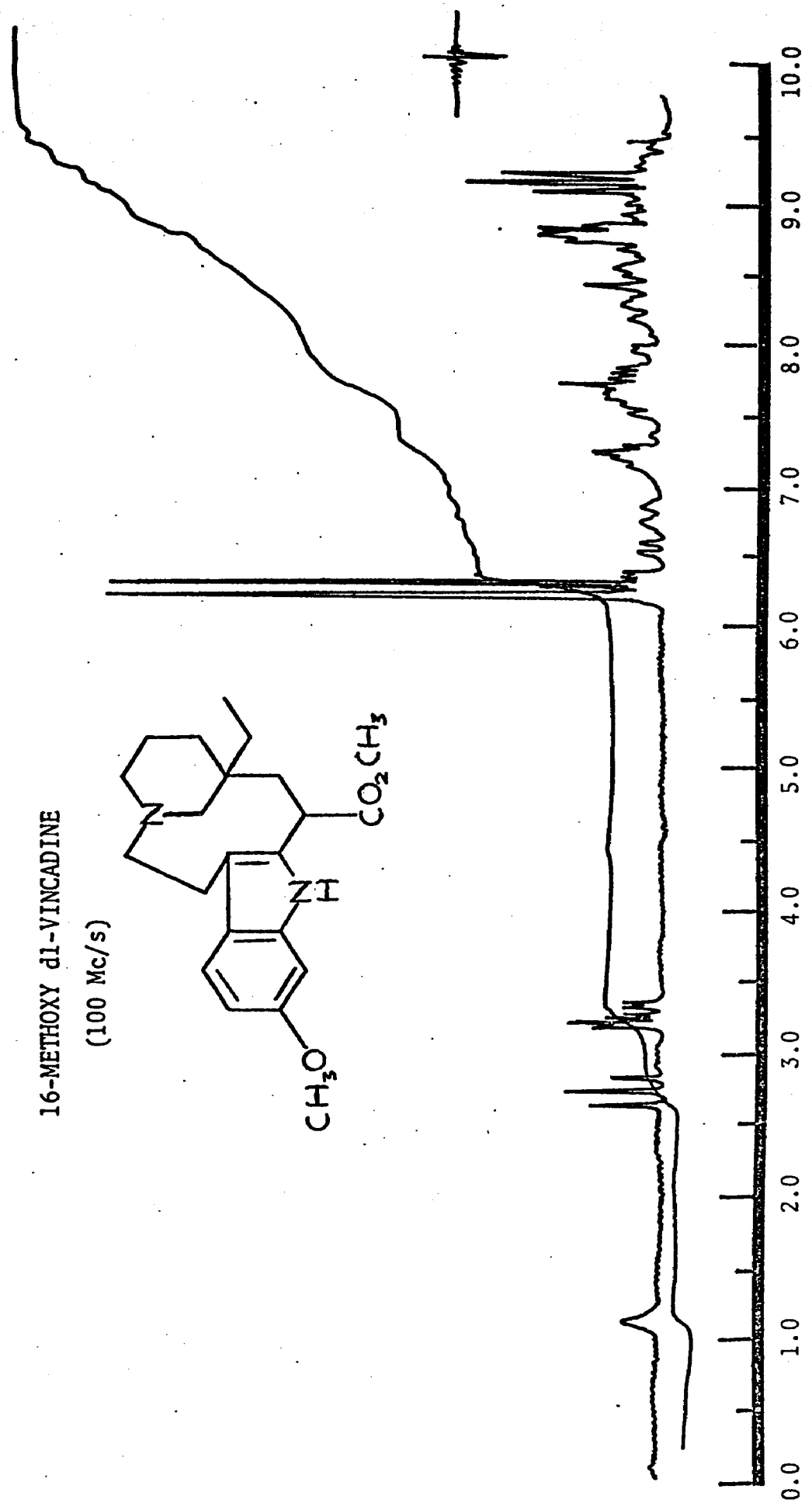

Figure 91. NMR spectrum of 16-methoxy dl-vincadine (170).

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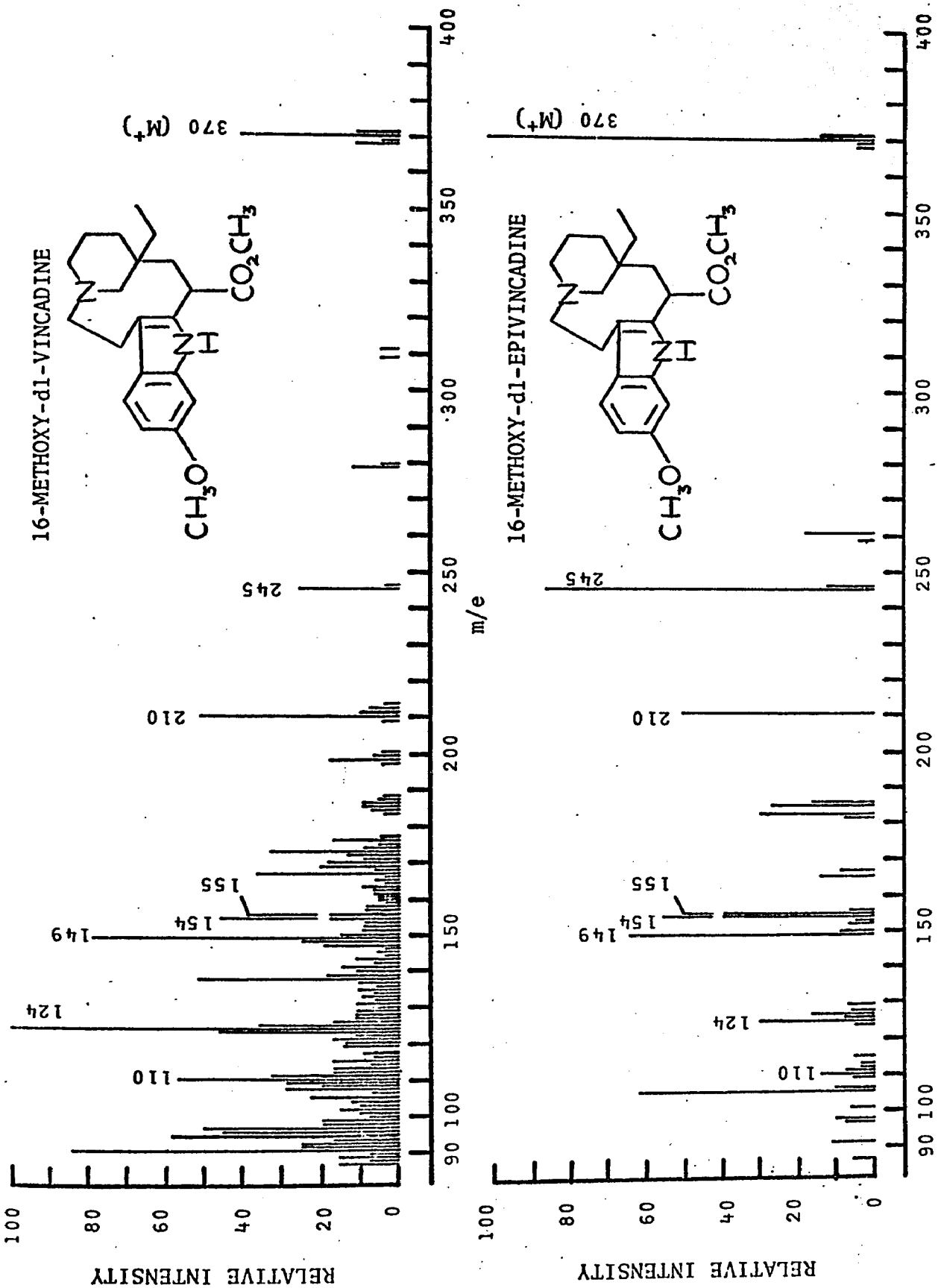

Figure 92. Mass spectra of 16-methoxy-dl-vincadine and its epimer.

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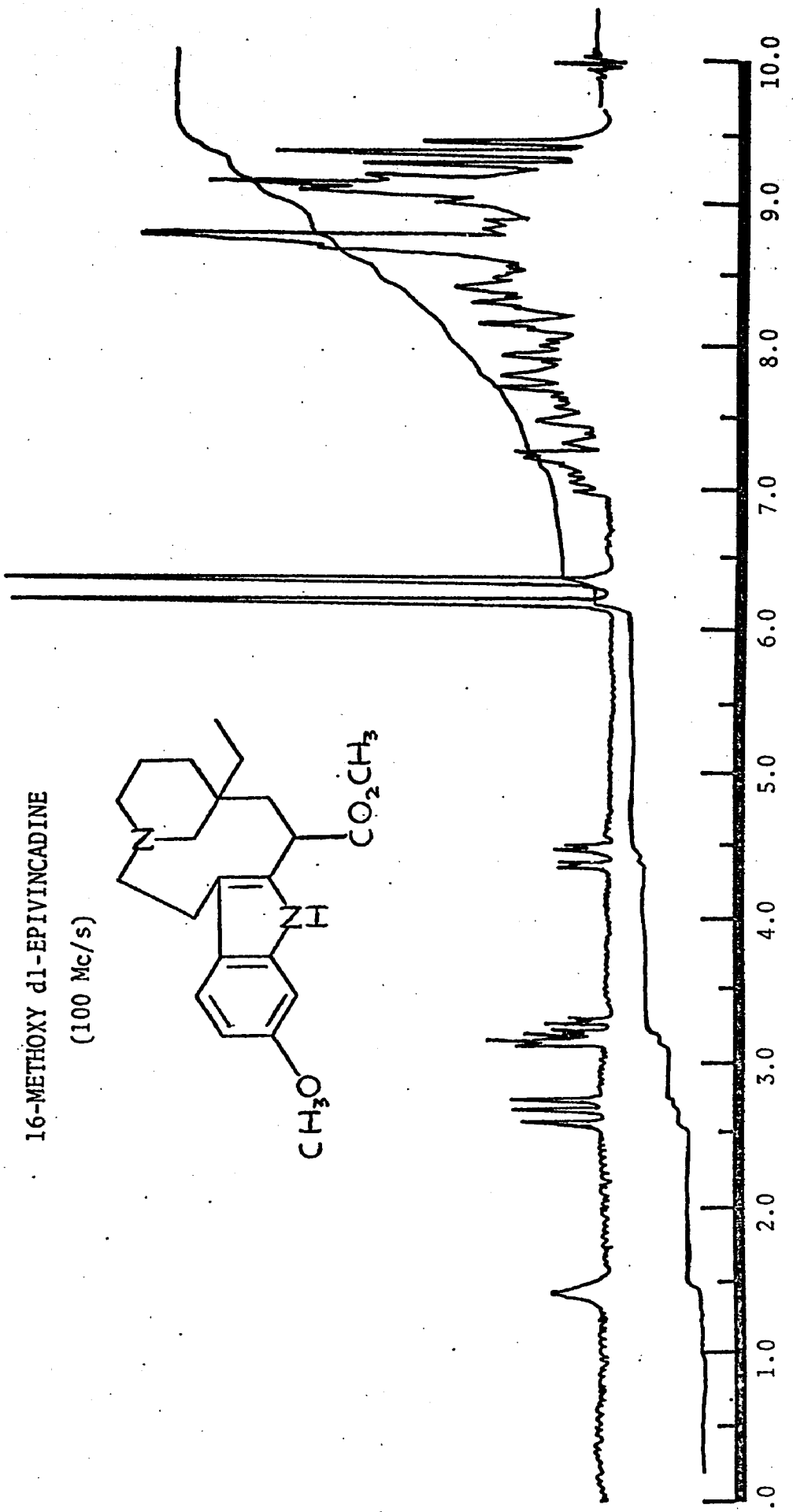

Figure 93. NMR spectrum of 16-methoxy dl-epivincadine

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(found: 370.225 and 370.224; calc: 370.225). On the basis of the above evidence this latter compound was named 16-methoxy-dl-epivincadine.

The next step in the sequence was the methylation of the indole nitrogen atom. Since only small amounts of these two alkaloids were available it was advisable to try and develop the best conditions for this reaction using readily available model compounds. In this respect a suitable model compound would be 18-carbomethoxydihydrocleavamine (172) (Figure 94). This

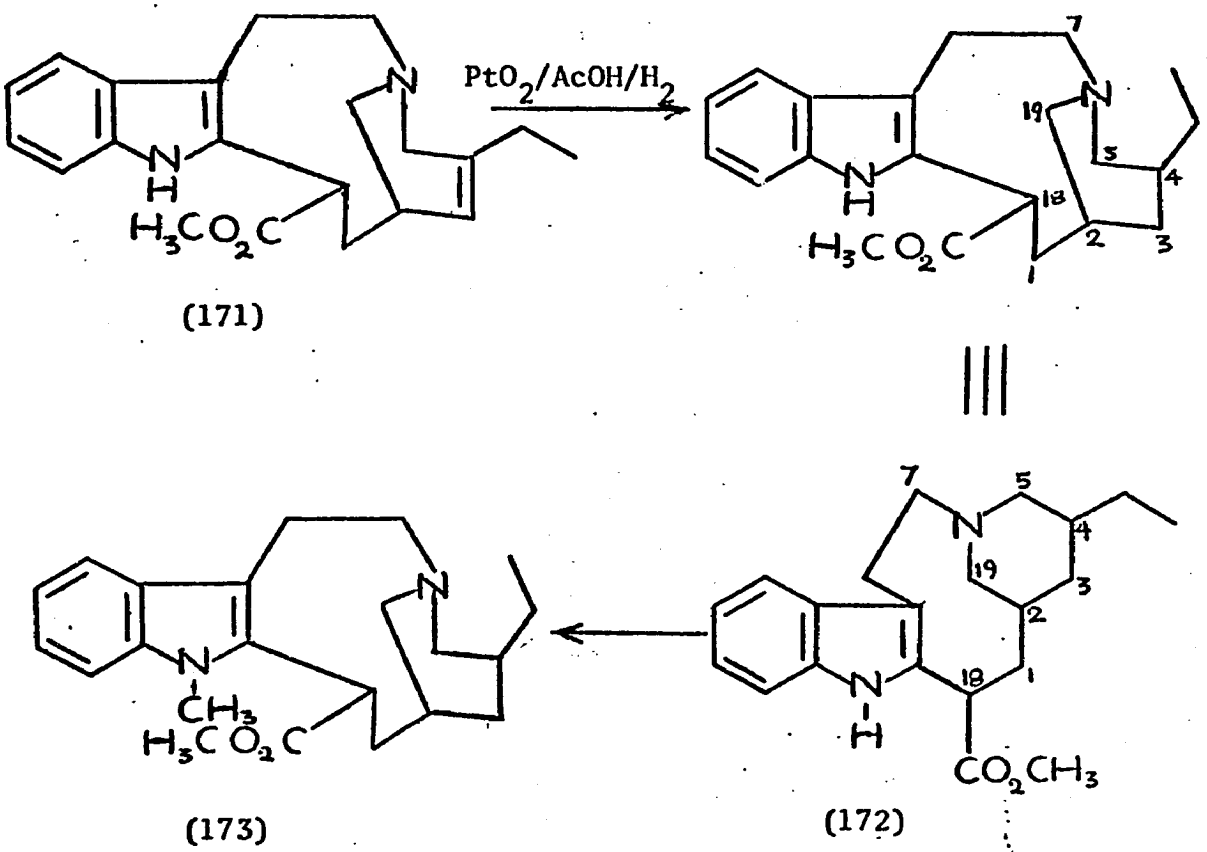

Figure 94. N-methylation of 18-carbomethoxydihydrocleavamine (172).

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compound was prepared from 18-carbomethoxycleavamine (171) by hydrogenation over Adam's catalyst (PtO_2) in glacial acetic acid at room temperature.[49] The yield in this reaction was quantitative. The NMR spectrum of the crystalline reaction product had a broad singlet at τ 1.32 (NH), four aromatic protons centered at τ 2.80, a doublet at τ 4.98 for the C-18 proton, a singlet at τ 6.36 due to the ester methyl group and finally a three-proton triplet at τ 9.12 for the methyl group of the ethyl side chain at C-4.

For the methylation reaction it was desirable to find a base strong enough to induce removal of the proton on the indole nitrogen but at the same time maintain anhydrous conditions to prevent hydrolysis of the ester group to the carboxylic acid. It is well known that compounds like (170) or (172) bearing the carboxyl function at the C-3 or C-18 positions decarboxylate easily.[77,83] Subsequent methylation of the formed anion by a suitable reagent would lead to the desired product (173). When we tried sodium hydride in DMF and then added methyl iodide, the isolated product showed incomplete methylation. The reaction product showed a less polar spot on the TLC chromatoplate along with starting material in an approximate ratio of 40:60. The infrared spectrum of this mixture had some NH absorption still present (3320 cm^{-1}), the ester group was still present (strong peak at 1725 cm^{-1}) and the rest of the spectrum was almost superimposable with that of the starting material. The NMR spectrum was most informative. It showed that these two spots were probably a mixture of three compounds. Two broad singlets at τ 1.3 and τ 2.0 each integrated for ca. 0.3 proton suggesting that a mixture of ca. 30% each of free NH indole compounds were present (Figure 95). This result was confirmed by two unresolved multiplets at τ 4.43 and 4.95 with each of them integrating for ca. 0.3 proton. These latter signals could be easily assigned to C-18 protons (Figure 96).

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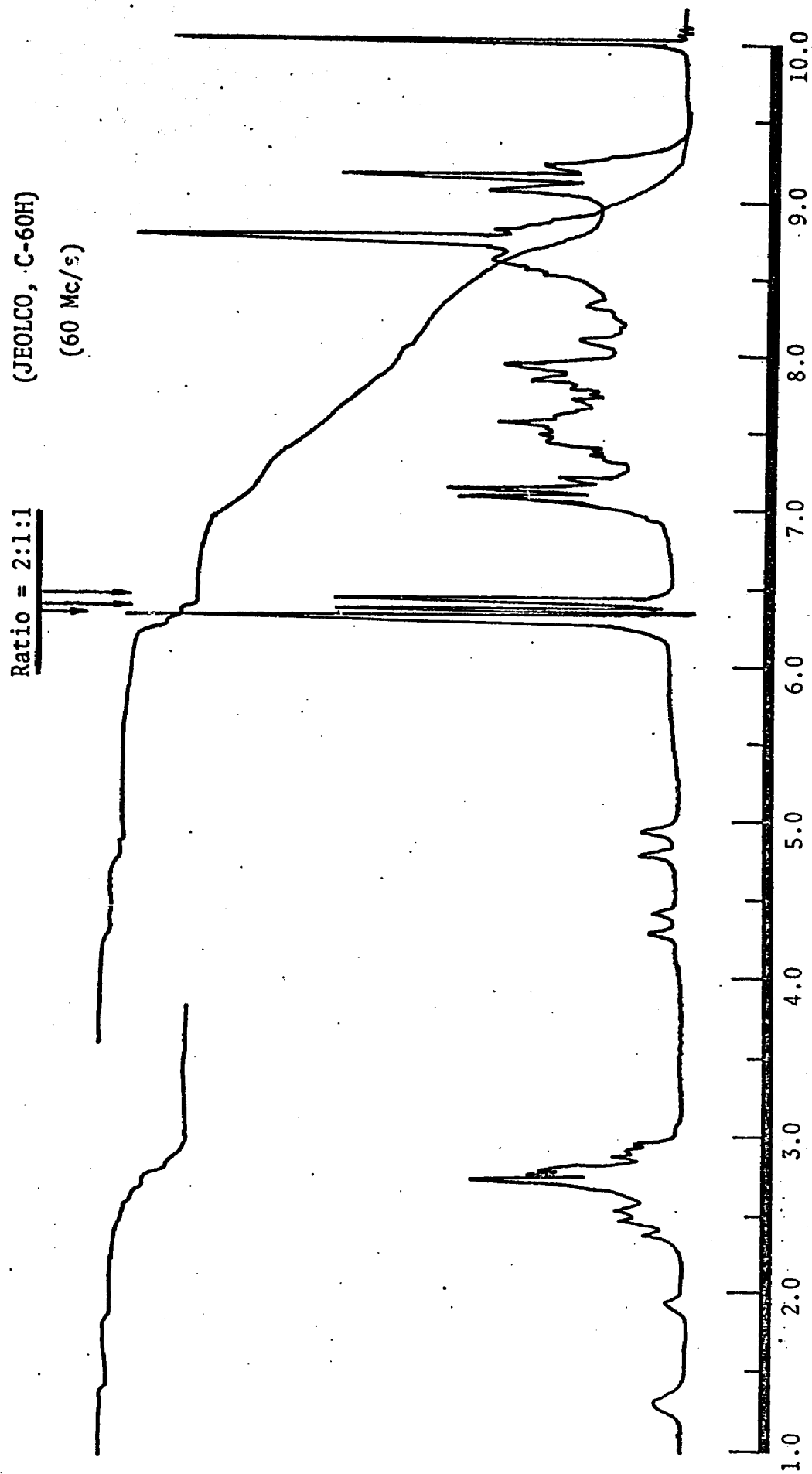

Figure 95. NMR spectrum of N-methylation reaction product.

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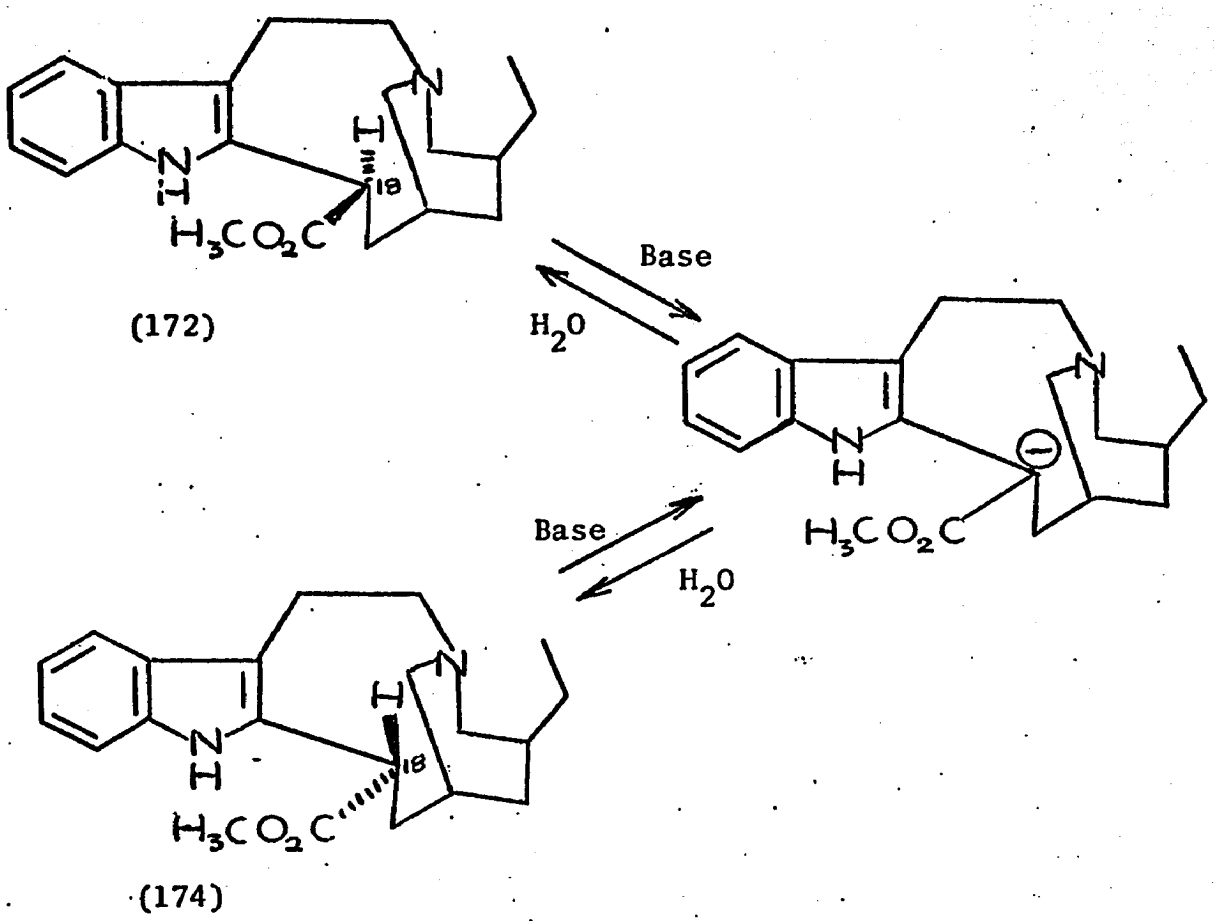

(172)

(174)

Figure 96. Epimerisation of 18-carbomethoxydihydrocleavamine.

A singlet in the above spectrum at τ 6.33, integrating for about one-proton might be assigned to the ester protons of the starting material, while its epimer and the methyl ester of the N-methyl compound might overlap as a singlet at τ 6.30, corresponding in area to about two protons. The N-methyl protons must then be at τ 6.41 as a singlet of approximately one-proton in intensity. In conclusion the above mixture seemed to consist of three components in 1:1:1 ratio, of which two were epimeric carbomethoxy-dihydrocleavamines (172 and 174) and the third was the N-methyl compound (173). When we tried the above reaction with sodium in liquid ammonia, we

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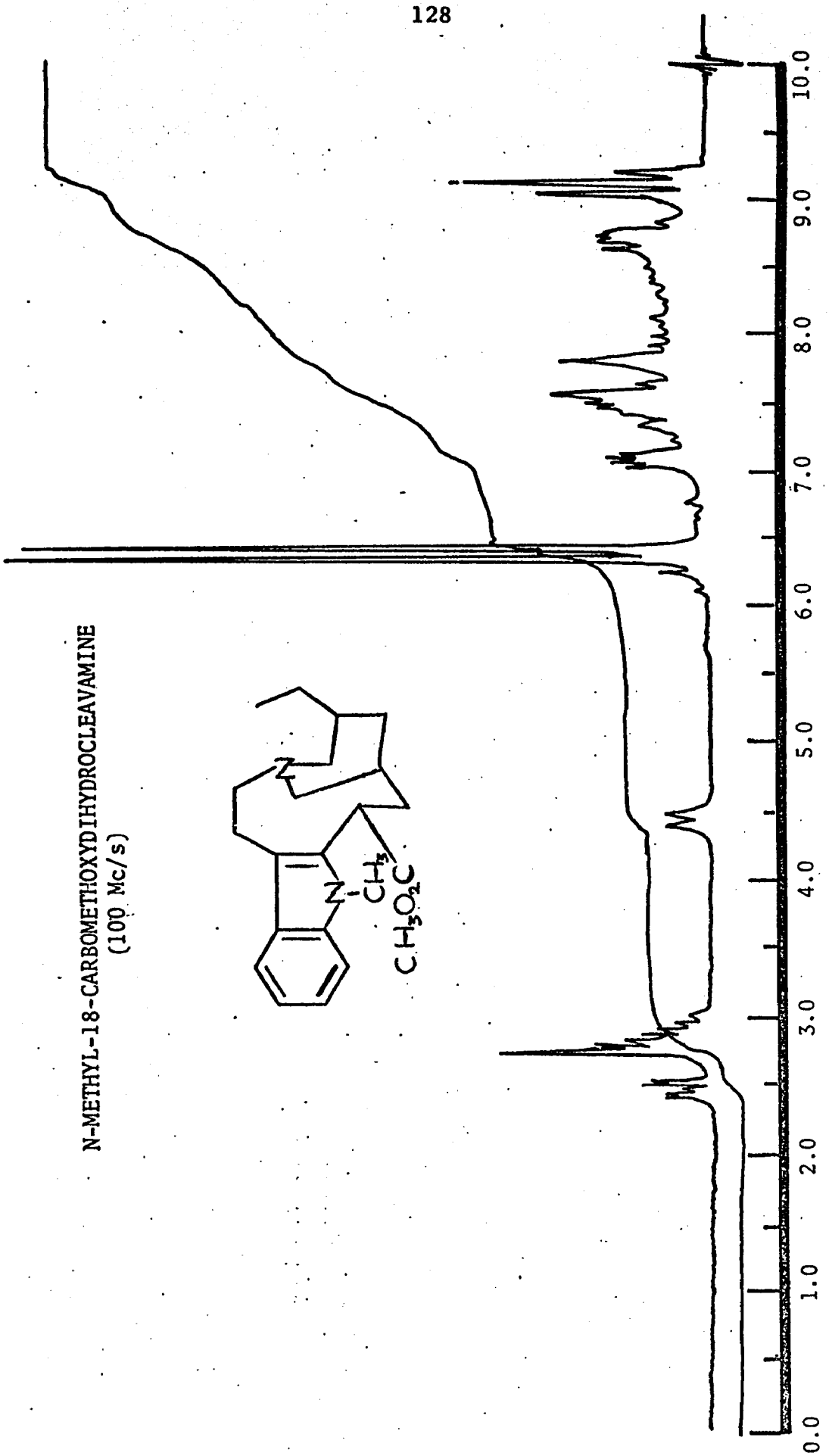

Figure 97. NMR spectrum of N-methyl-18-carbomethoxydihydrocleavamine (173).

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succeeded in preparing the N-methyl compound (173) in good yield.[83] The infrared spectrum of this compound showed no NH band but the ester absorption was still present. The NMR spectrum (Figure 97) confirmed the removal of the $N_{(\alpha)}$-proton and the presence of a new three-proton singlet at τ 6.47 could be assigned to $N_{(\alpha)}$-CH_3 protons.

Having developed sufficient reaction conditions for the N-methylation we applied these to a mixture of dl-epimers of (170). The product after purification by preparative TLC on silica gel gave the dl-epimers in 34% yield each (total 68%).

The more polar of these dl-pairs, on silica gel chromatoplates, compared well with the TLC properties of dl-vincadine and 16-methoxy-dl-vincadine. This compound had an infrared spectrum with no NH absorption and an unconjugated carbonyl was present at 1735 cm^{-1}. The ultraviolet spectrum demonstrated a methoxy indole chromophore (maxima 300, 288 and 232 mμ) which was in good agreement with this system as reported in the literature.[4,90] The NMR spectrum (Figure 98) showed no $N_{(\alpha)}$-proton signal and now a new three-proton singlet at τ 6.56 was present. The C-3 proton resonance occurred at τ 6.20 as a multiplet overlapping with one of the methoxyl signals. High resolution mass spectrometry established the formula, $C_{23}H_{32}O_3N_2$, for this compound (found: 384.239; calc: 384.241). The mass spectrum (Figure 99) showed the expected fragments at m/e 384(M^+), 259 (base peak), 210 and 124.

For the less polar component high resolution mass spectrometry established the formula, $C_{23}H_{32}O_3N_2$ (found: 384.240; calc: 384.241). The infrared spectrum of this material was almost superimposable with the one of the above compound. The ultraviolet spectrum also showed the typical chromophore (298, 288 and 232 mμ). The NMR spectrum (Figure 100) demonstrated

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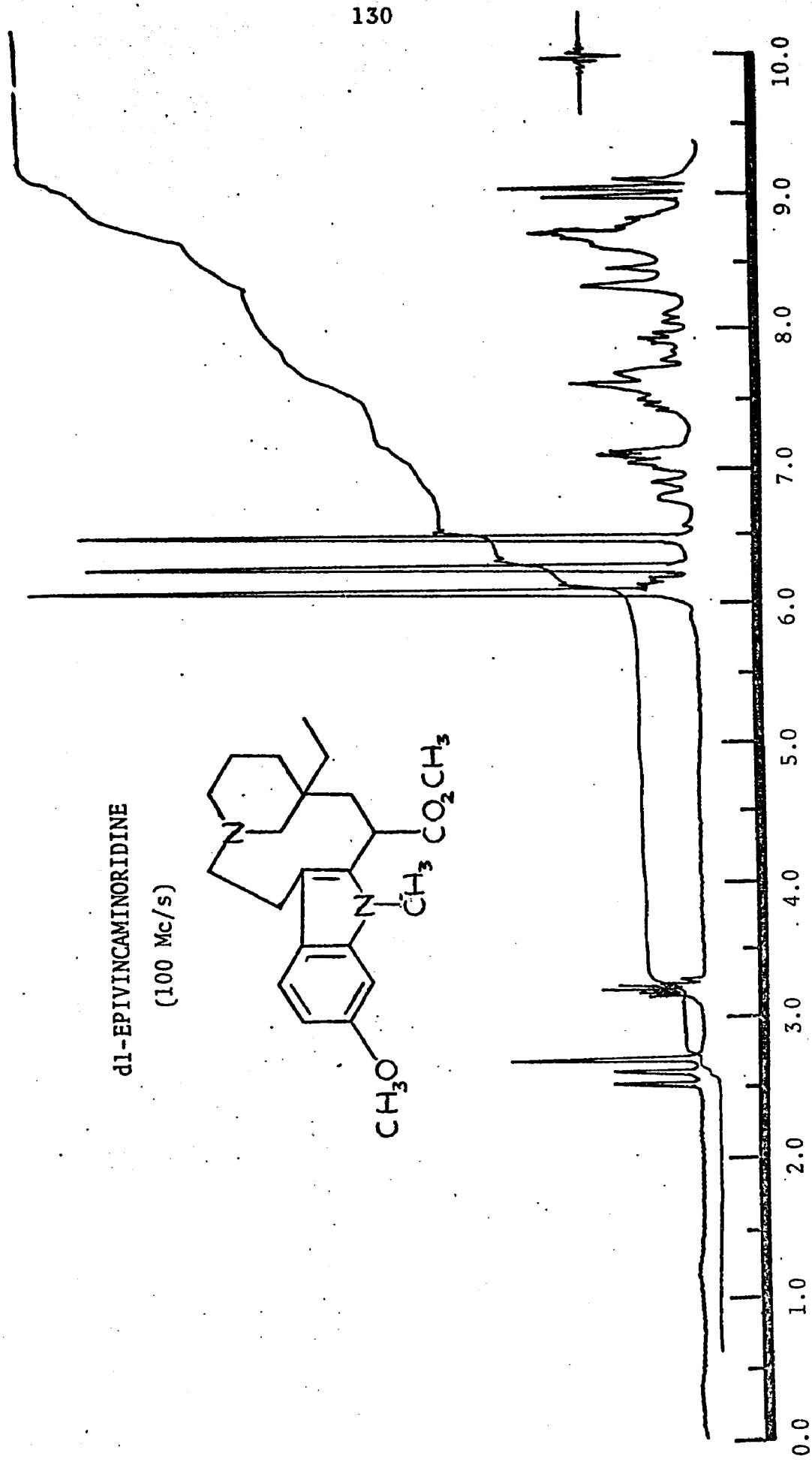

Figure 98. NMR spectrum of dl-epivincaminoridine (7).

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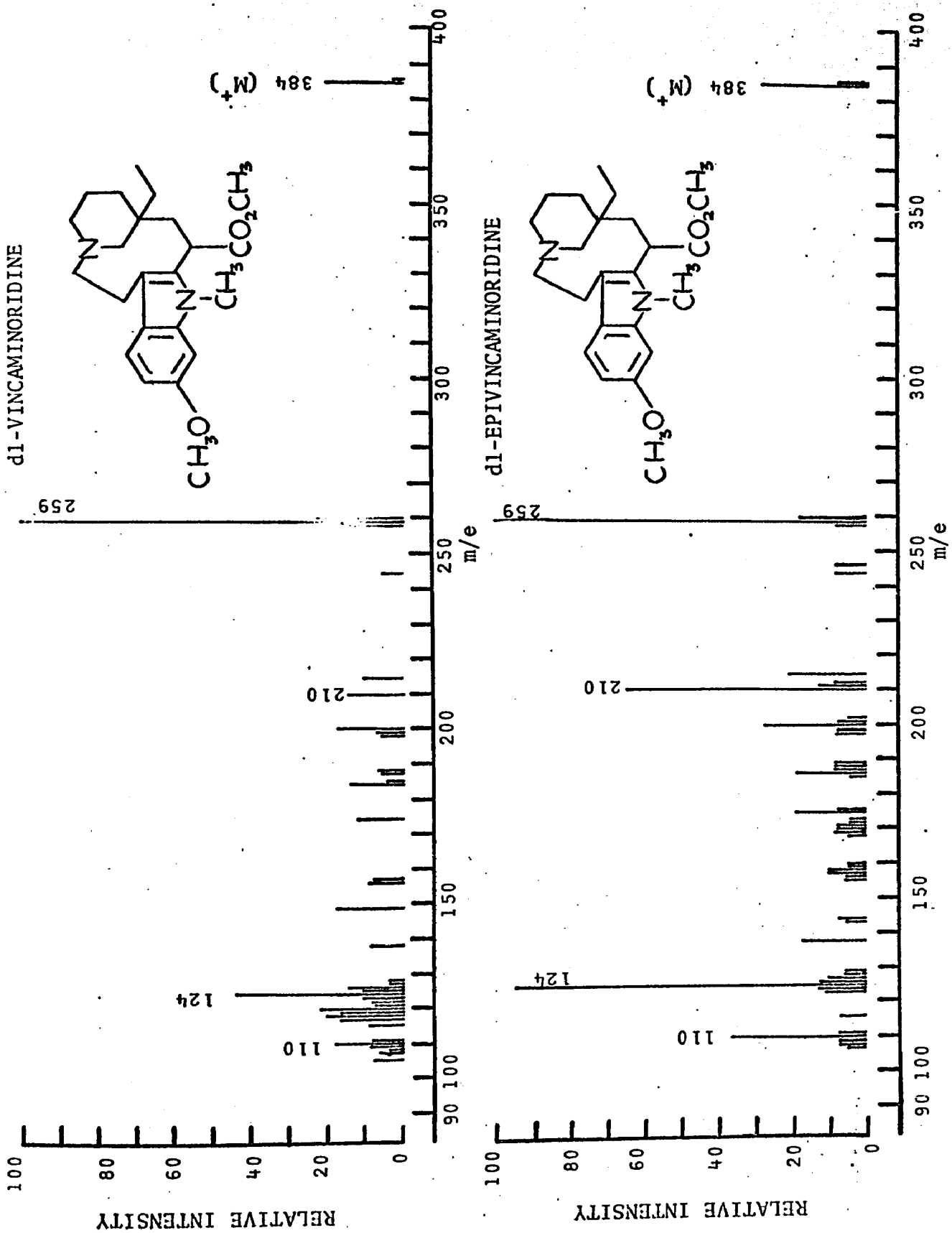

Figure 99. Mass spectra of dl-Vincaminoridine (7) and its epimer.

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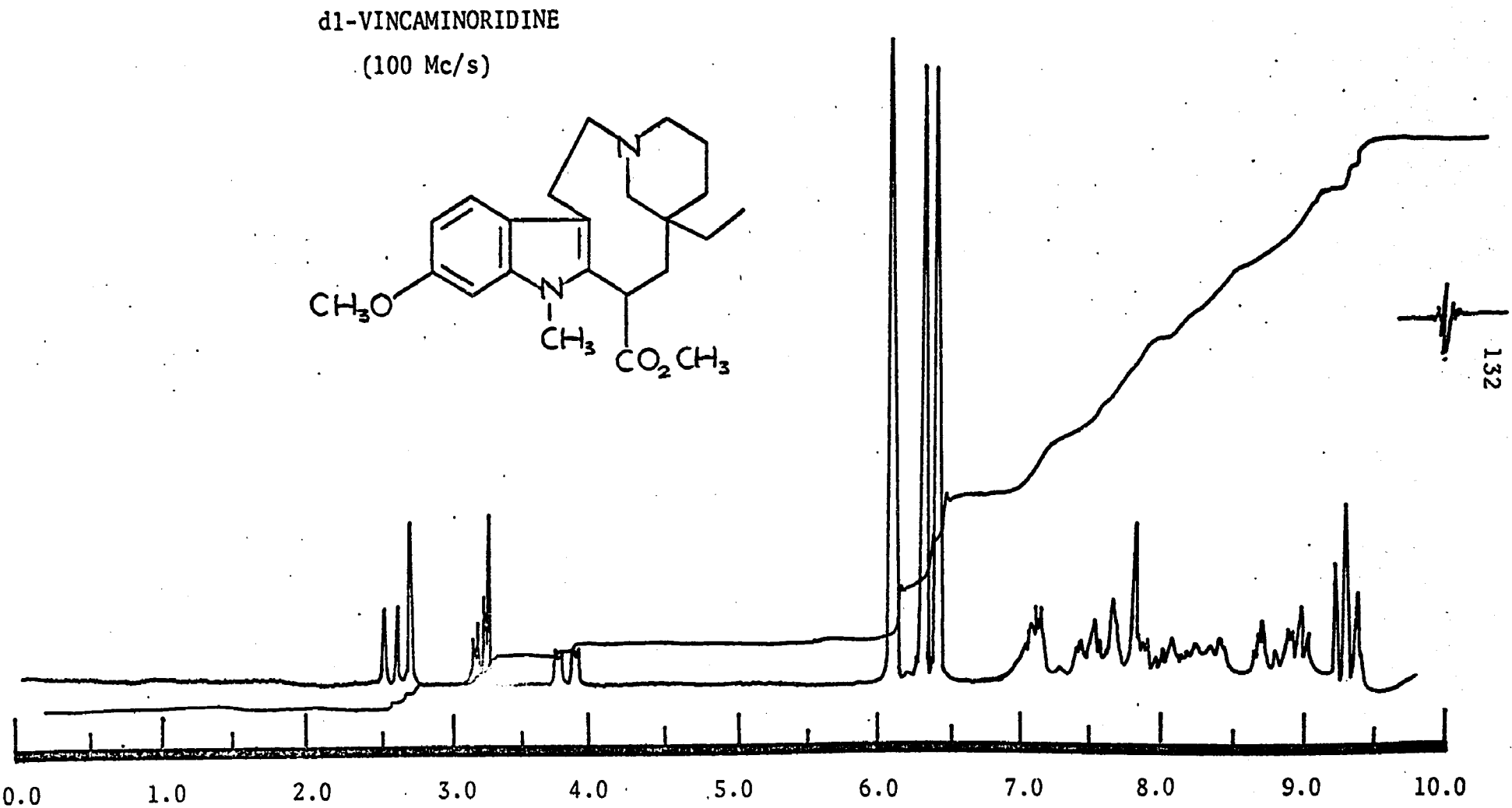

Figure 100. NMR spectrum of dl-vincaminoridine (7).

no $N_{(\alpha)}$-proton and again the N-methyl protons resonated at τ 6.46. The C-3 proton was present as a multiplet at τ 3.90. The mass spectrum (Figure 99) demonstrated the expected peaks at m/e 384, 259, 210 and 124.

These latter two substances bear the skeletal features of the natural system of vincaminoridine, an alkaloid isolated from Vinca minor Linn. and has been assigned structure (7).[4] The NMR, IR and mass spectra of the natural vincaminoridine became available to us recently from Dr. Kompis. Comparison of them with the above mentioned two dl-epimers confirmed that vincaminoridine is the (+) enantiomer[4] of the totally synthesized 16-methoxy-N-methyl-dl-epivincadine. This means that this latter dl-epimer (less polar in TLC) possesses the conformation features of dl-epivincadine and vincaminorine (Figure 69).

It is pertinent at this point to summarize some interesting similarities and differences of the chemical shifts in the NMR spectra of various compounds prepared in this study. In particular, as already mentioned, the NMR results provide an invaluable method for assigning stereochemistry in these compounds. The following table illustrates this point rather clearly.

The transannular cyclization reaction mentioned several times before could provide an obvious synthesis of the pentacyclic aspidosperma-type systems. Although the pentacyclic structure (10) has not been isolated from natural sources, it is a valuable intermediate for the total synthesis of the monomeric alkaloid, vindoline (20), and thereby provides entry into the dimeric series as well. We therefore turned our attention to the trans-annular cyclization of the above nine-membered ring intermediates, vinca-minoridine and its epimer to see whether we could complete the synthesis of (10)

Earlier attempts to prepare this compound using platinum on charcoal in

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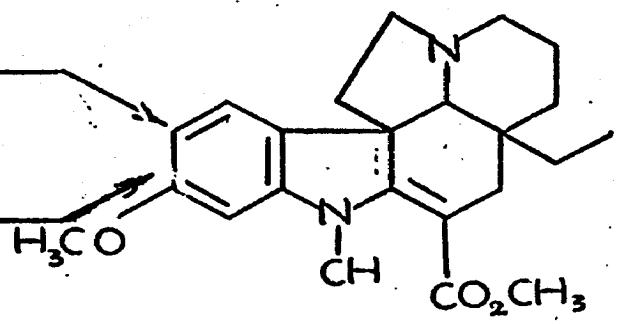
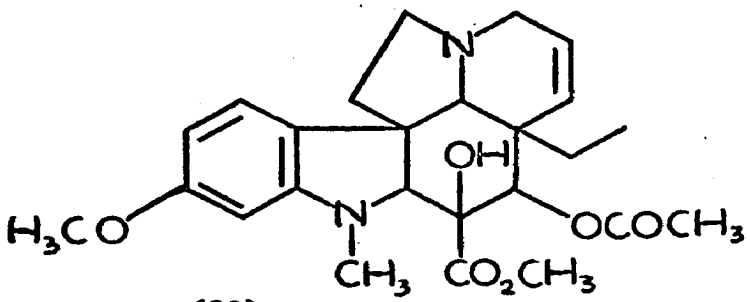
d1-VINCAMINORIDINE

(7)

d1-EPIVINCAMINORIDINE



(10)



(20)

SHIFTS OF PROTON RESONANCES DUE TO STEREOCHEMICAL CHANGES

(values are in τ units)

A/A	NUMBER	COMPOUND	C-3 H	CO_2CH_3	CH_3CH_2
1	(94)	Alcohol-I	5.86	--	9.15
2	(94)	" -II	5.78	--	9.30
3	(165)	11-Methoxy alcohol-I	6.00	--	9.18
4	(165)	" " -II	5.65	--	9.27
5	(139)	Cyanide-I	6.08	--	9.07
6	(139)	" -II	3.99	--	9.34
7	(168)	16-Methoxy-cyanide-I	6.12	--	9.07
8	(168)	" " -II	4.04	--	9.35
9	(3)	d1-Vincadine	6.20	6.28	9.16
10	(3)	d1-Epivincadine	4.41	6.33	9.33
11	(170)	16-Methoxy-d1-vincadine	6.31	6.31	9.18
12	(170)	" -d1-epivincadine	4.49	6.38	9.36
13	(7)	d1-Epivincaminoridine	6.20	6.34	9.08
14	(7)	d1-Vincaminoridine	3.90	6.38	9.33

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an oxygen atmosphere resulted in a large number of by-products (TLC information), and no major component could be separated. The ultraviolet spectrum of this crude product had a broad absorption with maxima at 296 and 210 mμ. No maximum was noticed in the region of 330 mμ which is the expected absorption for the chromophoric system inherent in (10).[91]

Mercuric acetate oxidation in glacial acetic acid at room temperature on a mixture of the above epimers gave a reaction product which was purified by preparative TLC on silica gel. Four components were isolated. One of these (30% of the mixture) was of medium polarity (TLC: chloroform-ethyl acetate, 1:1, alumina) and had an ultraviolet absorption at 337, 312 (infl.) and 227 mμ in close agreement with what was expected.[91] The infrared spectrum had demonstrated strong absorptions at 1715 cm^{-1} and 1660 cm^{-1} clearly suggesting a conjugated ester group. Unfortunately the small amount of this material did not allow us to take an NMR spectrum. Mass spectrum of this material had a peak at 382 (M^+) and other important peaks were at m/e 263, 202, 149 and 124. High resolution mass spectrometry revealed the formula, $C_{27}H_{32}O_4N_2$, (found: 382.224; calc: 382.225). The above results suggested that this was a desired cyclization compound. When we repeated the reaction with one of the dl-epimers (dl-vincaminoridine) we reproduced our yield and the same reaction mixture was obtained as with the mixture of dl-epimers. Preparative TLC on alumina gave two semicrystalline materials in 11% (less polar component) and 24.5% (more polar component) yield. The infrared spectra of both of these were superimposable and the same as previously mentioned. The ultraviolet spectra were slightly different. The less polar component had maxima at 335, 310 (infl.) and 225 mμ. The other one had maxima at 340, 310 (infl.) and 225 mμ. Again insufficient amounts of material were available to obtain further data on these two isomeric compounds.

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EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. The ultraviolet (UV) spectra were recorded in methanol on a Carey 11 recording spectrophotometer. The infrared (IR) spectra were taken on a Perkin-Elmer Model 21 and Model 137 spectrometers. The nuclear magnetic resonance (NMR) spectra were recorded in deuteriochloroform at 100 megacycles/sec on a Varian HA-100 instrument except if otherwise indicated. The position of all NMR absorption signals are given in the Tiers τ scale with reference to tetramethylsilane as the internal standard set at τ 10.0 units. For multiplets the τ values given represent the center of the signal.

Mass spectra were determined on an Atlas CH-4 or on an Associated Electrical Industries MS-9 high resolution mass spectrometer. The molecular formulae were determined by high resolution mass spectrometry on the MS-9 instrument. Suitable standards of known molecular weight were employed for this purpose.

Silica gel G and alumina Woelm containing 2% by weight of a fluorescent indicator were used for thin-layer chromatoplates. As spraying reagent a solution 1:2 of antimony pentachloride in carbon tetrachloride, or a solution of ceric sulfate in aqueous sulfuric acid were used extensively. Column chromatography was performed using either Woelm grade silica or neutral alumina and deactivated as required with the correct amount of water.

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Sometimes Shawinigan alumina neutralized and deactivated by 3% of 10% aqueous acetic acid was used as indicated. Distilled solvents were used.

Elemental analysis were performed by Dr. A. Bernhart and his Associates, Mulheim (Ruhr), West Germany and by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Preparation of sodium triphenyl methane

Sodium (3 g.) covered with dry xylene was carefully melted with a free flame in a thick walled bottle. To this melted sodium, kept under a dry nitrogen atmosphere, mercury (200 g.) was added with extra caution. The remaining xylene was decanted and the amalgam allowed to cool to room temperature. To the cold amalgam dry ethyl ether (50 ml) and triphenyl methyl chloride (11 g.) were added, the bottle stoppered well and the mixture was shaken vigorously for 6 hours. At the end of this time another 80 ml of the dry ethyl ether were added, the mixture was shaken well and allowed to rest for 5 to 6 hours. Small samples of the dark red solution were taken and titrated with 0.1 N sulfuric acid using methyl red as indicator followed. The concentration of this solution was approximately 0.25 mole/lit. The supernatant dark-red solution was transferred into the reaction flask with caution, under a dry nitrogen atmosphere.

Ethyl-α-(γ-benzyloxypropyl)-α-allylbutanoate (116).

To an ether solution of sodium triphenyl methane (73 ml, 0.26 N, 19 mmole) the ethyl ester (90a) (5.0 g., 19 mmole) was added and the mixture was stirred for 1 1/2 hours at room temperature. The transfer of reagents and the reaction itself was performed under oxygen free nitrogen in a dry apparatus. Allyl bromide (2.3 g, 19 mmole) freshly distilled /71°, was added dropwise under good stirring and it was left to react for about 20

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minutes more after the addition. The reaction mixture was kept at room temperature all the time by occasional cooling. By the end of this time the formation of insoluble sodium bromide resulted in a thick cloudy solution. Water (20 ml) was added and the layers separated. Extractions with ethyl ether (2 x 20 ml) followed. The combined ether layers were washed with water (2 x 25 ml) and dried over anhydrous magnesium sulfate. Filtration of the inorganic agent and removal of ether under reduced pressure at room temperature yielded a yellow viscous oil. To this oil benzene (10 ml) was added and the solution brought to its boiling point. The triphenyl methane crystallized out overnight. Filtration of the triphenyl methane and repetition of the crystallization once more with benzene gave a yellow oil (6.8 g). This oil was chromatographed on silica gel Woelm (316 g), activity III. Elution with petr. ether (30-60°)-benzene (1:1) gave 5.56 g (98%) of a colourless viscous oil. Purification was also possible by vacuum distillation, b.p. 155-160° (bath)/0.2 mm, to give in quantitative yield compound (116). Infrared (liq. film): 1725 (strong, $-CO_2Et$), 1645 (weak, C=C), 925 (medium, vinyl), 745 and 700 (medium, monosubstituted benzene) cm^{-1}. Ultraviolet spectrum; λ_{max} (log ϵ): 267.5 (2.15), 263.5 (2.32), 257.5 (2.43), 252 (2.36), 247 (2.28) and 222 (2.81) mμ. NMR signals (100 Mc/s): 2.72 (singlet, 5H, aromatic), 4.40 (multiplet, 1H, $-C\underline{H}=CH_2$), 5.00 (multiplet, 2H, $-CH=C\underline{H_2}$), 5.57 (singlet, 2H, $C_6H_5C\underline{H_2}O-$), 5.92 (quartet, J = 7 cps, 2H, $CH_3C\underline{H_2}O_2C-$), 6.60 (triplet, J = 6 cps, 2H, $C_6H_5CH_2OC\underline{H_2}-$), 8.42 (multiplet, 6H, $CH_3C\underline{H_2}CC\underline{H_2}C\underline{H_2}O-$), 8.80 (triplet, J = 7 cps, 3H, $-CO_2CH_2C\underline{H_3}$), and 9.20 (triplet, J = 7 cps, 3H, $C\underline{H_3}CH_2-$). Mass spectrum; main peaks: m/e 91 (base peak), 139, 156, 167, 197. Molecular weight: 304.204. Calc. for $C_{19}H_{28}O_3$: 304.204. Found: C, 74.71; H, 9.43. Calc. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27.

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Ethyl-α-(γ-benzyloxypropyl)-α-(β,γ-dihydroxypropyl)-butanoate (117)

To a solution of the allyl ester (116) (4.45 g, 14.7 mmole) in tetrahydrofuran (80 ml) a solution of osmium tetroxide (11.7 ml, 0.46 mmole) in tetrahydrofuran was added dropwise with stirring at room temperature, under a nitrogen atmosphere. The solution of osmium tetroxide was prepared by dissolving the tetroxide (250 mg) in absolute tetrahydrofuran (25 ml) (distilled over lithium aluminum hydride); conc.: 39.3 mmole/lit. This solution of the catalyst was kept in the dark and in the fridge. After the addition of the catalyst the stirring continued for 10 minutes longer. The solution turned black and a solution of sodium chlorate (1.84 g, 16.8 mmole) in water (80 ml) was added slowly. The reaction vessel was placed in a water bath (40-50°C) and stirring continued for a further 44 hours. The reaction mixture was checked at intervals by TLC, until almost all the starting material had disappeared. The solvent was removed under reduced pressure and water (150 ml) was added. Extraction with ethyl ether (3 x 300 ml) followed. The combined extracts were washed with water (2 x 150 ml) and dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of ether under reduced pressure gave a gray viscous oil (4.81 g). This oil was chromatographed on silica gel Woelm (270 g), activity IV. Elution with ethyl ether gave a clear viscous oil (3.47 g) in 68.5% yield. A small amount of this oil was dried in a vacuum pistol with phosphorus pentoxide over boiling benzene for 4 hours and then for 2 days at room temperature. Infrared (liq. film): 3400 (strong, 2 x OH), 1725 (strong, $-CO_2Et$), 1645 and 925 (no peaks), 745 and 700(medium, monosubstituted benzene) cm^{-1}. Ultraviolet: λ_{max} (log ε): 267 (2.33), 263.5 (2.43), 257.5 (2.51), 252 (2.45), 247 (sh. 2.41) and 218 (3.23) mμ. NMR signals (60 Mc/s):

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2.68 (singlet, 5H, aromatic), 5.50 (singlet, 2H, $C_6H_5\underline{CH_2}O$-), 5.86 (quartet, J = 7 cps, 2H, $CH_3\underline{CH_2}O_2C$-), 6.0-6.8 (broad multiplet, 3H, -$\underline{CH}OH\underline{CH_2}OH$), 6.53 (triplet, J = 6 cps, 2H, -$\underline{CH_2}OCH_2C_6H_5$), 6.88 (broad singlet, 2H, 2x$\underline{OH}$), 8.76 (triplet, J = 7 cps, 3H, $\underline{CH_3}CH_2O_2C$-), 9.19 (triplet, J = 7 cps, 3H, $\underline{CH_3}CH_2$-). Addition of one drop of D_2O caused disappearance of singlet at 6.88 τ. Mass spectrum; main peaks: m/e 91 (base peak), 99, 125, 135, 153, 199, 305. Molecular weight: 338.209. Calc. for $C_{19}H_{30}O_5$: 338.210. Found: C, 67.34; H, 9.05. Calc. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94.

Ethyl-α-(γ-benzoxypropyl)-α-(α-formylmethyl)-butanoate (118).

To a solution of diol (117) (520 mg, 1.53 mmole) in a mixture of tetrahydrofuran (25 ml) and water (25 ml), solid (powder) sodium meta-periodate (2.05 g, 5.88 mmole) was added in small portions. The mixture was stirred at room temperature under nitrogen for 51 hours. At this time only a trace of starting material was present. Water (10 ml) was then added and extraction with ethyl ether (3 x 30 ml) followed. The combined ether extracts were washed with water (2 x 15 ml) and the organic layer dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure afforded a viscous oil (527 mg). The oil was chromatographed on alumina neutral Woelm (30 g), activity II. Elution with benzene-ethyl ether (4:1) gave 315 mg (67%) of pure aldehyde (118). On further elution diol (72 mg) was recovered. For analytical purposes a small amount of this aldehyde was distilled quantitatively under vacuum (165°/0.1 mm) to give a colourless viscous oil. Infrared (liq. film): 2750 (weak, CH of CHO), 1722 (very strong, -CO_2Et and CHO), 742 and 705 (medium, monosubstituted benzene) cm^{-1}. Ultraviolet: λ_{max} (log ε): 267.5 (2.34), 263.5 (2.44), 257.5 (2.51), 252 (2.47), 247 (sh. 2.45), and 220 (3.11) mμ. NMR signals (60 Mc/s): 0.22

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(triplet, J = 2 cps, 1H, -C<u>H</u>O), 2.68 (singlet, 5H, aromatic), 5.52 (singlet, 2H, -OC<u>H</u>$_2$C$_6$H$_5$), 5.84 (quartet, J = 7 cps, 2H, -CO$_2$C<u>H</u>$_2$CH$_3$), 6.55 (triplet, J = 6 cps, 2H, -C<u>H</u>$_2$OCH$_2$C$_6$H$_5$), 7.36 (doublet, J = 2 cps, 2H, -C<u>H</u> CHO), 8.77 (triplet, J = 7 cps, 3H, -CO$_2$CH$_3$C<u>H</u>$_3$), and 9.15 (triplet, J = 7 cps, 3H, -CH$_2$C<u>H</u>$_3$). Mass spectrum; main peaks: m/e 91 (base peak), 141, 158, 182 and 199. Molecular weight: 306.181. Calc. for $C_{18}H_{26}O_4$: 306.183. Found: C, 70.47; H, 8.51. Calc. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55.

<u>Direct preparation of aldehyde (118)</u>

The allyl compound (116) (12.26 g, 40.4 mmole) was dissolved in a mixture of tetrahydrofuran (250 ml, distilled over sodium and lithium aluminum hydride) and water (250 ml). Osmium tetroxide (500 mg, 1.97 mmole, crystals) was added. The reaction was performed under oxygen-free nitrogen. The mixture was stirred at room temperature for 45 minutes followed by addition of solid (powder) sodium meta-periodate (21.1 g, 60.5 mmole). The reagent was added in small portions as soon as the previously added amounts had been dissolved. Stirring at room temperature was continued for 48 hours upon which the formation of the aldehyde ceased. The tetrahydrofuran was removed under reduced pressure and extraction with ethyl ether followed (3x200ml). The combined ether extracts were washed with water (2 x 80 ml). The ether layer dried over anhydrous sodium sulfate and upon filtration and removal of the solvent gave 12.2 g of a crude dark oil. This oil was chromatographed on silica gel Woelm (600 g), activity III. Elution with benzene-ethyl ether (19:1) gave 8.62 g of pure aldehyde (118) (70%) and with ethyl ether 1.93 g of diols (117) (11%) were recovered. Yield (based on recovered diols): 81.5%. The aldehyde (118) so prepared was identical in every respect with the one prepared by the stepwise procedure.

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Preparation of cyclic lactam (119)

A solution of tryptamine (2.33 g, 14.6 mmole) and aldehyde (118) (4.42 g, 14.4 mmole) in glacial acetic acid (20 ml) was refluxed in an oxygen-free nitrogen atmosphere for 1 hour. By the end of this time the aldehyde was not present any more. Removal of acetic acid under reduced pressure with gentle heating (~ 60°) gave a yellow gum. This material chromatographed on alumina neutral Woelm (200 g) activity III. Elution with benzene gave 5.23 g (90%) of a yellowish gum. The two dl-epimers were never separated. This material could stand molecular distillation (240°/0.1 mm) to give a yellowish glass, but the recovery was not quantitative. Infrared ($CHCl_3$): 3490 (medium sharp, -NH), 1675 (very strong, -CON-) cm^{-1}. Ultraviolet: λ_{max} (log ε): 326 (3.37), 312.5 (3.44), 290 (3.83), 282.5 (3.90), 273 (sh. 3.89), and 224 (4.57) mμ. NMR signals (100 Mc/s): 1.35 and 1.40 (broad overlapping singlets, 1H, NH), 2.75 (multiplet, 9H, aromatic), 5.21 and 5.24 (triplets, J = 8 cps, 1H, C-3 proton), 5.55 and 5.67 (singlets, 2H, $-OCH_2C_6H_5$), 9.04 and 9.29 (triplets, J = 7 and 8 cps, 3H, $-CH_2CH_3$). Mass spectrum; main peaks: m/e 91, 149, 168, 251, and 311 (base peak). Molecular weight: found 402.231. Calc. for $C_{26}H_{30}O_2N_2$: 402.231.

Preparation of cyclic amine (93)

The cyclic lactam (119) (5.2 g, 12.9 mmole) was dissolved in absolute tetrahydrofuran (300 ml, refluxed over sodium and distilled over lithium aluminum hydride) and lithium aluminum hydride (1.47 g, 38.0 mmole) was added in portions when under oxygen-free nitrogen. Stirring and refluxing were continued for 8 1/2 hours at which time no starting material was present. After cooling to room temperature the reaction complex was decomposed

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carefully by the slow addition of water. Some excess of water was added and the mixture was stirred for 10 minutes more. The resulting white sludge was filtered through a bed of celite and washed several times with tetrahydrofuran. The filtrate after removal of tetrahydrofuran under reduced pressure was extracted with ethyl ether (3 x 200 ml). The combined ether extracts were washed with water (2 x 80 ml) and dried over magnesium sulfate. Filtration and removal of solvent afforded a yellow viscous oil. This oil was purified by column chromatography on alumina neutral Woelm, activity II. Elution with benzene-chloroform (7:1) gave 4.76 g (95%) of pure mixture of the two dl-epimers. This compound could also be easily purified by molecular distillation (240°/0.05 mm) to give quantitative yield of the desired product (93). Infrared ($CHCl_3$): 3350 (medium sharp, -NH) cm^{-1} and no carbonyl absorption. Ultraviolet: λ_{max} (log ε): 291 (3.66), 283 (3.73), 275 (sh. 3.72), and 223 (4.30) mμ. NMR signals (100 Mc/s: 2.09, (broad singlet, 1H, NH), 2.75 (multiplet, 9H, aromatic), 5.50 and 5.62 (singlets, 2H, $-O\underline{CH_2}C_6H_5$), 5.89 (triplet, J = 6 cps, 1H, C-3 proton), 9.13 and 9.30 (triplets, J = 7 and 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: 91, 149, 184, 260, 297 and 388 (M^+) (base peak). Molecular weight: 388.253. Calc. for $C_{26}H_{32}ON_2$: 388.251. Found: C, 80.53; H, 8.56; N, 6.99. Calc. for $C_{26}H_{32}ON_2$: C, 80.37; H, 8.30; N, 7.21.

Hydrogenolysis of cyclic amine (93)

A solution of cyclic amine (93) (4.7 g, 12.1 mmole) in glacial acetic acid (30 ml) was added slowly to a suspension of 10% palladium on charcoal (2.0 g) in glacial acetic acid (100 ml). The catalyst was prehydrogenated until the absorption of hydrogen ceased (about 15 minutes). The reaction was performed in 1 Atm. of hydrogen and at room temperature. By the end of

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33 hours and when the absorption of hydrogen ceased, the reaction was stopped and the catalyst was filtered through a bed of celite and washed with warm acetic acid (20 ml) and some water. The solution was made basic by slow addition of a saturated solution of sodium carbonate. Extraction with methylene chloride followed (3 x 100 ml). The combined extracts were washed with water (2 x 50 ml) and the organic layer dried over magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave a yellow gum (3.6 g). The crude product was chromatographed on an alumina neutral Woelm (300 g), activity II, column. Elution with benzene-chloroform (1:1) gave the least polar fraction which was shown to be unreacted starting material (93) (0.6 g). The desired alcohols were eluted from chloroform-methanol (99:2) to give pure 1.37 g (37%) of alcohol-I (less polar), and 1.7 g (46%) of alcohol-II, as white glass.

Alcohol-I: It was easily crystallized from methylene chloride, m.p. 166-167°. Infrared ($CHCl_3$): 3440 (medium sharp, NH), 3280 (medium broad, OH) cm^{-1}. Ultraviolet: λ_{max}^{EtOH} (log ε): 291 (3.92), 283 (4.01), 275 (sh. 3.97), and 227 (4.54) mμ. NMR signals (100 Mc/s): 1.99 (broad singlet, 1H, -NH), 2.78 (multiplet, 4H, aromatic), 5.86 (triplet, J = 6 cps, 1H, C-3 proton), 6.55 (triplet, J = 6 cps, 2H, $-CH_2OH$), and 9.15 (triplet, J = 7 cps, 3H, $-CH_2CH_3$). Mass spectrum; main peaks: m/e 297 (M-1), 184, 170, and 156. Molecular weight: 298.204. Calc. for $C_{19}H_{26}ON_2$: 298.204. Found: C, 76.19; H, 8.92; N, 9.28. Calc. for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39.

Comparison of this alcohol-I with a crystallized sample of alcohol A showed that they were identical (TLC, IR, and NMR superimposable, mixed m.p.).

Alcohol-II: It was crystallized also from methylene chloride, m.p. 168-170°. Infrared ($CHCl_3$): 3390 (medium sharp, NH), 3240 (medium broad, OH) cm^{-1}.

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Ultraviolet: λ_{max}^{EtOH} (log ε): 291 (3.89), 283 (3.96), 275 (sh. 3.95), and 227 (4.52) mμ. NMR signals (100 Mc/s); 1.70 (broad singlet, 1H, NH), 2.75 (multiplet, 4H, aromatic), 5.78 (triplet, J = 6 cps, 1H, C-3 proton), 6.38 (collapsed triplet, 2H, $-CH_2OH$), and 9.30 (triplet, J = 7 cps, 3H, $-CH_2CH_3$). Mass spectrum; main peaks: m/e 297 (M-1), 184, 170 and 156. Molecular weight: 298.204. Calc. for $C_{19}H_{26}ON_2$: 298.204. Found: C, 76.81; H, 8.93, N, 9.15. Calc. for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39.

Comparison of this alcohol-II with a crystallized sample of alcohol C revealed that they were identical (TLC, IR and NMR superimposable, m.p. no depression).

Mesylation of alcohol-I and II (94)

a) Alcohol-I (94) (206 mg, 0.69 mmole) was dissolved in a mixture of dry triethylamine (2.5 ml) and chloroform (5.0 ml). The reaction mixture was cooled at -10-0° (ice-rock salt bath) and freshly distilled methane sulfonyl chloride (ca. 500 mg, 4.37 mmole) was added dropwise with efficient stirring. The resulting mixture was allowed to come slowly to room temperature (moisture was excluded). After 42 1/2 hours the solvent was removed under reduced pressure and the resulting deep red solid was dissolved in chloroform (15 ml) and extracted with 4 N ammonium hydroxide (3 x 20 ml.). The combined aqueous layers were washed with chloroform (1 x 10 ml). The water was removed under reduced pressure with gentle heating (water bath) to give a yellow gum. This gum was azeotroped several times with dry benzene to remove any trace of water. The resulting solid was treated with warm chloroform several times. The combined chlorofrom extracts after removal of the solvent under reduced pressure gave an amorphous yellowish compound. This compound was the pure mesylate of alcohol-I, 260 mg (100%) and was

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usually used directly for the next step. However, fast column chromatography on alumina neutral Woelm, activity II, followed by elution with chloroform-methanol (3:1) can be used if necessary. It was not important for our purpose to completely characterize this compound (95).

b) Alcohol-II was mesylated exactly as above to give an amorphous yellowish material consisting of pure mesylate (95) yield (100%).

Preparation of dl-quebrachamine (9)

a) The mesylate (95) of alcohol-I (130 mg, 0.345 mmole) was taken in N-methylmorpholine (50 ml, distilled over lithium aluminum hydride) and lithium aluminum hydride (390 mg, 10.3 mmole) was added in small portions to it under efficient stirring. The reaction was performed under oxygen-free nitrogen. The mesylate was almost insoluble in this solvent. Refluxion followed for 11 hours upon which the formation of more reaction product seemed to cease. The reaction mixture was cooled to room temperature and the excess of lithium aluminum hydride was decomposed carefully by slow addition of water in excess with vigorous stirring. The resulting gray sludge was stirred for 15 minutes more until white and then filtered through a bed of celite. The solid on the funnel was washed several times with warm chloroform and discarded. The filtrate was taken in some water (20 ml) and the organic layer was separated. The aqueous layer was washed with chloroform (2 x 20 ml), and the combined organic layers were washed with water (2 x 10 ml). The chloroform layer was dried over anhydrous sodium sulfate, the inorganic agent filtered and the solvent removed under reduced pressure to give a viscous colourless oil. This material was chromatographed on alumina neutral Woelm (50 g), activity I. Elution with benzene-chloroform (1:1) gave 50 mg of a colourless viscous oil which solidified upon standing

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in a desiccator. This material was pure quebrachamine (50% yield). For comparison purposes we crystallized this material from wet methanol, m.p. 141-144°. Mixed m.p. with an authentic sample of quebrachamine (1:1) showed no depression. The TLC properties in several solvent-absorbant systems were identical with those of authentic quebrachamine and the UV spectrum was in agreement. Finally, the IR were superimposable.

b) The mesylate (95) of alcohol-II was also converted to quebrachamine following the above reaction procedure. Similar comparison confirmed the identity of the purified reaction product. Yield was 51%.

c) Following described procedure,[3] the preparation of quebrachamine (9) was also achieved by using lithium in liquid ammonia. This reaction was performed with either of the mesylates of alcohol-I or II separately. The crude product was purified on alumina neutral Woelm, activity II and eluted with petroleum ether-chloroform (1:1). The yields were 6-9%. Comparison of this product was done as above with a sample of authentic quebrachamine. In addition to the reaction product, mesylate was always recovered from the aqueous layer.

Mercuric acetate oxidation of benzyl ether amine (92)

To a stirred absolute methanol (500 ml) in a well dried apparatus, a solution of benzyl ether amine (92) (920 mg, 2.3 mmole) in 10 ml of absolute methanol was added. This and the following procedure were performed under highly purified nitrogen ("L" Grade, Canadian Liquid Air Ltd.), dried by passing through traps of conc. sulfuric acid and diarite. Glacial acetic acid (15 ml) was added slowly to the stirred solution. To this mixture solid mercuric acetate (6.0 g, 18.8 mmole) was added in small portions and the reaction mixture was left at room temperature overnight. Then the

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reaction mixture was refluxed and the progress of the reaction followed by removing small aliquots of the reaction mixture, bubbling hydrogen sulfide through as described later, and observing the development of the strong light absorption at 353 mμ. The reaction mixture was allowed to come to room temperature and the yellowish crystalline mercurous acetate (2.35 g, 4.5 mmole) was filtered off under vacuum through a bed of celite on a sintered glass disc in a nitrogen atmosphere. The light greenish solution was immersed in a bath of hot water (about 50°C) and immediately hydrogen sulfide was bubbled through for about 10' to destroy the mercury complex. By checking, the completion of the precipitation of black mercuric sulfides was insured. Then the solution was left to come to room temperature and the precipitate of mercuric sulfide was allowed to settle down. Filtration under vacuum followed through a bed of celite. Evaporation of the solvent under reduced pressure at moderate temperature gave a redish oily residue. This residue was processed immediately to the next reaction step without any delay. It was dissolved in methanol (300 ml) and a large excess of solid sodium borohydride (7.1 g, 0.187 mmole) was added slowly with sufficient stirring. By the end of the addition, the strong absorption of light at 353 mμ had disappeared. The reaction mixture was left for 2 hours at room temperature and then the methanol was removed under vacuum with gentle heating. The resultant greenish sludge was taken in water (50 ml) and was extracted with chloroform (3 x 150 ml). The combined chloroform extracts were washed with water (1 x 50 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave a brown gum (754 mg). Complete separation of all the products of the reaction by alumina was not successful. Chromatography on alumina Shawinigan (45 g), neutralized by 10% acetic acid, activity II-III made on benzene, gave a

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mixture of the dl-epimers by elution with benzene-chloroform (1:1). This mixture of the dl-epimers (341 mg, brown gum, 38%) and of starting material (92) had very similar R_f values on thin layer chromatoplates (alumina, ethyl acetate/chloroform, 3:1). No further attempt to separate these components was made, although it seems easy to partially crystallize (from ethyl ether, yellow amorphous solid).

Spectra of this mixture of dl-epimers were taken. Infrared (neat): 3400 (-NH), 740 and 700 (aromatic) cm^{-1}. Ultraviolet: λ_{max}: 224, 275 (sh.), 283, 291 mμ. NMR signals (60 Mc/s): 1.94 (broad singlet, 1H, -NH), 2.75 (multiplet, 9H, aromatic), 5.53 (two overlapping singlets, 2H, $C_6H_5\underline{CH}O$-), 6.30 (multiplet, 1H, C-3 proton), 6.55 (collapsed triplet, 2H, $C_6H_5CH_2O\underline{CH_2}$-), 9.15 (triplet, 3H, $\underline{CH_3}CH_2$-). Molecular distillation of a sample of dl-epimers for elemental analysis was unsuccessful, leading to extensive decomposition as was shown by thin layer chromatography and ultraviolet spectra.

Debenzylation of a mixture of cyclized benzyl ether amines (93) + (96)

To a mixture of dl-epimeric cyclized benzyl ether amines (93) + (96) (242 mg, 0.25 mmole), glacial acetic acid (15 ml) and 10% palladium on charcoal (242 mg) were added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure with continuous stirring. The uptake of hydrogen was measured. When the uptake of hydrogen ceased (about 25 hours) the reaction was stopped. The catalyst was removed by filtration through celite and washed with warm acetic acid (2 x 4 ml) and warm water (2 x 4 ml). The clear yellowish filtrate was neutralized with 40% aqueous sodium carbonate (checked with litmus paper). The resulting solution was extracted with chloroform (3 x 100 ml) and the combined chloroform extracts were washed with water (2 x 60 ml). The organic layer was separated and

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dried over anhydrous sodium sulfate. Filtration of the inorganic agent and removal of the solvent under reduced pressure at moderate temperature gave the crude alcohols as a green-brown gum (160 mg).

The crude product was purified by column chromatography on alumina Shawinigan (8.5 g), neutralized by 10% acetic acid, activity II-III. The chromatography provided four pure alcohols designated as A', A, B and C in order of increasing polarity. Alcohols A' and A were eluted with benzene-chloroform (50:50), alcohol B with chloroform and finally alcohol C with chloroform-methanol (99:1).

Alcohol A': 18 mg, 10%, as a greenish glass; no attempt was made to crystallize it. Infrared (neat): 3250 (-OH), 740 (aromatic) cm^{-1}. Ultraviolet; λ_{max}: 227, 275(sh), 283, 290 mμ. NMR signals (100 Mc/s): 1.20 (broad singlet, 1H, -NH), 2.85 (multiplet, 4H, aromatic), 5.90 (multiplet, 1H, C-3 proton), 6.58 (triplet, J = 6 cps, 2H, CH_2OH), 9.12 (triplet, J = 7 cps, 3H, $-CH_2CH_3$). Mass spectrum; main peaks: m/e 297 (M-1), 184, 170, 156. Molecular weight: 298.204. Calc. for $C_{19}H_{26}ON_2$ 298.204.

Alcohol A: 20 mg, 11%, as a greenish glass; no attempt was made to crystallize it. Infrared (neat): 3200 (-OH), 740 (aromatic) cm^{-1}. Ultraviolet: λ_{max} 225, 275 (sh.), 283, 290 mμ. NMR signals (100 Mc/s): 1.36 (broad singlet, 1H, -NH), 2.75 (multiplet, 4H, aromatic), 5.95 Itriplet, J = 6 cps, 1H, C-3 proton), 6.64 (triplet, J = 6 cps, 2H, $-CH_2OH$), 9.20 (triplet, J = 7 cps, 3H, $-CH_2CH_3$). Mass spectrum; main peaks: m/e 297 (M-1), 184, 170, 156. Molecular weight: 298.204. Calc. for $C_{19}H_{26}ON_2$ 298.204.

Alcohol B: 32 mg, 17%, as a greenish glass; no attempt was made to crystallize it. Infrared (neat): 3230 (-OH), 745 (aromatic) cm^{-1}. Ultraviolet: λ_{max} 223, 274 (sh.), 283, 291 mμ. NMR signals (100 Mc/s): 1.90 (broad singlet, 1H, -NH), 2.75 (multiplet,4H, aromatic), 6.51 (triplet, J = 6 cps, 2H, $-CH_2OH$),

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8.04 (singlet, 2H, $-NC\underline{H}_2C-$), 9.16 (triplet, J = 7 cps, 3H, $-CH_2C\underline{H}_3$). Mass spectrum; main peaks: m/e 297 (M-1), 199, 170, 156, 140. Molecular weight: 298.204. Calc. for $C_{19}H_{26}ON_2$ 298.204.

Alcohol C: 25 mg, 14%, as a greenish glass; no attempt was made to crystallize it. Infrared (neat): 3270 (-OH), 740 (aromatic)cm^{-1}. Ultraviolet: λ_{max} 225, 275(sh.), 283, 291 mμ. NMR signals (100 Mc/s): 1.60 (broad singlet, 1H, $-N\underline{H}$), 2.75 (multiplet, 4H, aromatic), 5.80 (multiplet, 1H, C-3 proton), 6.50 (triplet, J = 6 cps, 2H, $-C\underline{H}_2OH$), 9.12 (triplet, J = 7 cps, 3H, $-CH_2C\underline{H}_3$). Mass spectrum; main peaks: m/e 297 (M-1), 199, 184, 170, 156, 140, 130. Molecular weight: 298.206. Calc. for $C_{19}H_{26}ON_2$ 298.204.

The overall yield of alcohols A', A, B and C from the cyclized amino benzyl ethers (93) + (96) was 52%.

Preparation of cyano compounds (144)

The mesylate of alcohol-I (95), (177 mg, 0.47 mmole) was dissolved in dimethylformamide (10 ml, reagent grade) and pulverised potassium cyanide (130 mg, 2.00 mmole) was added to it. The mixture was refluxed gently in an oxygen-free nitrogen atmosphere for 4 1/2 hours (160°, oil-bath temperature), with efficient stirring. The reaction progress was followed by TLC, and IR. The reaction mixture was brought to room temperature and aqeuous ammonium hydroxide (17 ml, 6 N) was added to it under stirring. The basic solution was extracted with warm benzene (3 x 30 ml). The combined benzene extracts were washed with saturated aqueous solution of sodium chloride (brine, 2 x 10 ml). The organic layer was dried over anhydrous sodium sulfate, the inorganic agent filtered off and the solvent removed under reduced pressure to afford a dark gum (112 mg). The aqueous layer was saturated with solid sodium chloride and extracted with chloroform (2 x 30 ml). The organic layer was dried over anhydrous sodium sulfate, filtration and removal of the solvent

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under reduced pressure gave 21 mg of pure unreacted mesylate.

The crude reaction product (112 mg) was chromatographed on alumina neutral Woelm (3.2 g), activity II, made up on n-hexane. Elution with n-hexane-benzene (1:1) gave an unidentified product (14 mg, yellow gum). A mixture of cyanide-I and II was eluted with benzene (19 mg, white solid), while elution with benzene-ethyl acetate (1:1) gave a mixture of cyanide-III (46 mg, yellow gum) containing some cyanide-I and II. Further elution with the latter solvent mixture gave 6 mg of an unidentified cyanide (IR information) and some polar material (41 mg) was also eluted with ethyl acetate.

The fraction containing mainly cyanide-III (46 mg) was rechromatographed on silica gel Woelm (4.6 g), activity IV. Elution with benzene-chloroform (1:1) gave a mixture of cyanide-I and II (2 mg), while elution with chloroform afforded pure cyanide-III (38 mg).

The fraction containing cyanide-I and II (19 mg) combined with the above (2 mg) and separation by preparative TLC on alumina Woelm developed with chloroform gave cyanide-I (9 mg) and cyanide-II (12 mg).

Cyanide-I: Colourless glass (9 mg, 6%). Crystallization from n-hexane gave a broad m.p., while from ethyl ether afforded a m.p. 208-210°. Infrared ($CHCl_3$): 3400 (medium sharp, NH), 2700-2800 (Bohlmann bands), and 2230 (small, -CN) cm^{-1}. Ultraviolet: λ_{max} (log ε) 292.5 (3.81), 285 (3.85), 278 (sh. 3.82), and 225 (4.47) mμ. NMR signals (100 Mc/s): 1.80 (broad singlet, 1H, -NH), 2.78 (multiplet, 4H, aromatic), 6.08 (quartet, J_{AB} = 5, J_{AC} = 2 cps, 1H, C-3 proton), and 9.07 (triplet, J = 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: m/e 124, 125, 177 and 307 (M^+). Molecular weight: 307.204. Calc. for $C_{20}H_{25}N_3$: 307.204.

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Cyanide-II: Colourless glass (12 mg, 8%). Crystallized from n-hexane had a m.p. 164-168°. Infrared ($CHCl_3$): 3370 (medium sharp, -NH), 2700-2800 (Bohlmann bands), and 2225 (medium, -CN) cm^{-1}. Ultraviolet: λ_{max} (log ε): 293 (3.82), 284 (3.87), 278 (sh. 3.83), and 225 (4.42), mμ. NMR signals (100 Mc/s): 1.80 (broad singlet, 1H, -NH), 2.80 (multiplet, 4H, aromatic), 3.99 (quartet, J_{AB} = 10 cps, J_{AC} = 4 cps, 1H, C-3 proton), and 9.34 (triplet, J = 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: m/e 124, 125, 177 and 307 (M^+). Molecular weight: 307.204. Calc. for $C_{20}H_{25}N_3$: 307.204.

Cyanide-III: Colourless glass (38 mg, 28%). Resisted crystallization. Infrared (neat): 3330 (medium sharp, -NH) and 2220 (medium, -CN). Ultraviolet: λ_{max} (log ε): 290 (3.84), 283 (3.90), 275 (sh. 3.89), and 226 (4.35) mμ. NMR signals (100 Mc/s): 0.94 (broad singlet, 1H, NH), 2.80 (multiplet, 4H, aromatic), 5.50 and 5.88 (two multiplets, 1H each, -CHCN and -CH-N-), 7.42 (singlet, 2H, $-NCH_2C-$), and 9.17 (triplet, J= 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: m/e 130, 155, 170, 267, and 307 (M^+). Molecular weight: 307.204. Calc. for $C_{20}H_{25}N_3$: 307.204.

When mesylate of alcohol-II was treated under the same conditions it gave the same mixture of cyanides as above, after separate purification and identification (TLC, IR, NMR comparison).

Preparation of dl-vincadine and dl-epivincadine (3)

A mixture of cyanides-I and II (144) (20 mg, 0.065 mmole) was placed in a small tube and it was dissolved in a solution of 20% potassium hydroxide in distilled diethylene glycol (0.20 ml). The reaction tube was connected to a purified nitrogen trap system, and it was immersed into an oil bath at ca. 160°. The evolution of some gas was noted, and the reaction was left on for 12 hours. Then the reaction mixture was cooled to room temperature

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and it was taken in methanol (2.0 ml). The diluted solution was cooled at -10-0° (ice-rock salt bath) and neutralized carefully with a saturated solution of hydrogen chloride in methanol (pH paper). Immediately after neutralization an ethereal solution of diazomethane (3% g/ml) was added to the reaction mixture in excess. The resulting solution was allowed to stand at 0°C for 15 minutes and then it was neutralized again. The solution was treated twice more with diazomethane and then the solvent was removed as far as possible with a nitrogen stream. The residue was treated with a small amount of aqueous 10% potassium carbonate (1 ml) and extracted with ethyl ether (3 x 6 ml). The ether solution was dried over anhydrous sodium sulfate, filtered and the solvent removed to give a gum. Fast filtration through alumina neutral Woelm, activity II and elution with benzene-chloroform (1:1) gave 15 mg of a yellow amorphous material (75% crude yield).

The above procedure was repeated precisely with cyanide-I (37 mg, 0.121 mmole) to give 33 mg (81%, crude yield) of a solid. With cyanide-II (37 mg, 0.121 mmole) the same process afforded 31 mg (77% crude yield) of the same reaction product (TLC, IR, NMR spectra).

Combination of the above (79 mg) crude reaction products (from three different reactions) and preparative thin-layer chromatography on silica gel Woelm, developed by benzene-ethyl acetate (1:1) failed to give a good separation. However, on silica gel G and using benzene-ethyl acetate (4:1), we separated the epimeric compounds.

dl-Vincadine: Amorphous solid (14 mg, 14.5%). Attempts to crystallize failed (decomposition). Infrared ($CHCl_3$): 3380 (small, -NH) and 1730 (strong, ester) cm^{-1}. Ultraviolet: λ_{max} (log ε): 292 (3.87), 286 (3.89), and 227 (4.48) mμ. NMR signals (100 Mc/s): 1.04 (broad singlet, 1H, -NH), 2.80 (multiplet, 4H, aromatic), 6.20 (quartet, J_{AB} = 6 cps, J_{AC} = 2 cps, 1H, C-3

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proton), 6.28 (singlet, 3H, $-CO_2\underline{CH_3}$), and 9.16 (triplet, J = 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: m/e 124, 138, 210, 215, 281, and 340 (M^+). Molecular weight: 340.215. Calc. for $C_{21}H_{28}O_2N_2$: 340.215.

dl-Epivincadine: Amorphous solid (11 mg, 11.5%). Attempts to crystallize failed (decomposition). It was less polar than natural vincadine on silica gel chromatoplates and benzene-ethyl acetate (1:1) as developer. Infrared ($CHCl_3$): 3380 (small, -NH), 1720 (strong, ester) cm^{-1}. Ultraviolet: λ_{max} (log ε): 293 (3.87), 287 (3.91), and 227 (4.52) mμ. NMR signals (100 Mc/s: 1.40 (broad singlet, 1H, NH), 2.80 (multiplet, 4H, aromatic), 4.40 (quartet, J_{AB} = 12 cps, J_{AC} = 2 cps, 1H, C-3 proton), 6.35 (singlet, 3H, $-CO_2\underline{CH_3}$), and 9.33 (triplet, J = 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: m/e 124, 210, 281, and 340 (M^+). Molecular weight: 340.215. Calc. for $C_{21}H_{28}O_2N_2$: 340.215.

Furthermore the synthetic dl-vincadine had the same TLC properties as the natural vincadine, IR were superimposable and mass spectra showed the same peaks and the same relative intensity.

Epimerisation of Vincadine to Epivincadine

To a stirred freshly prepared solution of sodium methoxide in absolute methanol natural vincadine (1 mg) was added. The solution of sodium methoxide was made by addition of 58 mg of freshly cut sodium in absolute methanol (3.5 ml) under a dry nitrogen atmosphere and efficient stirring. After the addition of vincadine the reaction mixture was refluxed under dry nitrogen for 1/2 hour. Cooling at room temperature followed and a mixture of ice-water was added. The base was neutralized by a cold saturated solution of ammonium chloride (pH checked by litmus paper). Extraction with methylene chloride (3 x 5 ml) followed. The combined organic layers were washed with

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a saturated solution of ammonium chloride (1 x 3 ml) and water (1 x 3 ml), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure gave 1 mg of a colourless semicrystalline material. TLC investigation of this reaction mixture with the above mixture of synthetic dl-vincadine and dl-epivincadine showed identity. Finally the IR spectra of these two mixtures of natural and synthetic products were superimposable.

Preparation of 6-methoxy succinimide (159).

6-Methoxytryptamine (158) (1.04 g, 5.48 mmole) was dissolved in 2, (2-ethoxyethoxy) ethanol (10 ml, freshly distilled) with gentle heating, under anhydrous conditions. To this solution, the diester (90) (0.62 g, 1.78 mmole) was added with stirring under dry nitrogen. Removal of 1-2 ml of water-ethanol from the reaction mixture by distillation followed. After gentle refluxion for 56 hours a change of colour of the reaction mixture from yellow to deep red was observed. Some more ethanol was removed from the reaction mixture as before (0.5-1.0 ml). Then the reaction mixture was cooled to room temperature and it was taken up in ethyl ether (100 ml). Washing with water (4 x 10 ml) first and then with aqueous 10% acetic acid (3 x 10 ml) and finally with water (3 x 10 ml) followed (pH neutral to litmus paper). The ether solution was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure to give a brown gum (880 mg). Some unreacted 6-methoxytryptamine was also recovered (557 mg) from the aqueous layer after basification followed by extraction.

The crude product (880 mg) was purified by column chromatography on alumina Shawinigan (72.0 g), neutralized by 10% aqueous acetic acid, activity III. Elution with benzene-chloroform (1:1) gave unreacted diester

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(90) 187 mg, while elution with chloroform afforded 500 mg of the pure desired product as a yellow gum (63%). This material could be purified also by molecular distillation (290°/0.1 mm) in quantitative yield. The product was a yellow glass. Infrared (neat): 3380 (NH), 1760 (medium) and 1680 (strong, characteristic for succinimide), 1610 (strong, aromatic) cm^{-1}. Ultraviolet: λ_{max} (log ε): 292.5 (3.57), 273 (3.54), and 227.5 (4.12) mμ. NMR signals (100 Mc/s): 2.20 (broad singlet, 1H, N<u>H</u>), 2.48 (doublet, J_{ortho} = 10 cps, 1H, C-4 proton), 2.71 (singlet, 5H, aromatic), 3.16 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-5 proton), 3.25 (doublet, J_{meta} = 2 cps, 1H, C-7 proton), 3.20 (eclipsed, 1H, C-2 proton), 5.59 (singlet, 2H, $C_6H_5C\underline{H}_2O$-), 6.21 (singlet, 3H, $C\underline{H}_3O$-), 6.23 (triplet, J = 7 cps, 2H, -$C\underline{H}_2CH_2N$-), 6.66 (triplet, J = 6 cps, 2H, $C_6H_5CH_2OC\underline{H}$ -), 7.02 (triplet, J = 8 cps, 2H, -$C\underline{H}_2N$-), 7.60 (singlet, 2H, -$C\underline{H}_2CO$-N-), and 9.24 (triplet, J = 7 cps, 3H, -$CH_2C\underline{H}_3$). Mass spectrum; main peaks: m/e 91, 160, 173, and 448 (M^+). Molecular weight: 448.237. Calc. for $C_{27}H_{32}O_4N_2$: 448.236. Found: C, 72.07; H, 7.04; N, 6.15. Calc. for $C_{27}H_{32}O_4N_2$: C, 72.29; H, 7.19; N, 6.25.

Preparation of 6-methoxy amine (160)

6-Methoxy succinimide (159) (440 mg, 0.98 mmole) was dissolved in 80 ml of dry tetrahydrofuran (distilled over sodium) in a dry apparatus under oxygen-free nitrogen. A large excess of pulverized lithium aluminum hydride (800 mg, 21.0 mmole) was added in small portions with efficient stirring. The reaction mixture was refluxed slowly for 10 hours. The heating was stopped and the reaction mixture left overnight under stirring. The excess of lithium aluminum hydride was destroyed by careful dropwise addition of water (ca. 25 ml), when cooled. The resulting white sludge was filtered

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through a bed of celite and the solid on the funnel was washed with warm tetrahydrofuran (2 x 25 ml) and chloroform (2 x 20 ml) successively. The organic layer of the filtrate was separated and the aqueous layer was extracted with chloroform (3 x 30 ml). The initial organic layer and the chloroform extracts were combined and washed with water (2 x 25 ml) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave a brown gum (425 mg). Of this crude product, 375 mg were chromatographed on alumina neutral Woelm (20 g), activity III column. Elution with benzene-ethyl ether (4:1) afforded the desired amine (160) in a 50% yield. The crude product (425 mg) could also be purified easily by molecular distillation (260°/0.03 mm) giving a quantitative yield of the desired product (160) as a yellow gum. Infrared (neat): 3410 (sharp, NH), no carbonyl absorption, 1610 (strong, aromatic) cm^{-1}. Ultraviolet: λ_{max} (log ε): 293 (3.56), 273 (3.51), and 230 (3.98) mμ. NMR signals (100 Mc/s): 2.06 (broad singlet, 1H, N$\underline{H}$), 2.57 (doublet, J_{ortho} = 10 cps, 1H, C-4 proton), 2.70 (singlet, 5H, aromatic), 3.20 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-5 proton), 3.22 (eclipsed, 1H, C-2 proton), 3.31 (doublet, J_{meta} = 2 cps, 1H, C-7 proton), 5.54 (singlet, 2H, $C_6H_5C\underline{H}_2O$-), 6.23 (singlet, 3H, $C\underline{H}_3O$-), 6.56 (triplet, J = 6 cps, 2H, $C_6H_5CH_2OC\underline{H}_2$-), 7.24 and 7.38 (triplets, J = 6 cps and J = 7 cps, 2H each, -$CC\underline{H}_2C\underline{H}_2N$-), 7.58 (singlet, 2H, -$CC\underline{H}_2N$-), and 9.16 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 91, 160, 170, 260 (base peak), and 420 (M^+). Molecular weight: 420.276. Calc. for $C_{27}H_{36}O_2N_2$: 420.277. Found: C, 77.16; H, 8.63; N, 6.42. Calc. for $C_{27}H_{36}O_2N_2$: C, 77.10; H, 8.63; N, 6.66.

Mercuric acetate oxidation of 6-methoxy amine (160).

The amine (160) (52 mg, 0.124 mmole) was dissolved in 10% aqueous acetic

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acid (5 ml) and pulverized mercuric acetate (395 mg, 1.24 mmole) was added. Addition of a small amount of methanol enhanced the amine to dissolve. This reaction and all subsequent steps was performed under nitrogen. Refluxion and stirring for 2 hours at 105° (oil-bath temperature) followed. The reaction was stopped and the hot reaction mixture was treated for 10 minutes with hydrogen sulfide gas bubbling through to decompose the mercuric salts. The black sludge was kept hot and stirred for 20 minutes more. The mercuric sulfide was filtered on a bed of celite and the cake was washed several times with hot ethanol. The combined filtrate was adjusted to pH 6 by the addition of solid sodium bicarbonate. To this solution solid sodium borohydride was added in large excess. The resulting white slurry was stirred for 17 hours under nitrogen and at room temperature. The excess of sodium borohydride was destroyed by careful addition of glacial acetic acid and the resulting solution made again alkaline (litmus paper) with conc. ammonium hydroxide. This solution was concentrated to a small volume by using reduced pressure. Water was added to dissolve the inorganic salts and the solution was extracted three times with chloroform. The chloroform extracts were combined and washed three times with water. The organic layer was dried over anhydrous potassium carbonate. Filtration and removal of the solvent gave 34.5 mg of a light yellow residue. This material on TLC showed several spots as it was expected. Attempts to separate the mixture of desired cyclic amines (161) from the undesired (162) were unsuccessful. However, column chromatography of the crude product (34.5 mg) on alumina neutral Woelm (4 g, activity II) followed. Elution with benzene-ethyl ether (19:1) gave a material (7 mg, 12% probably one of the cyclic amines), while elution with benzene-ethyl ether (9:1) gave a mixture of two components

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(3 mg, 6% probably a mixture of the isomeric cyclic amines). Finally, starting material (7 mg, 12%) was eluted with benzene-ethyl ether (6:1), and some polar unidentified products eluted with ethyl ether-methanol (13 mg).

Preparative TLC on alumina Woelm, developed by chloroform on this material (3 mg), obtained above resulted in the separation of one pure component. This compound (1 mg, 2%) had a 6-methoxyindole type chromophore in ultraviolet (λ_{max} 297, 270, 227 mμ) and a molecular peak at m/e 418 in the mass spectrum, while the familiar base peak at m/e 214 was present. No further attempts to separate and characterize these products were made, since the reaction yield was very low and at the same time we had developed a new sequence to obtain the desired amines (161).

Preparation of 11-methoxy cyclic lactam (166)

6-Methoxy tryptamine (158) (7.06 g, 3.72 mmole) was mixed with aldehyde (90) (8.62 g, 2.82 mmole) and glacial acetic acid (50 ml) was added. The reaction was performed under oxygen-free nitrogen. The reaction mixture was stirred and refluxed smoothly for 2 hours in an oil bath. The resulting dark reaction mixture was cooled at room temperature and poured slowly to a stirred aqueous solution of sodium carbonate (50 g, Na_2CO_3 in 200 ml water). The basic aqueous solution was extracted with methylene chloride (4 x 200 ml). The organic extracts were washed with brine (2 x 100 ml) saturated solution of sodium chloride), then with water (1 x 100 ml), and dried over anhydrous sodium sulfate. Filtration followed by removal of the solvent under reduced pressure afforded a dark gum. Purification on silica gel Woelm (350 g), activity III column and elution with benzene-chloroform (1:1) and chloroform gave the pure lactam (166) 9.35 g (75%). This lactam

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was a mixture of the two dl-epimers which were never separated. This mixture of dl-epimers could also be obtained from the crude product by molecular distillation (290°/0.3 mm) in a hot box, but extensive decomposition took place. Infrared (neat): 3250 (broad hydrogen bonded NH), 1715 (small) and 1670 (strong, lactam) cm^{-1}. Ultraviolet: λ_{max} (log ε): 335 (3.39), 321 (3.47), 295 (3.75), 272 (sh, 3.72), 264 (sh. 373), and 227 (4.12) mμ. NMR signals (100 Mc/s): 1.56 (broad singlet, 1H, NH), 2.75 (multiplet, 6H, aromatic), 3.20 (singlet, 1H, C-12 proton), 3.25 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-10 proton), 5.25 (broad triplet, J = 8 cps, 1H, C-3 proton), 5.55 and 5.66 (singlets, 2H, $C_6H_5CH_2O$-), 6.23 (singlet, 3H, CH_3O-), 9.05 and 9.28 (triplets, J = 7 and 7 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 91, 149, 188, 263, 341 and 432 (M^+). Molecular weight: 432.241. Calc. for $C_{27}H_{32}O_3N_2$: 432.241. Found: C, 75.21; H, 7.51; N, 6.52. Calc. for $C_{27}H_{32}O_3N_2$: C, 74.97; H, 7.46; N. 6.48.

Preparation of 11-methoxy cyclic amine (161)

The lactam (166) (9.2 g, 21.25 mmole) was dissolved in 600 ml of absolute tetrahydrofuran (refluxed with sodium and distilled over $LiAlH_4$) and pulverized lithium aluminum hydride (4.0 g, 105 mmole) was added in small portions. The reaction was performed under dry conditions over an atmosphere of oxygen-free nitrogen. Refluxion with adequate stirring for 33 hours followed. The reaction mixture was cooled to room temperature and then in an ice-water bath. Wet tetrahydrofuran (water in THF, 1:3) was added carefully with vigorous stirring to decompose the complex and excess of hydride. The white sludge was stirred for 15 minutes more and it was filtered through a bed of celite. The cake was washed twice with hot tetrahydrofuran. To the filtrate anhydrous magnesium sulfate was added in

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sufficient quantity. Filtration and removal of solvent under reduced pressure at room temperature gave a light yellow gum (9.18 g). This gum was chromatographed on alumina neutral Woelm (500 g), activity III. The desired product, a pure mixture of the two dl-epimers, was eluted with benzene-methylene chloride (5-25%). Yield 83%. Infrared (neat): no carbonyl absorption. Ultraviolet: λ_{max} (log ε): 300 (3.74), 270 (sh. 3.66), 263 (3.68), and 230 (4.18) mμ. NMR signals (100 Mc/s): 2.04 (broad singlet, 1H, NH), 2.70 (multiplet, 6H, aromatic), 3.25 (singlet, 1H, C-12 proton), 3.30 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-10 proton), 5.53 and 5.65 (singlets, 2H, $C_6H_5\underline{CH_2}O$-), 5.93 (broad triplet, J = 6 cps, 1H, C-3 proton), 6.26 (singlet, 3H, $\underline{CH_3}O$-), 9.16 and 9.30 (triplets, J = 7 and 7 cps, 3H, $\underline{CH_3}CH_2$-). Mass spectrum; main peaks: m/e 91, 149, 214, 260, 327 and 418 (M^+). Molecular weight: 418.265. Calc. for $C_{27}H_{34}O_2N_2$: 418.262. Found: C, 77.61; H, 8.21; N, 6.62. Calc. for $C_{27}H_{34}O_2N_2$: C, 77.47; H, 8.19, N, 6.69.

Debenzylation of mixture of dl-epimeric amines (161)

A mixture of amines (161) (9.00 g, 21.5 mmole) was dissolved in 350 ml glacial acetic acid and 10% palladium on charcoal (8.2 g) was added. The mixture was stirred and hydrogenated at room temperature and 1 Atm. pressure for 10 3/4 hours. When no more uptake of hydrogen was noted and no starting material was present the reaction was stopped. The catalyst was filtered through a bed of celite and the cake was washed several times with warm acetic acid and water. The clear filtrate was basified by careful addition of a saturated solution of sodium carbonate with vigorous stirring. The extensive foaming could be controlled by simultaneous blowing of nitrogen and additions in small portions. The resulting basic solution (litmus

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paper) was extracted with methylene chloride (3 x 500 ml) and the combined organic layers were washed with conc. solution of sodium carbonate (300 ml) and then with water (2 x 300 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give a yellowish foamy solid, (4.96 g). This material was chromatographed on alumina neutral Woelm (250 g), activity III. Benzene-chloroform (1:1) eluted first a less polar by-product (1.24 g). The amount of this material was found to increase with the hydrogenolysis time (as shown by the intensity of its 1730 cm^{-1} band in the IR spectrum). No further attempts to characterize this product were done. Further elution with chloroform gave alcohol-I and with chloroform-methanol (2-5%) afforded alcohol-II. Finally a more polar material was eluted with chloroform-methanol (1:1), which had a strong fluorescence in the ultraviolet. This material also was not characterized.

11-Methoxy alcohol-I: Amorphous solid (1.90 g, 27%). It was crystallized from methylene chloride-n-hexane (3:1), washed with cold acetone and recrystallized once more from wet methanol, m.p. 154-155°. Infrared ($CHCl_3$): absence of strong benzylic bands between 690-770 cm^{-1}. Ultraviolet: λ_{max} (log ε): 297 (3.73), 268 (3.66), and 227.5 (4.42) mμ. NMR signals (100 Mc/s): 1.36 (broad singlet, 1H, NH), 2.74 (doublet, J_{ortho} = 9 cps, 1H, C-9 proton), 3.26 (singlet, 1H, C-12 proton), 3.32 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-10 proton), 6.00 (distorted triplet, 1H, C-3 proton), 6.25 (singlet, 3H, CH_3O-), and 9.18 (triplet, J = 6 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 149, 186, 199, 214, and 328 (M^+). Molecular weight: 328.215. Calc. for $C_{20}H_{28}O_2N_2$: 328.215. Found: C, 71.43; H, 8.94; N, 8.09. Calc. for $C_{20}H_{28}O_2N_2 \cdot 1/2CH_3OH$: C, 71.48; H, 8.77; N, 8.13.

11-Methoxy alcohol-II: Amorphous solid (1.69 g, 24%). Crystallized easier than alcohol-I from methylene chloride and acetone several times to give a

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m.p. 168-169°. Infrared ($CHCl_3$): absence of strong benzylic bands between 690-770 cm^{-1} and almost superimposable with that of alcohol-I. Ultraviolet; λ_{max} (log ε): 297 (3.79), 269 (3.71), and 227 (4.50) mμ. NMR signals (100 Mc/s): 1.42 (distorted singlet, 1H, -NH), 2.73 (doublet, J_{ortho} = 8 cps, 1H, C-9 proton), 3.19 (doublet, J_{meta} = 2.5 cps, 1H, C-12 proton), 3.30 (quartet, J_{ortho} = 8 cps, J_{meta} = 2.5 cps, 1H, C-10 proton), 5.64 (distorted triplet, 1H, C-3 proton), 6.25 (singlet, 3H, CH_3O-), 6.40 (distorted triplet, 2H, -CH_2OH), 7.26 (singlet, 2H, -NCH_2C-), and 9.27 (triplet, J = 6 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 199, 214 and 328 (M^+). Molecular weight: 328.216. Calc. for $C_{20}H_{28}O_2N_2$: 328.215. Found: C, 73.21; H, 8.58; N, 8.48. Calc. for $C_{20}H_{28}O_2N_2$: C, 73.13; H, 8.59; N, 8.53.

Preparation of 11-methoxy mesylates (187)

a) 11-Methoxy alcohol-I (165) (130 mg, 0.32 mmole) was dissolved in a mixture of dry triethylamine (2.0 ml) and chloroform (4.0 ml) and cooled at -10°-0° (ice-rock salt bath). Keeping dry conditions, freshly distilled methane sulfonyl chloride (ca. 280 mg, 2.45 mmole was added dropwise with efficient stirring. The reaction mixture was allowed to come slowly to room temperature and let stand for 23 hours. The solvent was removed at room temperature and reduced pressure to give a deep red gum. This gum was dissolved in 10 ml of chloroform and extracted with aqueous ammonium hydroxide (4 N, 3 x 10 ml). The combined aqueous washings were washed with a little chloroform (1 x 3 ml) and the water was removed under reduced pressure with moderate heating. The resulting yellow solid was azeotroped several times with dry benzene and left for a period in the oil pump. Extraction with dry warm chloroform (3 x 10 ml) gave a yellowish solid 155 mg (96%). This material was pure mesylate (187) (TLC, IR and UV information), and it was

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used for the subsequent steps without further purification.

b) 11-Methoxy alcohol-II (165) (97 mg, 0.24 mmole) was mesylated exactly as is described above to give an amorphous yellowish solid 109 mg (91%). Again this material was used for the next step without further purification.

Preparation of 16-methoxy cyanides (168)

a) Direct method

To a solution of mesylate of alcohol-I (167) (245 mg, 0.604 mmole) in dry dimethylformamide (24.5 ml, distilled over sodium hydroxide), pulverized potassium cyanide (180 mg, 2.77 mmole) was added. The reaction was performed in an dry oxygen-free nitrogen atmosphere. Smooth refluxion for 5 hours at 165° (bath temperature) with efficient stirring followed. The dark reaction mixture was cooled to room temperature and aqueous ammonium hydroxide (25 ml, 6 N) was added to it under stirring. The resulting basic solution was extracted with warm benzene (3 x 35 ml). The combined benzene extracts were washed with saturated aqueous solution of sodium chloride (brine, 2 x 15 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure and at room temperature to afford a brown gum 125 mg. The aqueous layer after removal of water under reduced pressure afforded a dark solid. This solid was azeotroped several times with dry benzene and finally extracted with warm chloroform. The combined chloroform extracts after removal of the solvent gave 60 mg of unreacted starting material (167).

By using exactly the above procedure on the mesylate of 11-methoxy alcohol-II (167) (2.35 mg, 0.578 mmole) and checking the reaction products (TLC, IR, NMR information) it was shown that both mesylates gave the same

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mixture of epimeric cyanides.

The combined crude reaction products (210 mg) were filtered through a short column of alumina neutral Woelm, activity III. Elution with benzene gave 135 mg of a yellow solid consisting mainly of cyanide-I and II, while elution with chloroform afforded some cyanide-III (46 mg).

This mixture of cyanide-I and II (135 mg) was rechromatographed on alumina neutral Woelm (10 g), activity III, and was eluted with petr. ether-benzene (3:1) and (1:1) respectively.

16-Methoxy cyanide-I: Amorphous solid 31 mg, 9%. Recrystallized from methanol, n-hexane-acetone and methylene chloride, m.p. 186-187°. It was less polar on alumina chromatoplates developed by benzene chloroform (4:1). Infrared (neat): 3340 (medium, NH) and 2240 (medium, -CN) cm^{-1}. Ultraviolet: λ_{max} (log ε): 300 (3.81), 275 (3.69), and 227 (4.48) mμ. NMR signals (100 Mc/s): 1.80 (broad multiplet, 1H, N<u>H</u>), 2.69 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.20 (singlet, 1H, C-17 proton), 3.27 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 6.12 (quartet, J_{AB} = 4 cps, J_{AC} = 2 cps, 1 H, C-3 proton), 6.21 (singlet, 3H, $C\underline{H}_3O$-), and 9.07 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 126, 177, 212, and 337 (M^+). Molecular weight: 337.218. Calc. for $C_{21}H_{27}ON_3$ 337.215. Found: C, 74.61; H, 8.52; N; 12.39. Calc. for $C_{21}H_{27}ON_3$: C, 74.74, H, 8.07; N, 12.45.

16-Methoxy cyanide-II: Amorphous solid 61 mg, 15%. Recrystallized from methanol and n-hexane had a m.p. 191-192°. Infrared ($CHCl_3$): 3360 (sharp small, NH), and 2230 (sharp small, -CN) cm^{-1}. Ultraviolet: λ_{max} (log ε): 298 (3.83), 277 (3.73), and 226 (4.45) mμ. NMR signals (100 Mc/s): 1.80 (broad singlet, 1H, -N<u>H</u>), 2.67 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton),

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3.18 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 3.27 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 4.04 (quartet, J_{AB} = 10 cps, J_{AC} = 3 cps, 1H, C-3 proton), 6.21 (singlet, 3H, $\underline{CH_3}O$-), and 9.35 (triplet, J = 7 cps, 3H, $-CH_2\underline{CH_3}$). Mass spectrum; main peaks: m/e 124, 126, 177, 212 and 337 (M^+). Molecular weight: 337.216. Calc. for $C_{21}H_{27}ON_3$: 337.215. Found: C, 74.57; H, 8.31; N, 12.41. Calc. for $C_{21}H_{27}ON_3$: C, 74.74; H, 8.07; N, 12.45.

6-Methoxy cyanide-III: Amorphous solid 46 mg, 13%. Resisted cystallization and it is more unstable than cyanide-I and II to air oxidation etc. TLC, infrared, ultraviolet and NMR information suggested that it was of the same nature as cyanide-III in the non-methoxy series. Because of the extensive decomposition we were unable to completely characterize this by-product.

It was noted that the amount of the latter cyanide varies with the dry conditions applied during the reaction. The total amount of desired cyanide-I and II remains the same but the amount of cyanide-III decreases, the drier the conditions used.

When the above reaction was repeated with mesylate of alcohol-II it gave exactly the same reaction products. This was checked by comparing ultraviolet and NMR spectra as well as TLC of the crude mixtures obtained under identical reaction conditions. This result was consistent with the experiments in the non-methoxy series.

b) Using catalytic amounts of ammonium chloride

A mixture of mesylates of 11-methoxy alcohol-I and II (167) (188 mg, 0.463 mmole) was dissolved in 4.6 ml of dimethylformamide and 0.4 ml of water added. To this stirred solution potassium cyanide (120 mg, 1.845 mmole) and ammonium chloride (37 mg, 0.680 mmole) were added under oxygen-free nitrogen.

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The reaction mixture was heated in an oil bath at 110-120° for 4 1/2 hours whereupon no formation of cyanides was apparent (TLC). The oil bath temperature was brought to 170-175° (smooth refluxion) and after 14 1/4 hours the reaction was stopped. The formation of cyanides ceased by this time, while some starting material was still present. The reaction mixture was cooled at room temperature and aqueous ammonium hydroxide (15 ml, 6 N) was added with continuous stirring. The agitation was continued for 5 minutes more and the reaction mixture was extracted with warm benzene (4 x 20 ml). The combined benzene extracts were washed with water (2 x 10 ml) and dried over anhydrous sodium sulfate. Removal of the inorganic agent and of the solvent under reduced pressure at room temperature gave a brown gum. This gum was filtered through alumina neutral Woelm, activity III, and eluted with benzene. This product, consisting of the same mixture of three cyanides-I, II and III, was identical (TLC and infrared consistent) with the one obtained from the previous reaction. Starting material was removed from the aqueous layer, after evaporation of water under reduced pressure with moderate heating, and extracted with chloroform. Quantitative estimation (TLC) of these mixtures of cyanides from both reactions as well as of the recovered starting material showed that the latter modification was not an improvement of the reaction for obtaining the desired cyanides-I and II.

c) Base induced method

A mixture of epimeric mesylates I and II (167) (1.06 g, 2.62 mmole), was stirred together with sodium hydride (0.143 g of 52.6% dispersion in mineral oil, ca. 3.13 mmole) and 110 ml of purified dry dimethylformamide. The reaction was performed under dry oxygen-free nitrogen. The above mixture

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was stirred at room temperature for 40 minutes. The evolution of hydrogen had ceased by this time while the colour of the reaction mixture had changed from yellow to orange.

Potassium cyanide (0.680 g, 10.44 mmole) pulverised and dry was added and the reaction mixture was refluxed smoothly for 5 hours in an oil bath (ca. 165°). The resulting dark suspension cooled to room temperature and aqueous ammonium hydroxide (5N) was added. Extraction several times with chloroform followed. The combined chloroform extracts were washed with water and dried over anhydrous sodium sulfate. Filtration and removal of solvent gave 0.922 g of a dark gum. This material was chromatographed on alumina neutral Woelm (50 g), activity III. Elution with petr. ether-benzene (4:1) gave 0.327 g of a pure mixture of cyanide-I and II as a white solid (35%).

Considering the direct method (yield 24%), this base induced method was slightly superior.

Preparation of 16-methoxy dl-vincadine and its epimer (170)

16-Methoxy cyanide-I (168) (20.5 mg, 0.061 mmole) was placed in a small test tube and mixed with a solution of 20% potassium hydroxide in diethylene glycol (0.48 ml). This tube was connected to an oxygen-free nitrogen system and immersed into an oil bath (150-160°). Evolution of gas was noted and the reaction was left at this temperature for 10 hours. Then the reaction mixture was taken up in some methanol and cooled at -10°-0° (ice-rock salt bath). This solution was slightly acidified with careful addition of a saturated solution of hydrochloride in methanol. An ethereal solution of diazomethane (3.0 g/100 ml) was added in excess under shaking and the reaction mixture was left to stand for 15 minutes. This process was repeated

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twice more by slight acidification followed by addition of excess of diazomethane etc. The excess of diazomethane was removed by blowing a stream of nitrogen over the solution and finally the rest of the solvent was removed at room temperature and reduced pressure to give a brown gum. This gum was treated with an aqueous solution of 10% sodium carbonate (1 ml) and extracted with ethyl ether (3 x 6 ml). The combined ether layers were washed twice with brine (saturated solution of sodium chloride) and once with water and then dried over anhydrous sodium sulfate. Filtration and removal of solvent under reduced pressure gave 17 mg of a yellow amorphous material.

The above reaction was repeated precisely by using 16-methoxy cyanide-II and identical mixtures of carbomethoxy derivatives were obtained (TLC, infrared, ultraviolet and NMR spectra).

Column chromatography of the above crude mixture on aluminum neutral Woelm, activity II, failed to separate the two dl-epimers. However, it gave a pure mixture of these dl-epimers as an amorphous material. Further separation was obtained by preparative TLC on silica gel Woelm, developed by a mixture of benzene-ethyl acetate (4:1).

16-Methoxy dl-vincadine: Amorphous solid (18% yield). Resisted crystallization, leading to decomposition products. It was more polar from silica gel chromatoplates developed with benzene:ethyl acetate (4:1). Infrared ($CHCl_3$): 3370 (small sharp, NH) and 1730 (strong carbonyl) cm^{-1}. Ultraviolet: λ_{max} (log ε): 301 (3.76), 278 (3.65), and 228 (4.43) mμ. NMR signals (100 Mc/s): 1.16 (collapsed singlet, NH), 2.70 (doublet, J_{ortho} = 8 cps, 1H, C-14 proton), 3.21 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 3.30 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-15 proton), 6.22 (singlet, 3H, CH_3O-), 6.31 (singlet, 3H, $-CO_2CH_3$), 6.35 (multiplet, 1H, C-3 proton), and 9.18

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(triplet, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 138, 210, 245, and 370 (M^+). Molecular weight: 370.225. Calc. for $C_{22}H_{30}O_3N_2$: 370.225.

16-Methoxy dl-epivincadine: Amorphous solid (12%). Resisted crystallization, leading to decomposition products. Infrared ($CHCl_3$): 3370 (small sharp, NH) and 1725 (strong, carbonyl) cm^{-1}. Ultraviolet: λ_{max} (log ε): 300 (3.76), 278 (3.65), and 228 (4.43) mμ. NMR signals (100 Mc/s): 1.49 (collapsed singlet, 1H, N$\underline{H}$), 2.70 (doublet, 1H, J_{ortho} = 8 cps, 1H, C-14 proton), 3.20 (doublet, J_{meta} = 2.5 cps, 1H, C-17 proton), 3.30 (quartet J_{ortho} = 8 cps, J_{meta} = 2.5 cps, 1H, C-15 proton), 4.49 (quartet, J_{AB} = 11 cps, J_{AC} = 2 cps, 1H, C-3 proton), 6.23 (singlet, 3H, $C\underline{H}_3O$-), 6.38 (singlet, 3H, -$CO_2C\underline{H}_3$), and 9.36 (triplet, J = 7 cps, 3H, $C\underline{H}_3CH_2$-). Mass spectrum; main peaks: m/e 124, 126, 210, 245, and 370 (M^+). Molecular weight: 370.224. Calc. for $C_{22}H_{30}O_3N_2$: 370.225.

$N_{(\alpha)}$-methylation of 18β-carbomethoxy-4α-dihydrocleavamine (172)

a) By use of sodium hydride

The starting material (172) was prepared from 18β-carbomethoxycleavamine (171) by catalytic hydrogenation over platinum oxide (Adam's catalyst) in ethyl acetate in quantitative yield.

Sodium hydride (10 mg, 52.6% in mineral oil, 0.22 mmole) was placed in a dry reaction vessel and it was washed several times with n-hexane to remove all oil, under highly purified nitrogn. The resulting pure sodium hydride was dissolved in 4.0 ml of dry dimethylformamide with stirring. The dry dimethylformamide was prepared by distillation over anhydrous magnesium sulfate, filtered through alumina neutral Woelm, activity I and it was kept

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over molecular sieves. To this solution of sodium hydride in dimethylformamide crystalline 18β-carbomethoxy-4α-dihydrocleavamine (172) (54 mg, 0.16 mmole) was added. This solution was stirred at room temperature for 10 minutes and then 5 minutes in a water bath at 40°, while it changed from colourless to yellow. The reaction mixture was cooled to 0° in an ice-water bath and methyl iodide (12 µl, 0.19 mmole) was added from a syringe. Stirring for 20 minutes at room temperature was followed by the addition of a mixture of ethyl ether-water. The organic layer was separated, while the aqueous layer was washed with ethyl ether (2 x 20 ml). The combined organic layers were washed twice with water and dried over anhydrous sodium sulfate. Filtration and removal of solvent gave a yellowish glass 38 mg. This material was shown to be a mixture of three compounds (TLC investigation, NMR spectrum), the desired product being in 30-40% yield. This mixture had infrared (neat): 3330 (small broad, NH) and 1725 (strong, carbonyl) cm^{-1}. NMR signals (JEOL, C-60H, 60 Mc/s): 1.30 and 2.00 (broad singlets, ca. 1/3H each, N<u>H</u>), 2.80 (multiplet, 4H, aromatic), 4.43 and 4.95 (distorted doublets, ca. 1/3H each, C-18 protons), 6.30 and 6.33 (singlets, ca. 2H and 1H respectively, $-CO_2\underline{CH_3}$), 6.41 (singlet, ca. 1H, $\underline{CH_3}N-$), and 9.10 (distorted triplet, J = 6 cps, 3H, $\underline{CH_3}CH_2-$). No further separation of the components of this mixture were made, since the results using sodium amide for base were quite successful (see below).

b) <u>By use of sodium amide</u>

A solution of sodium amide was prepared from redistilled (over sodium) liquid ammonia (3 ml) and sodium metal (5 mg, 0.217 mmole) using a grain of ferric nitrate. The mixture was stirred over a dry oxygen-free nitrogen atmosphere for 30 minutes. During this period the colour of the solution

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changed from deep blue to yellow. This yellow solution was left to stir for 10 minutes more and a solution of the alkaloid (172) (67 mg, 0.197 mmole) in dry tetrahydrofuran (1 ml) was added to it. After stirring for 25 minutes a solution of methyl iodide (18 ml, 0.28 mmole) in a few drops of tetrahydrofuran was added with a syringe. Stirring was continued for 15 minutes and the ammonia was allowed to evaporate by warming at room temperature. The resulting gum was taken in a mixture (10 ml) of aqueous ammonium chloride and ethyl ether. The organic layer separated and the aqueous layer was washed three times with ethyl ether. The combined ethereal extracts were washed once with water and dried over anhydrous sodium sulfate. Filtration and removal of solvent under reduced pressure provided a yellowish viscous oil (77 mg). This product on TLC showed as almost one compound and it was not further purified. Infrared ($CHCl_3$): No NH signal and 1730 (strong, carbonyl) cm^{-1}. NMR signals (100 Mc/s): No NH signal, 2.8 (multiplet, 4H, aromatic), 4.47 (distorted doublet, J = 9 cps, 1H, C-18 proton), 6.40 (singlet, 3H, $-CO_2\underline{CH_3}$), 6.47 (singlet, 3H, $\underline{CH_3}N-$), and 9.13 (triplet, J = 7 cps, 3H, $\underline{CH_3}CH_2-$).

$N_{(\alpha)}$-methylation of 16-methoxy dl-vincadine and its epimer (170)

Sodium amide (ca. 0.25 mmole) was prepared from redistilled liquid ammonia (4-5 ml) and freshly cut sodium metal (5.85 mg, 0.25 mmole). A trace of ferric nitrate was added as catalyst.

To the solution of sodium amide in liquid ammonia, kept under highly purified nitrogen and efficient stirring, a solution of epimeric esters (170) (85 mg, 0.23 mmole) in dry tetrahydrofuran (1 ml) was added with a syringe. The dark solution was kept in a dry ice-acetone bath and stirring continued for 30 minutes more. A mixture of methyl iodide (20 µl, 0.31 mmole,

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redistilled and filtered through a short column of alumina neutral Woelm, activity I) in a few drops of dry tetrahydrofuran was added with a syringe. The reaction mixture was kept cold and stirred for 25 minutes more and then the ammonia allowed to evaporate slowly under a stream of nitrogen. The removal of ammonia was enhanced by blowing a stream of warm air around the reaction vessel. The dark residue was taken into a mixture of aqueous ammonium chloride ethyl ether (10 ml, 1:1) and extracted several times with ethyl ether and chloroform. The combined organic layers, after washing with water were dried over anhydrous sodium sulfate. Filtration of the inorganic agent and removal of solvent under reduced pressure at room temperature gave a yellow gum (82 mg, 93% crude). Preparative TLC on alumina neutral Woelm, developed with petr. ether-acetone (5:1) allowed good separation of the mixture of N-methyl epimers, but failed to separate each of them. Finally preparative TLC on 60 mg (from the 82 mg crude product) on silica gel G was used. The plate was developed with a mixture of benzene-ethyl acetate (4:1) and the two N-methylated epimers were separated.

dl-Vincaminoridine: As an amorphous solid (22 mg, 34%). It was never attempted to recrystallize it, because of the small amount of material available and of the danger of decomposition. This was the less polar epimer in silica gel G chromatoplates developed with benzene:ethyl acetate (4:1). Infrared ($CHCl_3$): No NH absorption and 1735 (strong, carbonyl) cm^{-1}. Ultraviolet: λ_{max} (log ε): 299 (3.82), 288 (sh. 3.78), and 232 (4.47) mμ. NMR signals (100 Mc/s): 2.65 (doublet, J_{ortho} = 9 cps, 1H, C-14 proton), 3.25 (quartet, J_{ortho} = 8 cps, J_{meta} = 2 cps, 1H, C-17 proton), 3.90 (quartet, J_{AB} = 10 cps, J_{AC} = 2 cps, 1H, C-3 proton), 6.16 (singlet, 3H, $\underline{CH_3}O$-), 6.38 (singlet, 3H, $-CO_2\underline{CH_3}$), 6.46 (singlet, 3H, $\underline{CH_3}N$-), and 9.33 (triplet, J = 6 cps, 3H, $\underline{CH_3}CH_2$-). Mass spectrum; main peaks: m/e 124, 210

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259 and 384 (M^+). Molecular weight: 384.240. Calc. for $C_{23}H_{32}O_3N_2$: 384.241.

Comparison of the spectral values given in the literature for the natural vincaminoridine as well as the infrared, NMR and mass spectrum (which recently became available to us from Dr. I. Kompis) showed the identity of it with our dl-epimer.

dl-Epivincaminoridine: As an amorphous solid (22 mg, 34%). It was never attempted to recrystallize it because of the small amount of material available and of the danger of decomposition. Infrared ($CHCl_3$): No NH absorption and 1725 (strong, carbonyl) cm^{-1}. Ultraviolet; λ_{max} (log ε): 300 (3.81), 288 (sh. 3.78), and 232 (4.53) mμ. NMR signals (100 Mc/s): 2.66 (doublet, J_{ortho} = 9 cps, 1H, C-14 proton), 3.30 (quartet, J_{ortho} = 10 cps, J_{meta} = 2 cps, 1H, C-15 proton), 3.31 (doublet, J_{meta} = 2 cps, 1H, C-17 proton), 6.15 (singlet, 3H, CH_3O-), 6.20 (distorted quartet, 1H, C-3 proton), 6.34 (singlet, 3H, $-CO_2CH_3$), 6.56 (singlet, 3H, CH_3N-), and 9.08 (triplet, J = 7 cps, 3H, CH_3CH_2-). Mass spectrum; main peaks: m/e 124, 210, 259 and 384 (M^+). Molecular weight: 384.239. Calc. for $C_{23}H_{32}O_3N_2$: 384.241.

Oxidative cyclization of dl-vincaminoridine (7) and its epimer

In earlier experiments 5% platinum on charcoal in ethanol was used on a mixture of dl-epimers, while a stream of molecular oxygen was passing through. A large number of products resulted in which none was the major.

By using mercuric acetate in glacial acetic acid under reflux, several products were formed. There was an indication (TLC, UV, IR) that some of them might be the desired pentacyclic ones. Also, it was shown during these experiments that the longer the time of refluxing the lower the amount

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of the expected desired products. Therefore milder reaction conditions were considered.

A mixture of dl-vincaminoridine and its epimer (1:1) (21 mg, 5.74 mmole) was dissolved in glacial acetic acid (11.5 ml). Solid pulverized mercuric acetate (90 mg, 28.3 mmole) was added under stirring. The reaction was carried out in a dry oxygen-free nitrogen atmosphere and at room temperature. The mercuric acetate dissolved immediately and the first appearance of cloudy mercurous acetate took place after a short time. The reaction was stopped after 31 hours, when no starting material was detectable (TLC, UV, IR) and the ultraviolet spectrum of the crude product showed a maximum absorption around 335 mμ. The formed precipitate of mercurous acetate was filtered off and the filtrate was basified by careful addition of a 10% aqueous solution of sodium bicarbonate. The basic solution was extracted with methylene chloride several times and the combined organic layers were washed with water, dried over anhydrous sodium sulfate and filtered. Removal of the solvent gave an amorphous yellowish solid (17 mg). Preparative TLC on 15 mg of this crude product on silica gel G developed with chloroform-ethyl acetate (1:1) among other products gave a yellowish glass, which had the most promising physical properties and it was thought initially that it was one compound. Infrared ($CHCl_3$): 1715 (strong, α,β conjugated ester) and 1670 (strong, C=C in conjugation) cm^{-1}. Ultraviolet: λ_{max} 337, 312 (infl.), and 227 mμ. Mass spectrum; main peaks: m/e 124 (base peak), 149, 263, and 382 (M^+). Molecular weight: 382.224. Calc. for $C_{23}H_{30}O_3N_2$: 382.225.

The reaction was repeated with dl-vincaminoridine (22 mg, 5.75 mmole) in glacial acetic acid (11.5 ml), mercuric acetate (96 mg, 30.25 mmole) and 43 hours at room temperature. The crude product, a yellowish glass 18 mg, had the same TLC and spectral properties as the one obtained starting with

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a mixture of dl-epimers. Preparative TLC on alumina neutral Woelm, developed with chloroform-ethyl acetate (1:1) in 15 mg of the latter product gave three main products. TLC investigation of two of them showed that on silica gel both of them behaved the same and had the same R_f values as the material isolated previously. On alumina it was shown that they were in fact two different compounds (presumably two epimeric desired products).

a) The less polar of them (2.0 mg, 11%) was a colourless amorphous and unstable material. Infrared ($CHCl_3$): No NH absorption, 1715 (strong, α,β conjugated ester), 1660 (strong, C=C in conjugation) cm^{-1}. Ultraviolet: λ_{max} 335, 310 (infl.), and 225 mμ.

b) The medium polarity compound (4.5 mg, 24.5%) was a colourless amorphous and unstable material. Infrared ($CHCl_3$): No NH absorption, 1715 (strong, α,β conjugated ester), 1660 (strong C=C in conjugation) cm^{-1}. Ultraviolet: λ_{max} 340, 310 (infl.), and 225 mμ.

c) The most polar component was isolated as a yellowish solid (7.5 mg, ca. 41%) and did not move from the base line. The following information suggested that it might be some oxidation product of the starting material or the acid. Infrared ($CHCl_3$): 2850 (small, CH absorption), 1730 (very strong, unconjugated ester or acid), no C=C conjugated, and the rest of the spectrum was very similar to the one of the starting material. Ultraviolet: λ_{max} 350, 305 and 232 mμ.

The scarcity of starting material and the small amounts of the above reaction products did not allow us to collect more information about them.

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