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SYNTHETIC COMPOUNDS RELATED TO RESERPINE

By

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A thesis submitted in partial fulfilment
of the requirements of the degree of
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2. PREFACE

During the past few years, there has developed an increasing interest in both synthetic and natural hypotensive agents.

This present work records the synthesis of a compound structurally related to reserpine. This synthesis was carried out via a procedure which had not previously been used for the preparation of ring E substituted epialloyohimbanes.

Acknowledgement

The author wishes to express his sincere thanks to Dr. F.A.L. Anet for his encouragement and patience, and for the support he provided from his National Research Council of Canada grant-in-aid of research.

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4. ABSTRACT

Woodward's synthesis of sempervirine has been used to prepare 18-methoxysempervirine and 18-benzyloxysempervirine. In each case, the appropriate 4-alkoxycyclohexanone was condensed with ethylformate in the presence of sodium methoxide, and then with 2-iodopropane in acetone solution containing potassium carbonate. The resulting 2-isopropoxymethylene-4-alkoxycyclohexanone was reacted with the di-lithium salt of harman to give, after acid hydrolysis, the sempervirine derivative.

Attempts to demethylate the methoxysempervirine or its reduction product 18-methoxyalloyohimbane were unsuccessful. Hydrogenolysis of 18-benzyloxysempervirine in the presence of palladium gave 18-hydroxysempervirine, which on further reduction with Adams' catalyst gave 18-hydroxy-alloyohimbane. The stereochemistry of the hydroxyl group was shown in two different ways. The alcohol was oxidized to alloyohimbane-18-one, and the reduction of the ketone with lithium tri tertiary-butoxyaluminum hydride returned the original alcohol. This reducing agent is known to give almost entirely the equatorial isomer. The nuclear magnetic resonance spectrum of the acetate prepared from the 18-hydroxyalloyo-himbane showed that the acetoxy group, and therefore the original hydroxyl group was equatorial. The compound was therefore 18-β-hydroxyalloyohimbane.

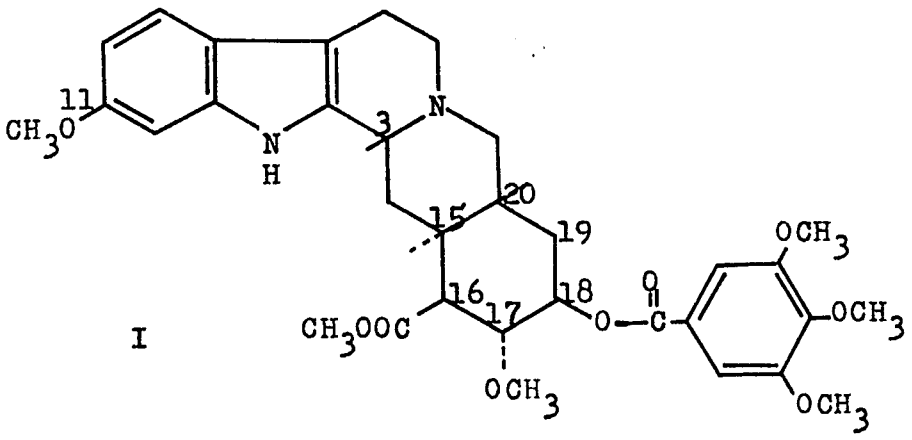
The oxidation of 18-β-hydroxyalloyohimbane with mercuric acetate gave 3-dehydro-18-β-hydroxyalloyohimbane (isolated as the perchlorate salt) and reduction of this with zinc and aqueous acetic acid gave 18-hydroxyepialloyohimbane. The stereochemical assignment of this compound was confirmed by the nuclear magnetic spectrum of its' acetate.

The 3,4,5-trimethoxybenzoate of 18-β-epialloyohimbane was prepared for pharmacological testing.

5. INTRODUCTION

The roots and leaves of Rauwolfia serpentina were long used in the Ayruvedic medicine of India as antidotes against a wide variety of ailments. Long before the root of Rauwolfia serpentina was introduced into clinical medicine in the western world for the treatment of hypertension and various nervous disorders, including insanity, it was used in the modern rational therapy of India for the same purposes. Within recent years certain of its more potent alkaloids, notably reserpine, have gained widespread use in the therapy of most countries of the world for their hypotensive, sedative, and tranquilizing effects.

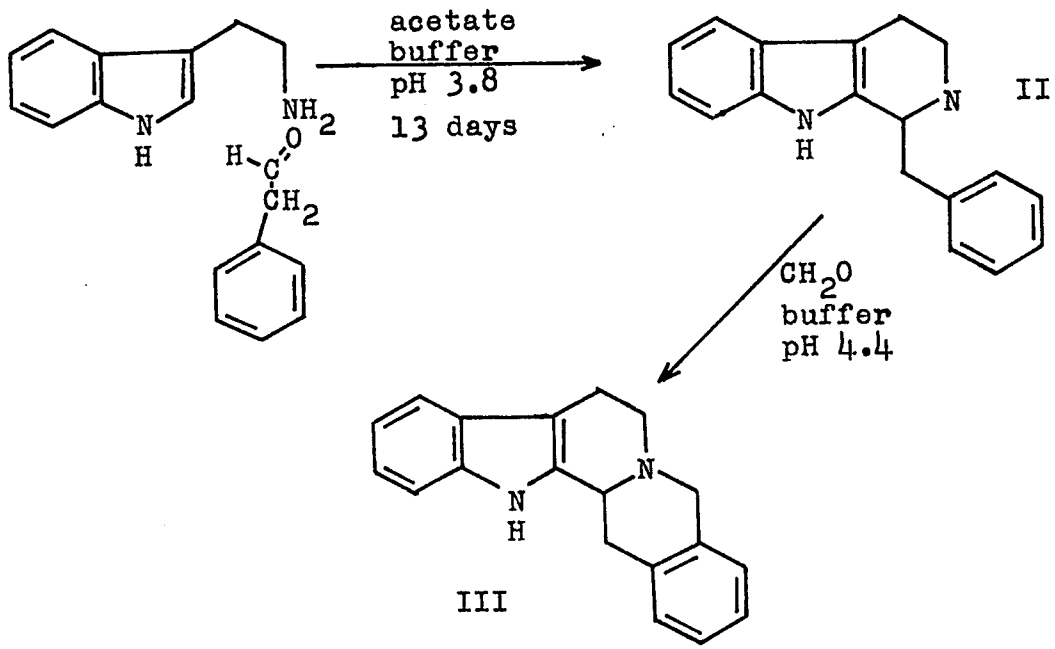
The structure and stereochemistry of reserpine (I) have been established (1,2,3,4) as the following:



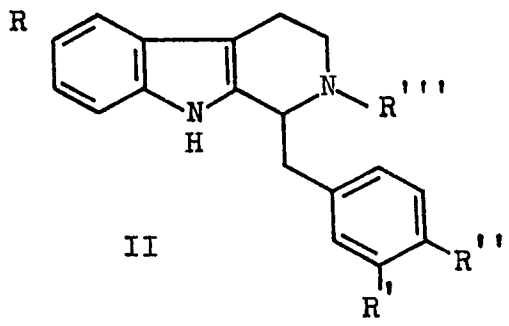
I

The relationship between the structure of the reserpine molecule and its physiological activity have not as yet been fully elucidated. There are two main approaches to the problem: first, the synthesis of compounds containing certain structural features of reserpine and determination of the kind and degree of activity that they possess; second, modification of the structure or stereochemistry of reserpine itself and the consequent effect of this on the pharmacological activity.

The first approach is typified by a series of compounds prepared by Logemann and coworkers (5) employing the synthetic method essentially due to Hahn (6,7,8). Following this procedure they synthesized a series of compounds having an aromatic ring E (11) and open as well as closed ring D (111)

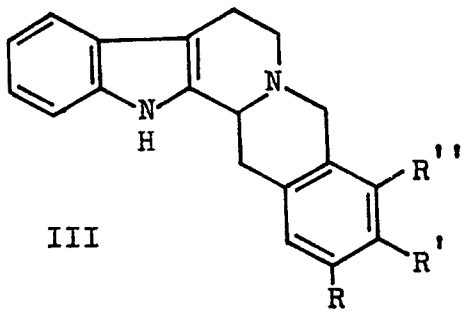


The compounds they prepared were:



II

R	R'	R''	R'''
H	OH	H	H
H	3,4,5-trimethoxy benzoyloxy	H	3,4,5-trimethoxy benzoyloxy
H	OCH_3	OH	H
H	OCH_3	-3,4,5-trimethoxy benzoyloxy	$-COCH_3$
H	OCH_3	-3,4,5-trimethoxy benzoyloxy	3,4,5-trimethoxy benzoyloxy
H	OCH_3	$-O-CO-(CH_2)_{16}-CH_3$	$-O-CO-(CH_2)_{16}CH_3$
OCH_3	OCH_3	OH	H
OCH_3	OCH_3	-3,4,5-trimethoxy benzoyloxy	-3,4,5-trimethoxy benzoyloxy

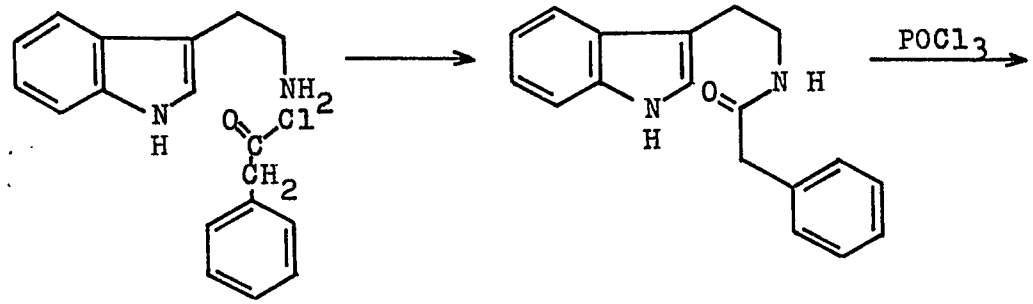


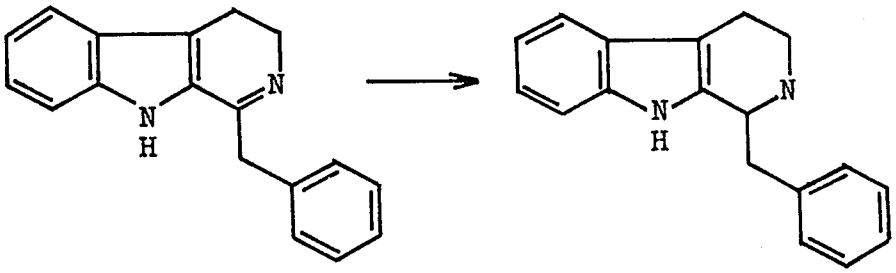
III

R	R'	R''
OCH_3	OH	H
OCH_3	$O\text{-}COCH_3$	H
OCH_3	$O\text{-}COCH_2CH_3$	H
OCH_3	$O\text{-}COCH_2CH_2CH_3$	H
OCH_3	$O\text{-}COC_6H_5$	H
OCH_3	OCH_3	OCH_3

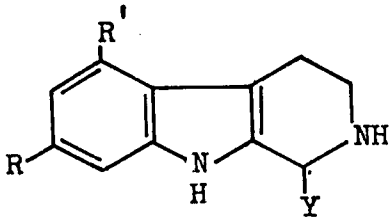
They reported that these compounds seemed to show little promise of useful pharmacological activity.

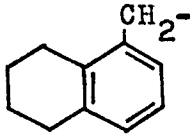
A somewhat similar series of compounds having ring D open (IV) were prepared by Protiva et al. (9,10) in the following manner:



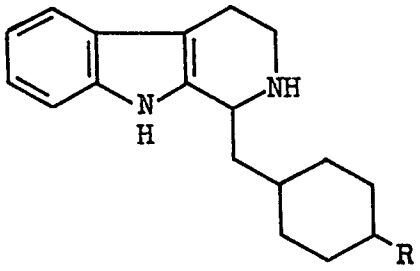


The compounds they prepared were:



R	R'	Y
H	H	4-methoxy benzyl
H	H	3,4-dimethoxy benzyl
H	H	
H	H	$-CH_2CH_2CH_2C_6H_5$
H	H	$-CH_2CH_2C_6H_5$
H	H	$-CH_2C_6H_5$
OCH_3	H	$-CH_2C_6H_5$
H	OCH_3	$-CH_2C_6H_5$
H	H	$-C(CH_3)_2C_6H_5$

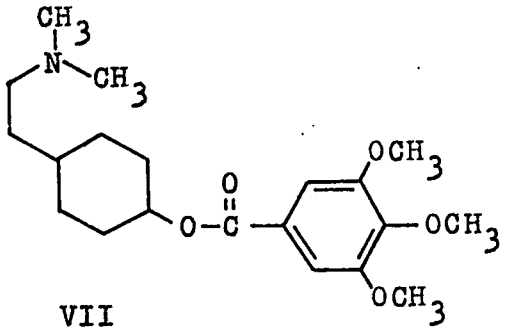
They reported that methane sulfonates of these applied intravenously in doses of 1.5 mg/kg to anesthetized dogs, cats, and rabbits lowered the blood pressure by 10-70% and exerted a significant antiseratonin effect on isolated rat intestine. The hypotensive effect was of a type similar to that of reserpine. They also prepared several similar compounds having a saturated ring E (11, 12).



V R = H

VI R = OCH_3

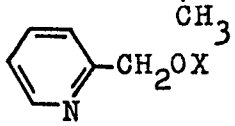
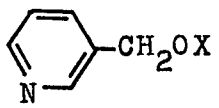
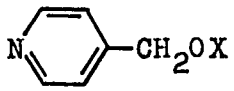
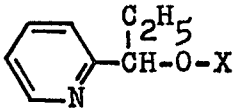
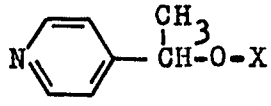
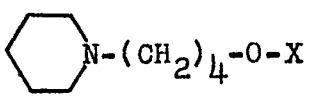
The methane sulfonates of these were again reported to have a hypotensive effect. A much simpler analogue



VII

was also prepared, but found to be inactive.

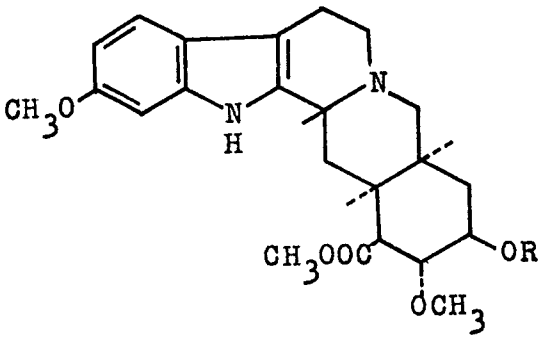
Vejdelek and Treka prepared a series of simple basic esters of 3,4,5-trimethoxy benzoic acid (13) of the following structure:

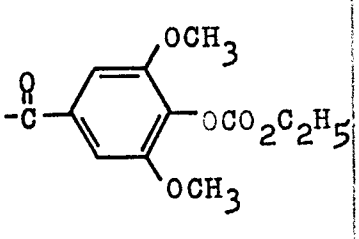
X = 3,4,5-trimethoxybenzoyl	Dose in mg/kg intravenously in anesthetized dogs which gave a 25% drop in blood pressure	Duration of effect (minutes)	LD_{50} in mg/kg intravenously in mice
$(CH_3)_2N-CH_2CH_2CH_2O-X$	6.0-7.5	6-10	70
$(C_2H_5)_2N-CH_2CH_2CH_2O-X$	2.5-4.5	3-10	54
$(CH_3)_2N-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-O-X$	6.5-7.5	1	111
$(C_2H_5)_2N-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CHO}}-X$	1.0-3.0	1	60
	7.5-15	1	195
	5.0-10	1	185
	1.0-2.0	1	1.2
	4.5-7.5	1	150
	2.5-4.5	1	136
	2.0-5.0	1	44
reserpine	0.01-0.03	24-74 hrs.	28

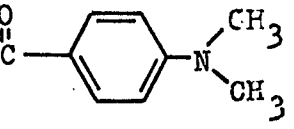
As can be seen from the table, all of these showed some hypotensive activity, but not of the order of reserpine.

The second approach to the relationship of structure and activity in reserpine was begun by Huebner in 1954, when he showed (14) that substitution of the indole nitrogen with methyl and allyl groups produced substances totally lacking in reserpine-like action. The N-oxide of the other nitrogen had a reserpine like effect (15), but the quaternary salt was found (16) to be completely inactive. This was also true of such degradation products as methyl reserpate, reserpic acid and its lactone.

In an effort to separate the hypotensive and sedative components characteristic of reserpine, Lucas and coworkers (17) prepared over one hundred derivatives of methyl reserpate. Of these, two were found to be outstanding;

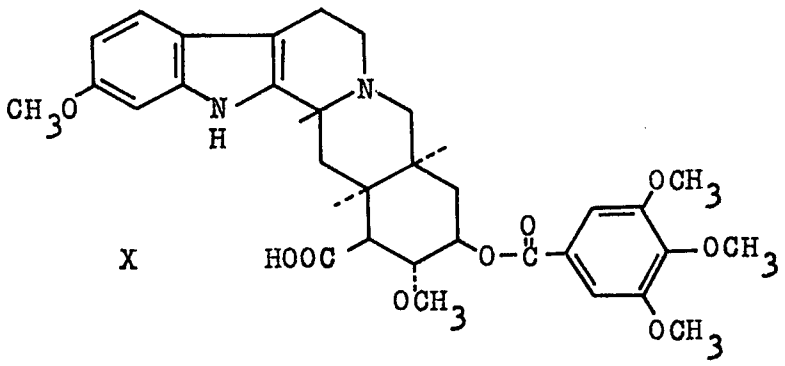


VIII R = 

IX R = 

The carbethoxy syringate ester (VIII) was almost equipotent to reserpine as a hypotensive agent but had only one-twentieth its activity as a sedative, while the 3-dimethylaminobenzoate ester (IX) had approximately one-fourth the sedative effect of reserpine, yet was only one-fortieth as potent a hypotensive agent.

In a later paper (18) they prepared the previously unknown O-(3,4,5-trimethoxybenzoyl) reserpic acid (X),

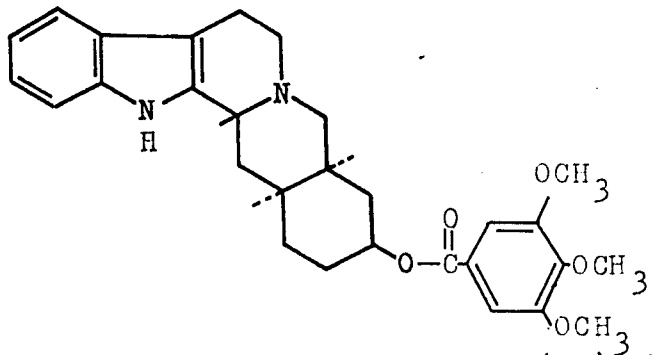


X

and stated that it's biological activity was very low. From this they concluded that the C_{16} position must be substituted in order to elicit reserpine-like activity. Their conclusion, seems unjustified. Their evidence indicates only that the substituent present at C_{16} cannot be a free carboxyl group, and does not mean that a compound lacking substitution at C_{16} would necessarily be devoid of reserpine-like activity.

Of greater interest than the variation in the esterifying acid and other minor structural alterations are

the more deep-seated changes in the molecule of reserpine. In this connection, it was of considerable interest that deserpidine, the naturally occurring 11-desmethoxy analogue of reserpine exhibited identical physiological properties. It was also found that the 11,17-didesmethoxy analogue, which was synthesized by Weisenborn and Applegate (19,20) also showed the characteristic reserpine-like response. Because of this, it was of interest to synthesize the even simpler reserpine analogue (XI)

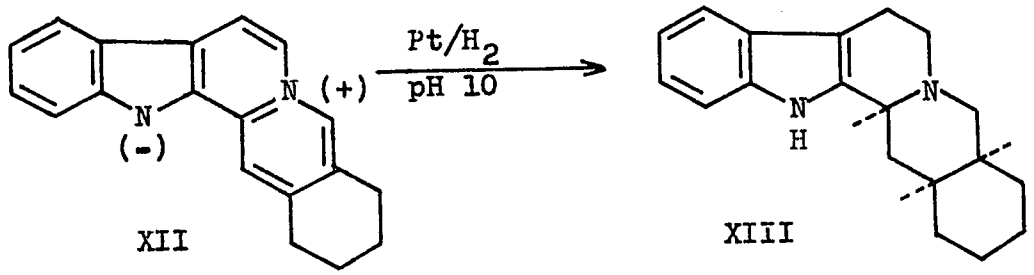


This compound, 18-β-hydroxyepialloyohimbane (XI), has the same stereochemistry at C_3, C_{15}, C_{18} and C_{20} as reserpine, but does not have the carbomethoxyl group at C_{16} or the methoxyl groups at C_{11} and C_{17}.

The synthetic approaches to alloyohimbanes and epialloyohimbanes have been of three distinct types. These will be discussed in chronological order.

The first of these was based on the observation made by Le Hir and coworkers (21,22) that sempervirine (XII),

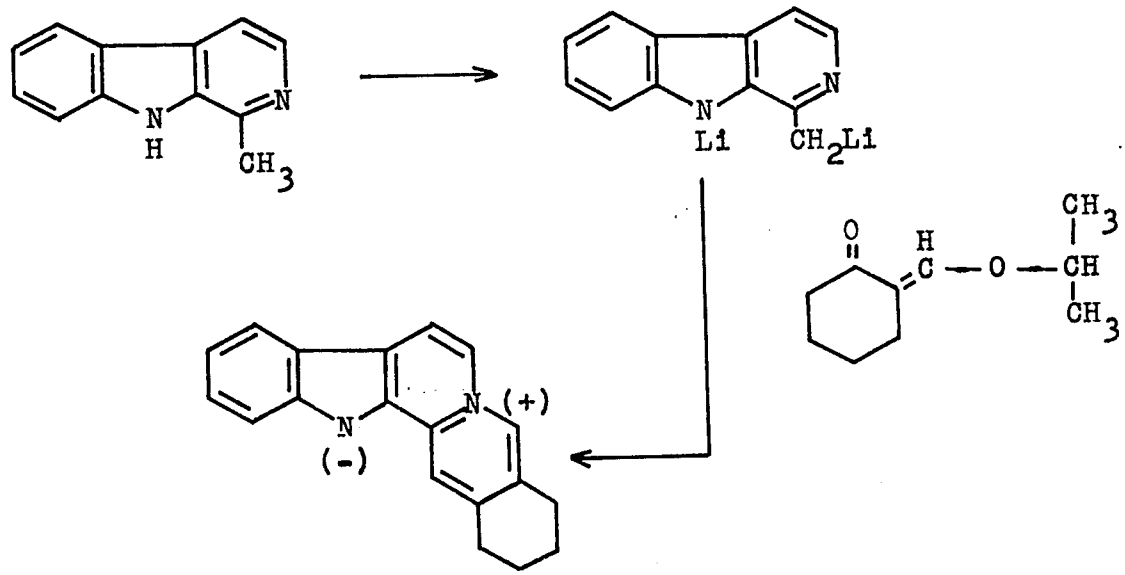
a naturally occurring alkaloid from Gelsemium sempervirins, could be hydrogenated over Adams' catalyst at pH 10 to give d,l-alloyohimbane (XIII) in 60% yield.



XII XIII

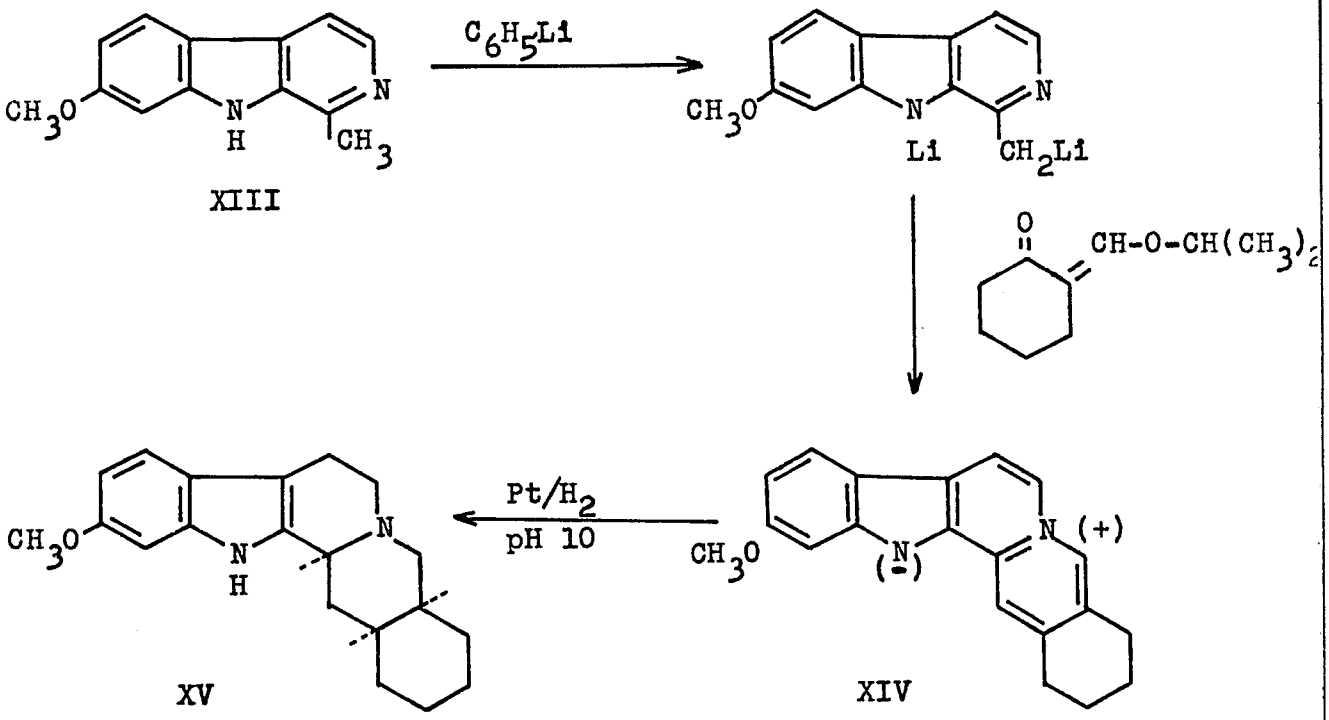
It was later shown (4) that this hydrogenation also gave 2-6% yield of 3-epialloyohimbane.

Sempervirine itself had been previously synthesized by Woodward and McLamore (23) in the following manner:



XII

A synthesis of this type was carried out by Schlittler and coworkers (3) to give a ring A substituted alloyohimbane. Starting from harmine (XIII) they obtained 11-methoxysempervirine (XIV) in 16% yield, which on catalytic reduction gave d,l-11-methoxyalloyohimbane (XV)

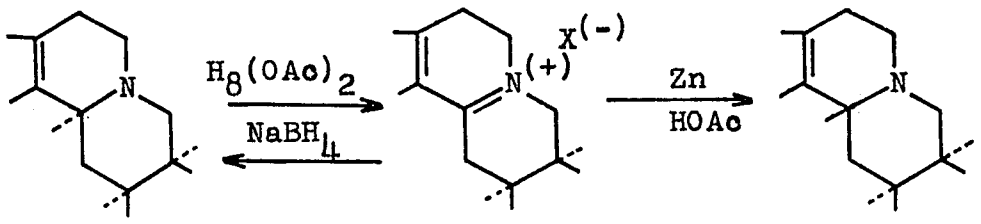


Two principle methods have been found (24,25,26,27,28) for the conversion of alloyohimbanes to the corresponding epialloyohimbanes; these will be described briefly.

The first was discovered early in the structural elucidation of reserpine, when it was found that the centre of asymmetry at C_3 could be epimerized under acidic conditions

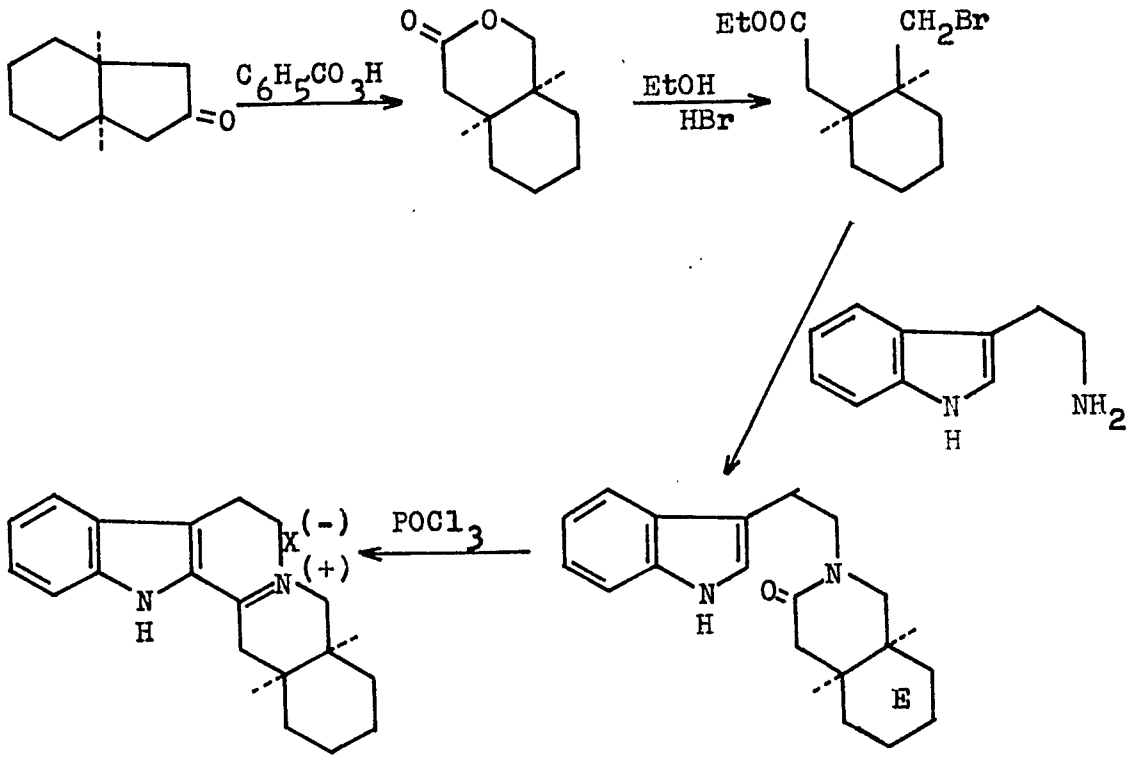
(1,2,3,4) to give an equilibrium mixture of allo- and epi-alloyohimbanes; in the case of the parent compounds alloyohimbane and epialloyohimbane, the equilibrium mixture was found (24) to be 74% ± 5% epialloyohimbane and 26% ± 5% alloyohimbane. The interconversion of reserpine and 3-iso reserpine depended somewhat on experimental conditions, although it always produced the 3-iso system in preponderance. For example, refluxing acetic anhydride transformed reserpine almost exclusively to its 3-epimer (2) whereas refluxing acetic acid converted 3-isoreserpine to a mixture of 3-epimers containing 15% reserpine (25). Equilibration of 3-isoreserpic acid lactone under acidic conditions (31) or 11,17-didesmethoxy isoreserpic acid lactone with a platinum catalyst (20) led exclusively to the epialloyohimbane system. The position of the equilibrium is therefore markedly dependent upon the substituents present in the molecule and conformational arguements have been advanced by Wenkert (24) to explain this dependence.

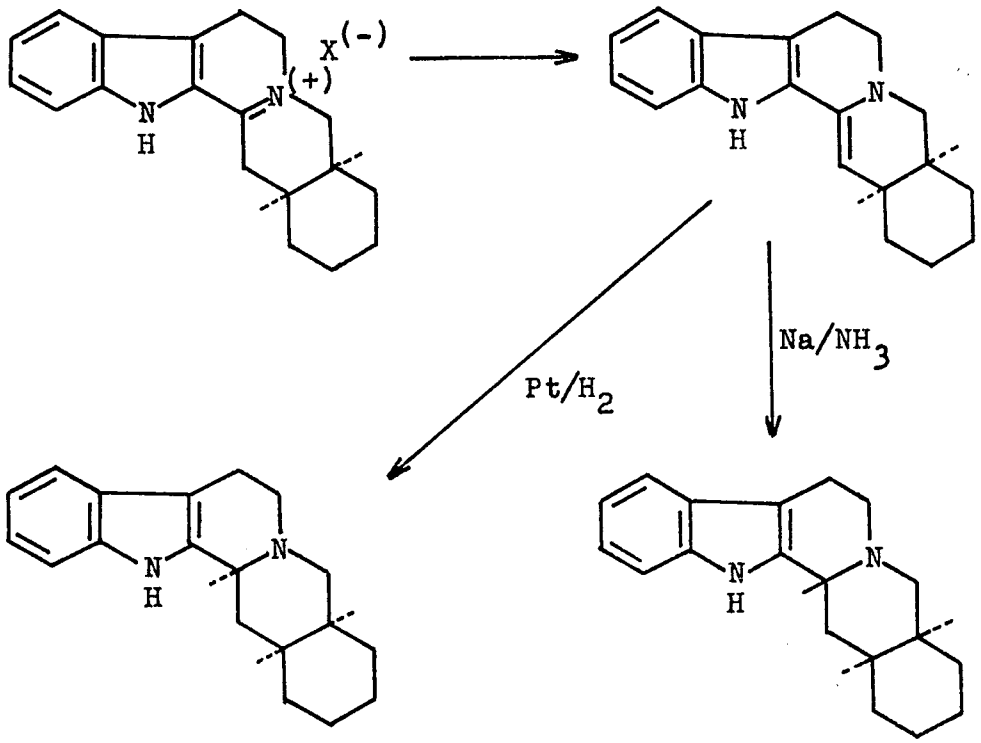
The second method of conversion was based on the fact that alloyohimbanes could be oxidized at C_3 by mercuric acetate to yield the corresponding 3-dehydro derivatives (26,27,28) and that by selection of the appropriate reducing agent, these could be converted to either the allo- or epi-alloyohimbane.



As an example of this method, Weisenborn and Diassi (27) oxidized 3-isoreserpine to the dehyro compound and reduced this in two different ways; sodium borohydride gave 3-isoreserpine and zinc-acetic acid gave reserpine.

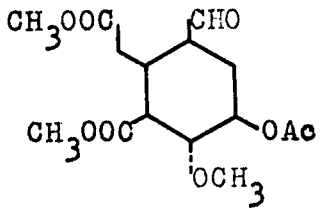
The second general method was that developed by Stork and Hill (28,29) for their stereospecific synthesis of (±) alloyohimbane (XVII) and (±) epialloyohimbane (XVIII). Their procedure was the following:





XVII XVIII

A variation in this procedure was subsequently used in the total synthesis of reserpine by Woodward and coworkers (30), where they prepared compound XIX,

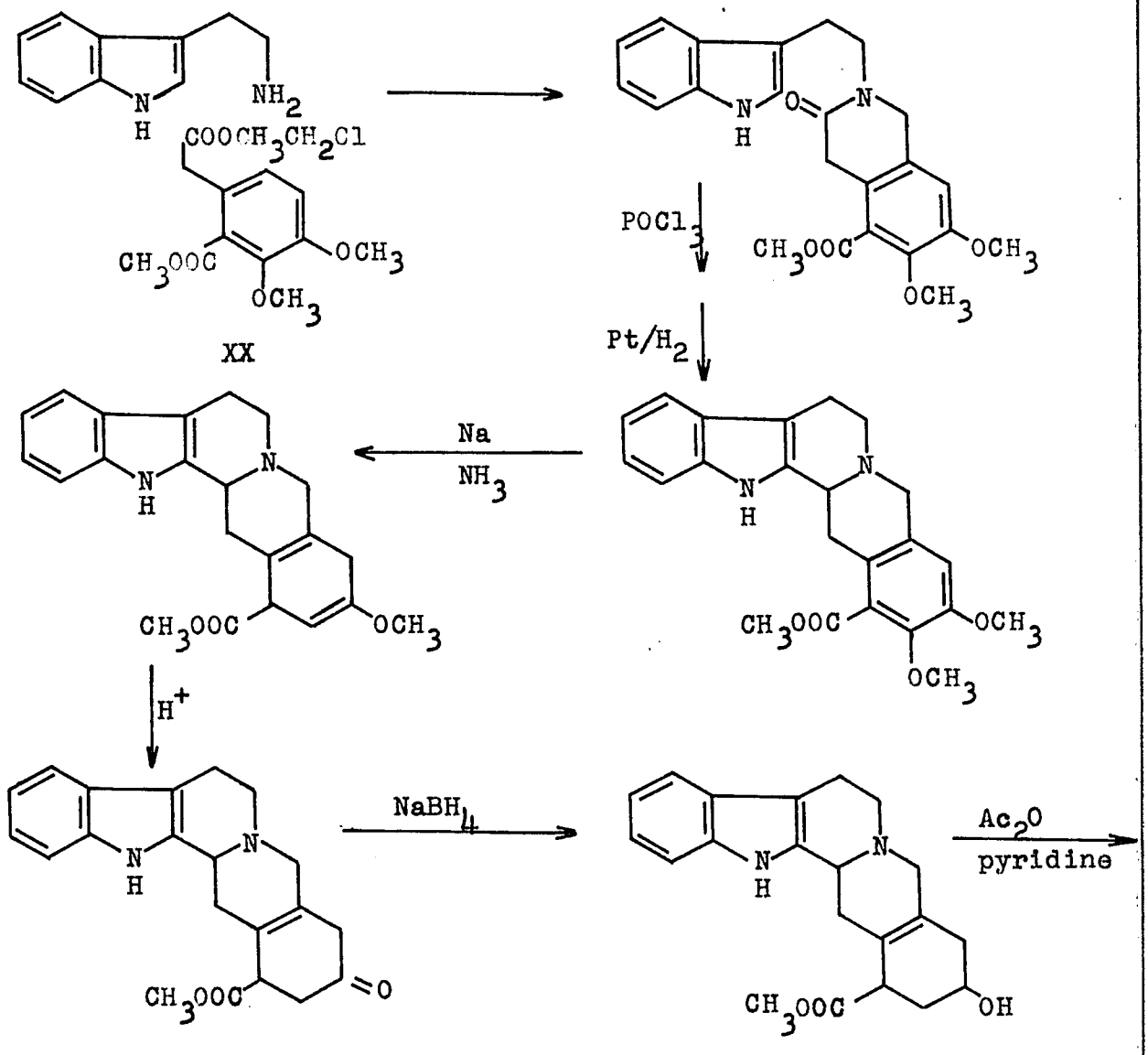


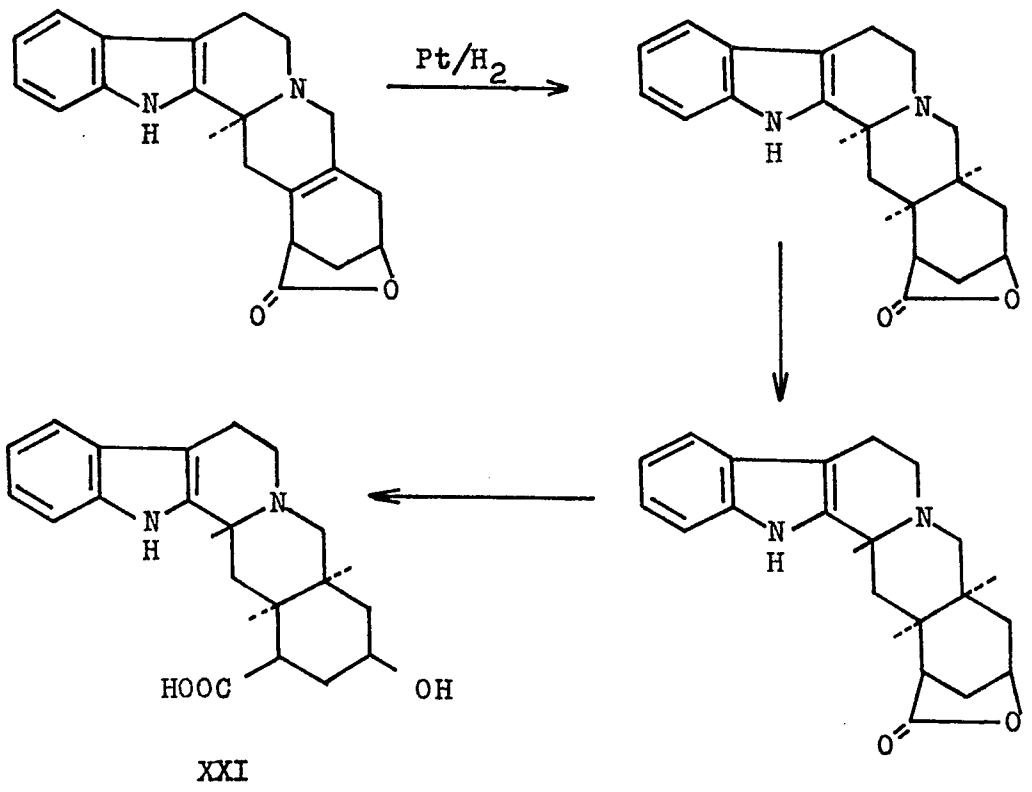
XIX

and employed this in place of the cis-2-bromomethylcyclohexane acetic acid ester (XVI) used by Stork to introduce ring E.

Another variation in this method was used by

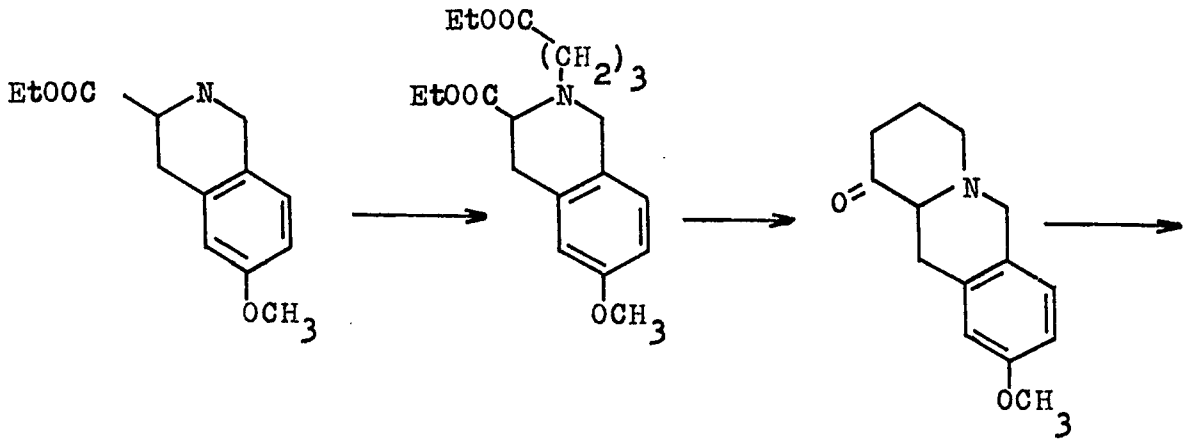
Weisenborn (19,20) in the synthesis of 17-desmethoxy deserpic acid (XXI). Stork and Woodward both used a cyclohexane derivative to construct ring E; Weisenborn, however, used methyl-2-carbomethoxy-3,4-dimethoxy-6-chloromethyl phenyl acetate (XX).

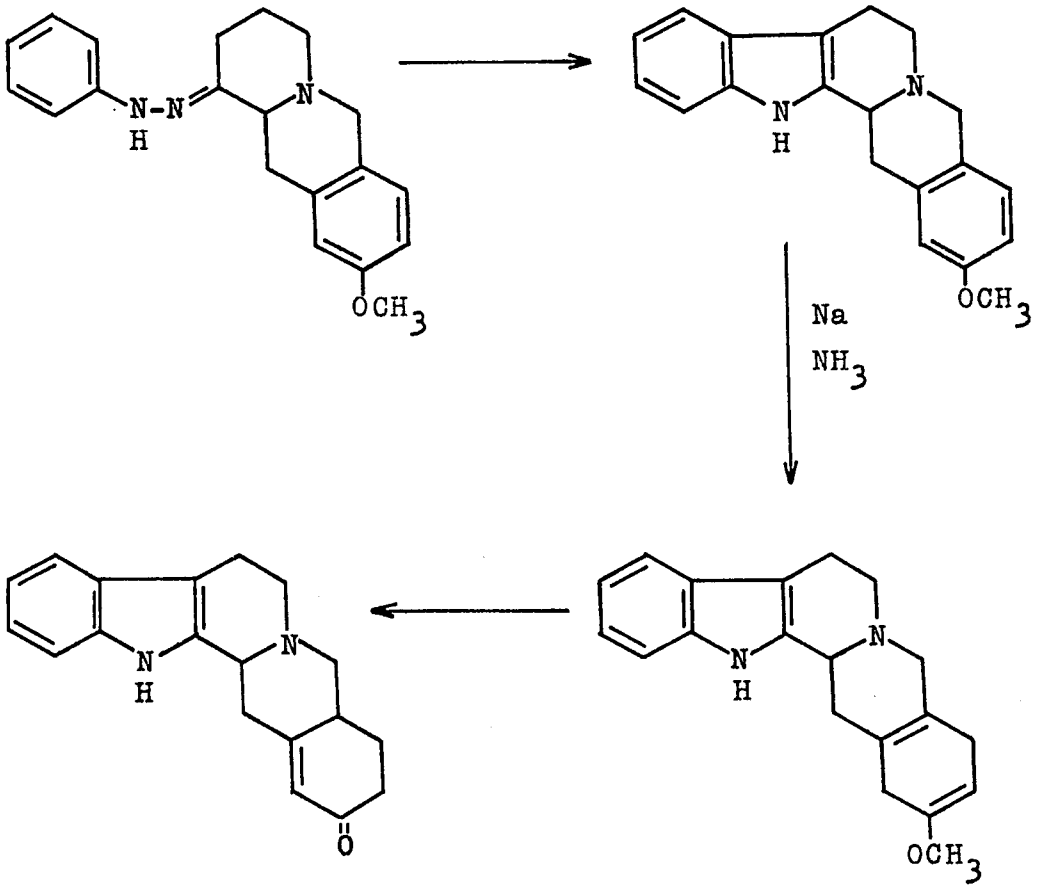




XXI

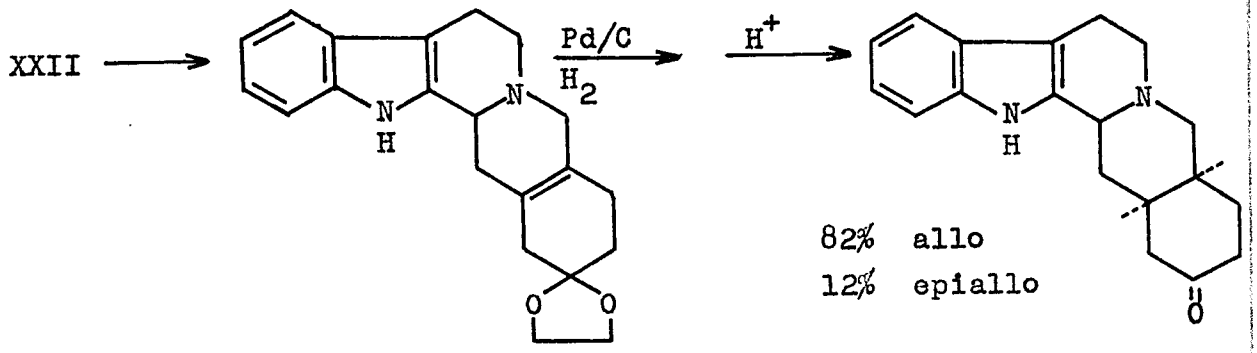
The third method for synthesis of alloyohimbane and epialloyohimbane compounds is essentially due to Swan (31). It consisted of a Fischer indole synthesis on the phenylhydrazone of the appropriate ketone.



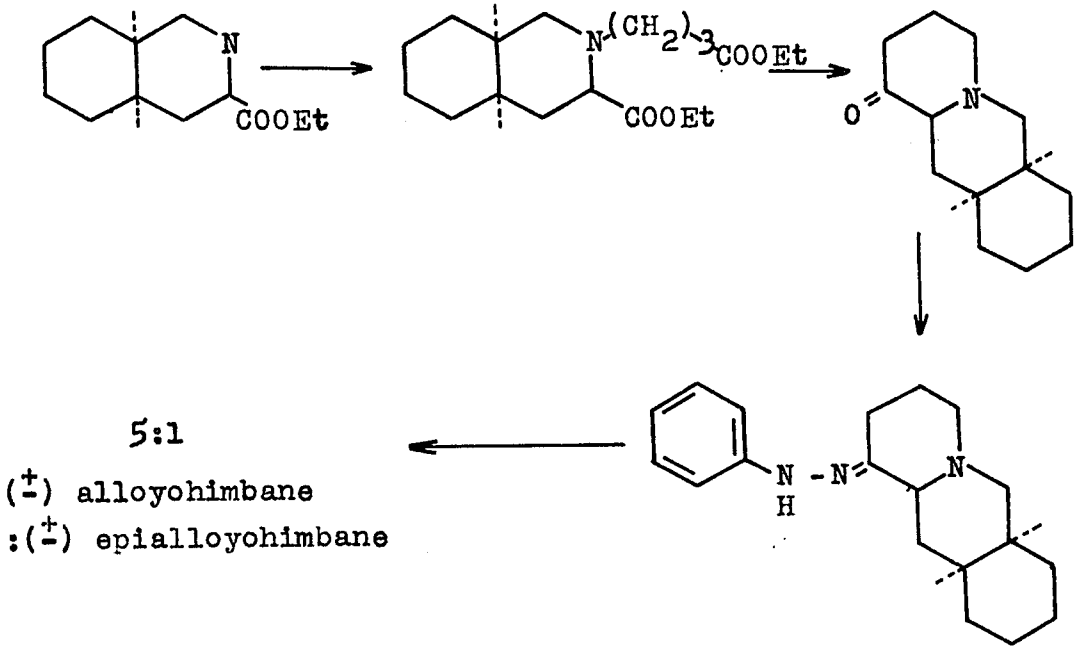


XXII

Swan converted XXII by catalytic hydrogenation to yohimbone, having the C-D ring juncture trans. Philpott and Parsons (32) were able to convert XXII to a mixture of (±) alloyohimbone and (±) epialloyohimbane in the following manner:



This procedure of Swan's was used by Farkas and coworkers (33) for their synthesis of alloyohimbane and epialloyohimbane.



This method however allows little control over the stereochemistry introduced at C_3.

6. EXPERIMENTAL

a) Spectra

The infrared spectra were measured on a Perkin-Elmer "infracord".

The ultraviolet spectra were measured in 1 cm cells on a Beckman DK-2 spectraphotometer.

The nuclear magnetic resonance spectra were recorded on a Varian Model V-4302 spectrometer operating at 60 Mc/sec.

The analyses were done by Geller Laboratories, West Englewood, New Jersey, and by Miss E. Busk of the University of Ottawa.

6. EXPERIMENTAL

Preparation of Quinitol

Following essentially the procedure of Purves and coworkers (34) a solution of 150 gm hydroquinone in 250 ml of hot absolute ethanol was hydrogenated over Raney nickel (35) at 2250 lb pressure and 180°C for 4 hrs. The catalyst was filtered off, the ethanol removed by distillation and the residue distilled to give 150.5 gm (95.4%), b.p. 244-5°, of a mixture of cis and trans quinitol.

Preparation of 4-benzoyloxycyclohexanol

a) Direct esterification (36)

To a stirred solution of 40.5 gm cis-trans mixture of quinitol in 125 ml of chloroform and 95 ml dry pyridine was added 48 gm of benzoyl chloride in 100 ml of chloroform over a period of five hours, the temperature being kept at 0-5° by external cooling. After standing overnight at room temperature, the chloroform solution was freed from pyridine by thorough extraction with water and then with dilute sulfuric acid. The chloroform solution was dried over sodium sulfate and the solvent removed under reduced pressure. Fractionation of the residue gave 41.6 gm (53%) of a mixture of quinitol monobenzoate as a viscous oil b.p. 175-80°/.2 mm.

b) Ester interchange (37)

Quinitol (189 gm; cis-trans mixture) and 240 gm dry ethyl benzoate were added to a solution of 100 mg of sodium in 50 ml ethanol. The solution was heated for 30 minutes to distil out ethanol, during which the internal temperature was raised to 250°, then acidified with acetic acid, and distilled under vacuum to give 197 gm (54.8%) of a cis-trans mixture of 4-benzoyloxycyclohexanol b.p. 176-78 /.2 mm.

Preparation of 4-benzoyloxycyclohexanone

Using the procedure of Jones and Sondheimer (36) a solution of 29.3 gm chronium trioxide in 20 cc of water and 80 cc acetic acid was added to a cooled solution of 66.5 gm of 4-benzoyloxy cyclohexanol in 130 cc acetic acid, the temperature being kept below 35°. The reaction mixture was allowed to stand overnight, 450 cc of ether was added and most of the acetic acid removed by repeated washings with water. The solution was then washed with sodium hydroxide solution and water, dried over sodium sulfate, and the ether removed under reduced pressure. The solid residue was crystallized from 40-60° petroleum ether to give 50 gm (76%) 4-benzoyloxycyclohexanone m.p. 60-61°.

Attempted preparation of 2-hydroxymethylene-4-benzoyloxycyclohexanone

The procedure used for this preparation is essentially due to Woodward and coworkers (38).

Sodium methoxide, prepared from 0.92 gm sodium and 25 ml dry methanol was dried at 170° and 1 mm for one hour. It was cooled under nitrogen, the solid broken up and suspended in 20 ml dry benzene. The stirred suspension was kept under nitrogen and 2.96 gm of dry, freshly distilled ethyl formate added over thirty minutes. The reaction mixture was stirred for a further one-half hour, and was then cooled in ice. A solution of 4.36 gm 4-benzoyloxycyclohexanone in 20 ml of dry benzene was added over thirty minutes with stirring and cooling. The ice bath was removed, the reaction mixture allowed to warm to room temperature (26°), and the reaction mixture stirred overnight. The solution was diluted with 20 ml benzene and 20 ml ice cold 10% aqueous sulfuric acid, the aqueous layer separated and extracted with 3 x 10 ml 1:1 ether-benzene. The combined organic extracts were shaken with excess ice cold 2% potassium hydroxide solution, washed with water, dried over magnesium sulfate and the solvent removed. The residue was distilled to give 2.70 gm (90%) of methyl benzoate b.p. 195-98°, indicating almolst complete hydrolysis of the benzoyl group under the reaction

conditions used. In a series of attempted preparations of 2-hydroxymethylene-4-benzoyloxycyclohexanone, it was found that reaction times as short as fifteen minutes still lead to virtually complete hydrolysis of the benzoyl group.

Preparation of 4-hydroxycyclohexanone (30)

To a solution of 100 mg sodium in 200 ml of dry methanol was added 52.6 gm 4-benzoyloxy-cyclohexanone, and the mixture refluxed for twenty hours. After the addition of 10 ml water, the solution was saturated with carbon dioxide and the methanol removed under reduced pressure. The residue was dissolved in water and the methyl benzoate extracted with ether. The aqueous layer, after removal of water under reduced pressure and distillation of the residue gave 17.8 gm (61%) of 4-hydroxycyclohexanone. b.p. 96-98°/0.5 mm; 2,4-dinitrophenylhydrazone, m.p. 160-61° reported 151° (36).

Preparation of 4-tetrahydropyranyloxycyclohexanone

To a mixture of 21.9 gm of freshly distilled dihydropyran and 14.9 gm 4-hydroxycyclohexanone was added 2 drops of concentrated hydrochloric acid. After standing overnight at room temperature, 50 ml of ether was added, the ether solution washed twice with 20 ml of 5% sodium hydroxide solution, twice with 25 ml of water, and dried over

magnesium sulfate. The excess dihydropyran and ether were removed by distillation, and the residue distilled under reduced pressure to give 24.0 gm (93%) of 4-tetrahydropyranyloxycyclohexanone. b.p. 116-18°/0.05 mm.

Calc. for $C_{11}H_8O_3$: C, 66.64; H, 9.15

Found: C, 65.74; H, 9.14

The infrared spectrum showed a strong carbonyl bond at 1704 cm^{-1}. No hydroxyl band was present.

Preparation of 2-hydroxymethylene-4-tetrahydropyranyloxycyclohexanone

Using Woodward's procedure for the preparation of hydroxymethylene compounds (38), sodium methoxide was prepared from 5.34 gm of sodium and 75 ml of dry methanol and dried at 160° and 1 mm for one hour. The sodid was cooled under nitrogen, broken up and suspended in 100 ml of dry benzene. The suspension was kept under nitrogen and 32.4 ml of dry, freshly distilled ethyl formate added over thirty minutes. The reaction mixture was stirred for a further thirty minutes cooled to 0°, and a solution of 16.0 gm of 4-tetrahydropyranyloxycyclohexanone in 100 ml of dry benzene was added over one-half hour. The ice bath was removed, the reaction mixture allowed to warm to room temperature and stirring continued overnight. The solution was diluted with 100 ml of benzene, and 100 ml ice cold water added. The two layers

were separated and the benzene layer extracted twice with 30 ml of ice cold 2% potassium hydroxide solution. The alkaline layer and the alkaline extracts were combined, washed twice with 40 ml benzene, cooled to 0°C, and carefully adjusted with disodium phosphate-citric acid buffer solution to pH 6.5. The buffered solution was well extracted with a 1:1 benzene ether mixture, the organic extract washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 14.7 gm (75%) of crude 2-hydroxymethylene-4-tetrahydropyranyloxycyclohexanone. Since this compound decomposed readily, it was not purified further, but was used immediately in the succeeding reaction.

Preparation of 2-isopropoxymethylene-4-tetrahydropyranyloxycyclohexanone

This preparation was carried out using essentially the procedure of Johnson and Posvic (39).

To a stirred suspension of 20.2 gm of freshly ignited and finely powdered potassium carbonate in 75 ml of dry acetone was added 14.5 gm of 2-hydroxymethylene-4-tetrahydropyranyloxycyclohexanone and 22.1 gm of isopropyl iodide. The mixture was heated under reflux for six hours, cooled, and the solvent evaporated under reduced pressure. Sufficient water was added to dissolve the inorganic solid, and the

organic material was extracted three times with 25 ml of ether. The combined organic extracts were washed twice with 50 ml of ice cold 2% potassium hydroxide, twice with water, and then dried over potassium carbonate. The solvent was removed under reduced pressure, and the residue rapidly distilled through a short column to give 7.50 gm (43%) of 2-isopropoxymethylene-4-tetrahydropyranyloxycyclohexanone, b.p. 152-56°/0.05 mm.

Calc. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01

Found: C, 67.21; H, 9,24

The infrared spectrum showed a strong carbonyl bond at 1675 cm^{-1}; the ultraviolet spectrum (Fig. 1) showed absorption at 275 mμ Log ε403.

Preparation of 18-hydroxysempervirine

To a stirred suspension of 1.82 gm harman in 25 ml of anhydrous tetrahydrofuran under an atmosphere of dry nitrogen was added 18 ml of a 0.55 N ethereal solution of phenyl lithium. After two hours, the reaction mixture was cooled to 0° and a solution of 1.88 gm 2-isopropoxy methylene-4-tetrahydropyranyloxycyclohexanone in 10 ml of anhydrous tetrahydrofuran added over thirty minutes. Stirring was continued for a further one and one-half hours, 15 ml of concentrated hydrochloric acid added, and the reaction mixture stirred overnight. The solvent was removed under reduced pressure,

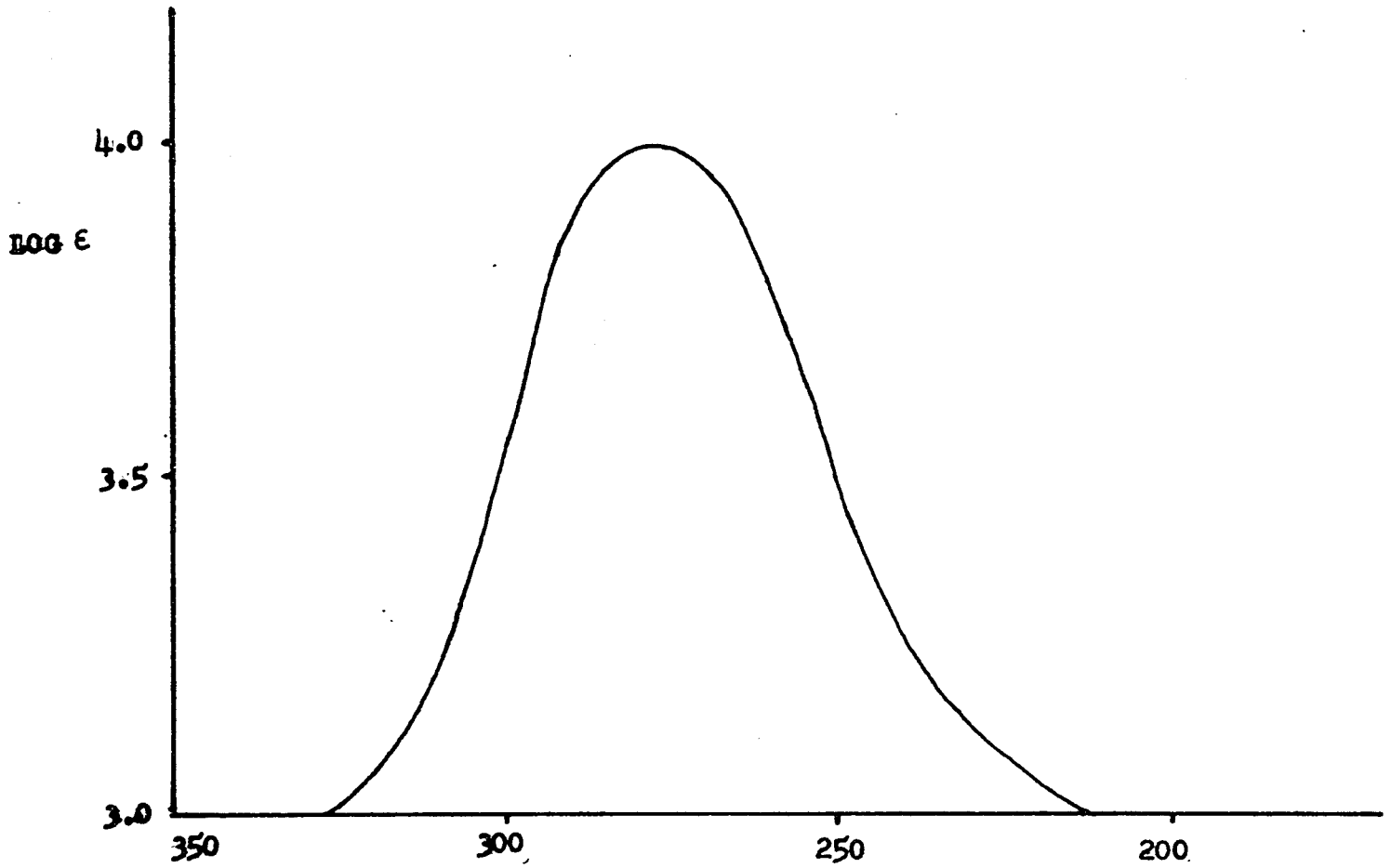


Fig. 1 - Ultraviolet absorption spectrum of 2-isopropoxymethylene-4-tetrahydropyranyloxycyclohexanone in ethanol.

50 ml of water added, the solution made alkaline with 10% sodium hydroxide and extracted six times with 50 ml of chloroform. The chloroform extracts were washed twice with 25 ml of water and then extracted three times with disodium phosphate-citric acid buffer of pH 6. The combined buffer extracts were washed three times with 50 ml of chloroform, made alkaline and extracted six times with 50 ml of chloroform. The chloroform solution was washed twice with 50 ml of water, dried over sodium sulfate, the solvent evaporated under reduced pressure, and the residue crystallized from methanol to give 20mg (1%) of 18-hydroxysempervirine m.p. 210-15° (decomp.). This reaction was carried out under a wide variety of reaction conditions such as temperature and reaction period; yields ranged from 0-1%.

Preparation of 4-methoxycyclohexanol

This was prepared using the procedure of Purves and coworkers (34).

A solution of 124 gm p-methoxy phenol in 100 ml of methanol was hydrogenated over Raney nickel (1) at 2000 lbs pressure and 175° for 2 hrs. The catalyst was filtered off, the ethanol removed by distillation and the residue distilled to give 120 gm (92%) of a mixture of cis and trans 4-methoxy-cyclohexanol, b.p. 56-57°/0.5 mm.

Preparation of 4-methoxycyclohexanone

This oxidation was carried out under the same reaction conditions used by Jones and Sondheimer (36) for the preparation of 4-benzoyloxycyclohexanone.

A solution of 65 gm of chromium trioxide in 40 ml of water and 150 ml glacial acetic acid was added to a stirred, cooled solution of 87.3 gm 4-methoxycyclohexanol in 250 ml glacial acetic acid, the temperature being kept below 35°. The reaction mixture was allowed to stand overnight, one litre of ether was added and most of the acetic acid removed by repeated washings with water. The solution was then washed with cold 15% sodium hydroxide solution followed by water, dried over magnesium sulfate, and the ether removed under reduced pressure. The residue was distilled to give 56.0 gm (65%) of 4-methoxycyclohexanone, b.p. 41-42°/0.7 mm; 2,4-dinitrophenylhydrazone, m.p. 141-43° (reported 142.5-143.5) (40).

Preparation of 2-hydroxymethylene-4-methoxycyclohexanone

Following the procedure used by Woodward and coworkers (38) for the preparation of hydroxymethylene compounds, sodium methoxide was prepared from 19.3 gm of sodium and 250 ml of dry methanol and dried at 160° and 1 mm for one hour. The solid was cooled under nitrogen, broken up and suspended in 230 ml of dry benzene. The suspension

was kept under nitrogen and 115 ml of dry, freshly distilled ethyl formate added over thirty minutes. The reaction mixture was stirred for a further thirty minutes, cooled to 0°, and a solution of 39.5 gm of 4-methoxycyclohexanone in 230 ml of dry benzene was added over one-half hour. The ice bath was removed, the reaction mixture allowed to warm to room temperature and stirring continued overnight. The solution was diluted with 230 ml of benzene, and excess ice cold 10% sulfuric acid added. The layers were separated, the aqueous layer washed twice with 100 ml benzene, and the combined organic extracts shaken with excess ice cold 2% potassium hydroxide solution. The alkaline layer was washed with ether, acidified with dilute hydrochloric acid, and well extracted with a benzene-ether mixture. The organic extract was washed with water, dried, and the solvent removed under reduced pressure to give a crude yield of 131.7 gm (91%) 2-hydroxymethylene-4-methoxycyclohexanone. This compound was not purified further, but was used immediately in the succeeding reaction.

Preparation of 2-isopropoxymethylene-4-methoxycyclohexanone

The conditions used for this reaction were essentially those of Johnson and Posvic (39).

To a stirred suspension of 280 gm of freshly

ignited potassium carbonate in 1 litre of dry acetone was added 131.7 gm of 2-hydroxymethylene-4-methoxycyclohexanone and 165 ml of isopropyl iodide. The mixture was stirred vigorously under reflux for six hours, cooled, and the solvent evaporated under reduced pressure. Sufficient water was added to dissolve the inorganic solid, and the organic material extracted twice with 250 ml of ether. The combined organic extracts were washed twice with 100 ml of ice cold 5% sodium hydroxide, twice with water, and dried over potassium carbonate. The solvent was removed under reduced pressure and the oily residue distilled to give 87.2 gm (52%) of 2-isopropoxymethylene-4-methoxycyclohexanone, b.p. 95-100°/0.08.

Calc. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15

Found: C, 66.85; H, 9.46

The infrared spectrum showed a strong carbonyl absorption at 1677 cm^{-1}; the ultraviolet spectrum (Fig. 2) showed an absorption band at 274 mμ, Log ε 4.04.

Preparation of 18-methoxysempervirine

To a stirred suspension of 18.2 gm of harman in 250 ml of anhydrous tetrahydrofuran under an atmosphere of dry nitrogen was added 193 ml of a 1.08 N ethereal solution of phenyl lithium. After two hours, the reaction mixture was cooled to 0°, and a solution of 15.1 gm of 2-isopropoxymethylene-4-methoxycyclohexanone in 50 ml of anhydrous tetrahydrofuran

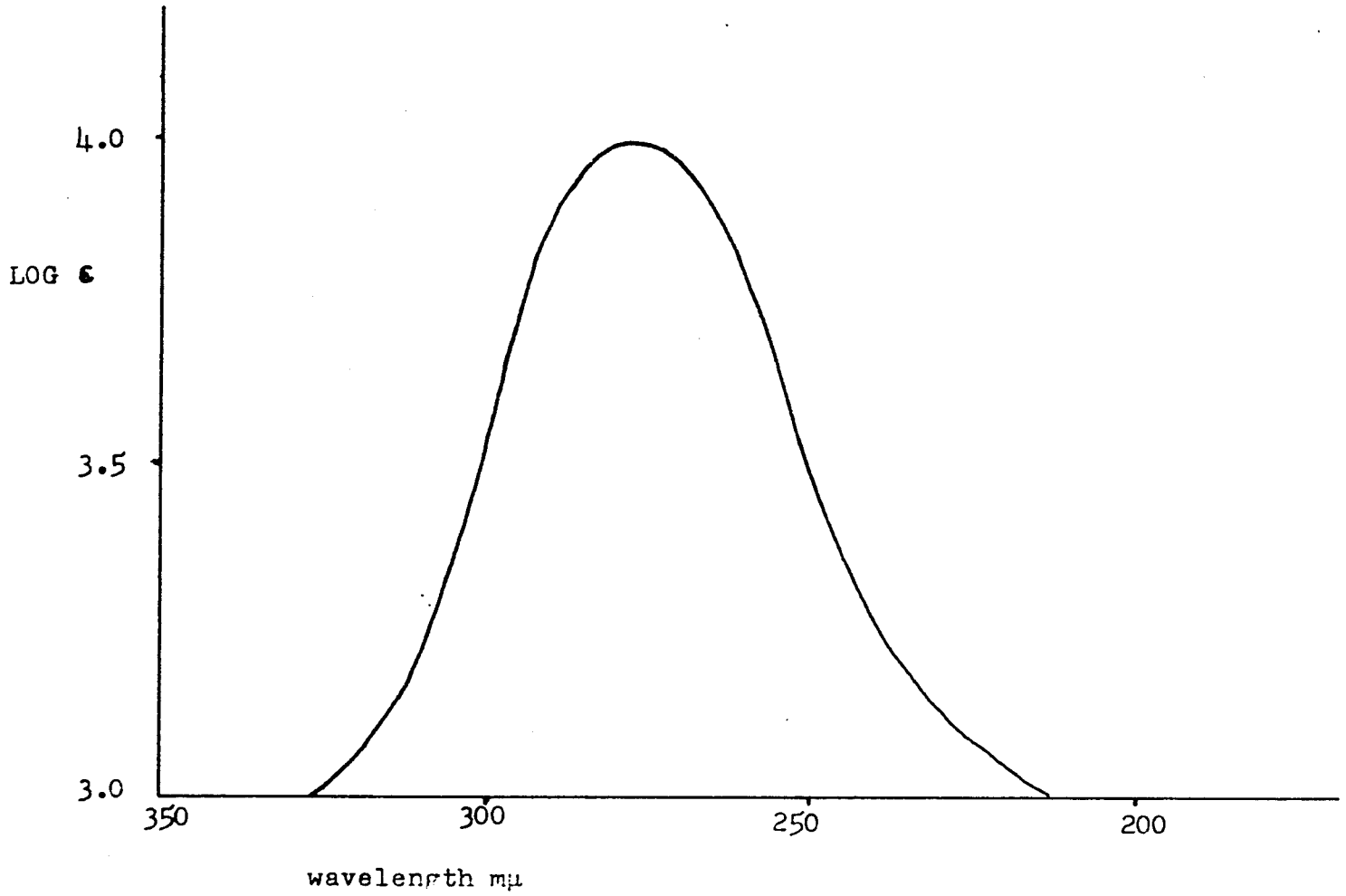


Fig. 2 - Ultraviolet absorption spectrum of 2-isopropoxymethylene-4-methoxycyclohexanone in ethanol.

added dropwise over thirty minutes. Stirring was continued for a further seventy five minutes, 150 ml of concentrated hydrochloric carefully added, and the reaction mixture stirred overnight. The solvent was removed under reduced pressure, 200 ml of water added, the solution made alkaline with ice cold 15% sodium hydroxide and extracted four times with 200 ml of chloroform. The chloroform extracts were washed twice with 100 ml of water and then extracted three times with 200 ml of disodium phosphate-citric acid buffer of pH 6. The combined buffer solutions were washed four times with 100 ml of chloroform, once with 100 ml of ether, made alkaline and extracted five times with 200 ml of chloroform. The chloroform solution was washed twice with 200 ml of water dried and the solvent evaporated under reduced pressure. The residue crystallized to give 9.90 gm (46%) of 18-methoxysempervirine, m.p.170-75°

Calc. for $C_{20}H_{18}ON_2$: C, 79.44; H, 6.00; N, 9.27

Found: C, 78.96; H, 6.03; N, 9.10

The ultraviolet spectrum (Fig. 4) showed the characteristic sempervirine absorption peaks at 242 mμ (Log ε 4.57), 294 mμ (Log ε 4.21), 344 mμ (Log ε 4.28), and 387 mμ (Log ε 4.25). The infrared spectrum is shown in Figure 6.

Attempted preparation of 18-hydroxysempervirine

A solution of 200 mg of 18-methoxysempervirine in 3 ml of 47% hydrobromic acid was refluxed under nitrogen for

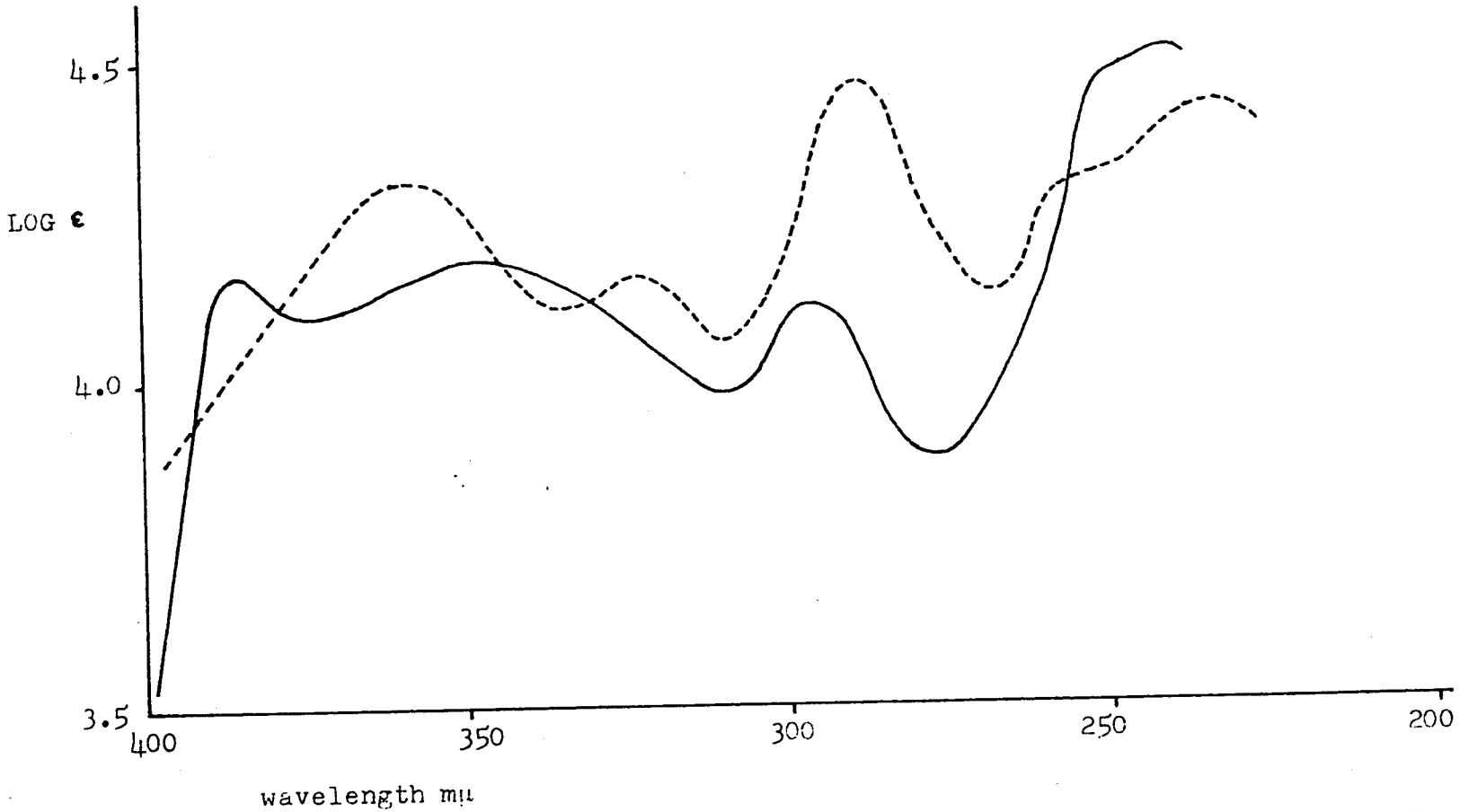


Fig. 3 - Ultraviolet spectrum of sempervirine in ethanol (-) and in alkaline ethanol (---).

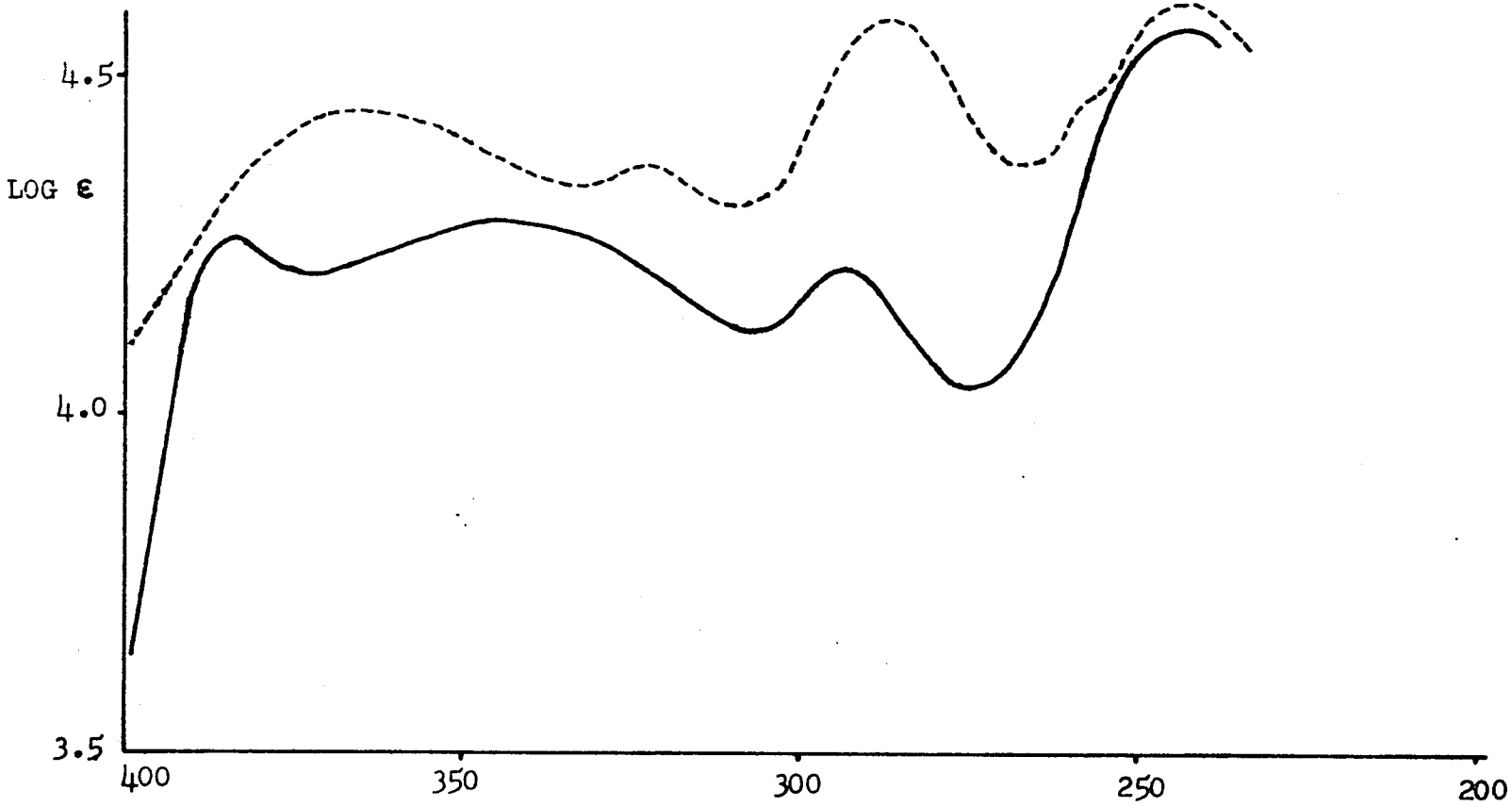


Fig. 4 - Ultraviolet spectrum of 18-methoxysempervirine in ethanol (-) and in alkaline ethanol (---).

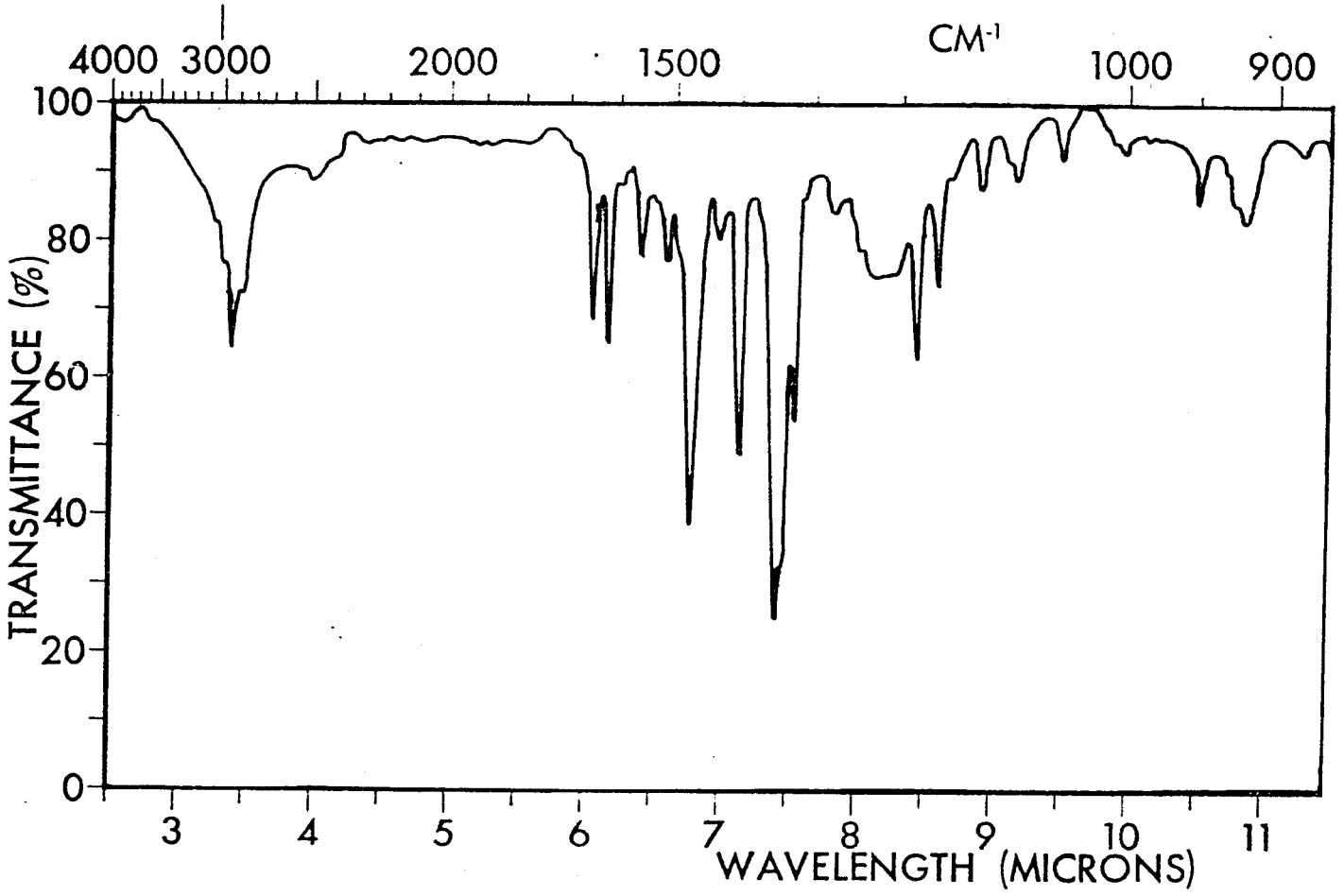


Fig. 5 - Infrared absorption spectrum of sempervirine in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

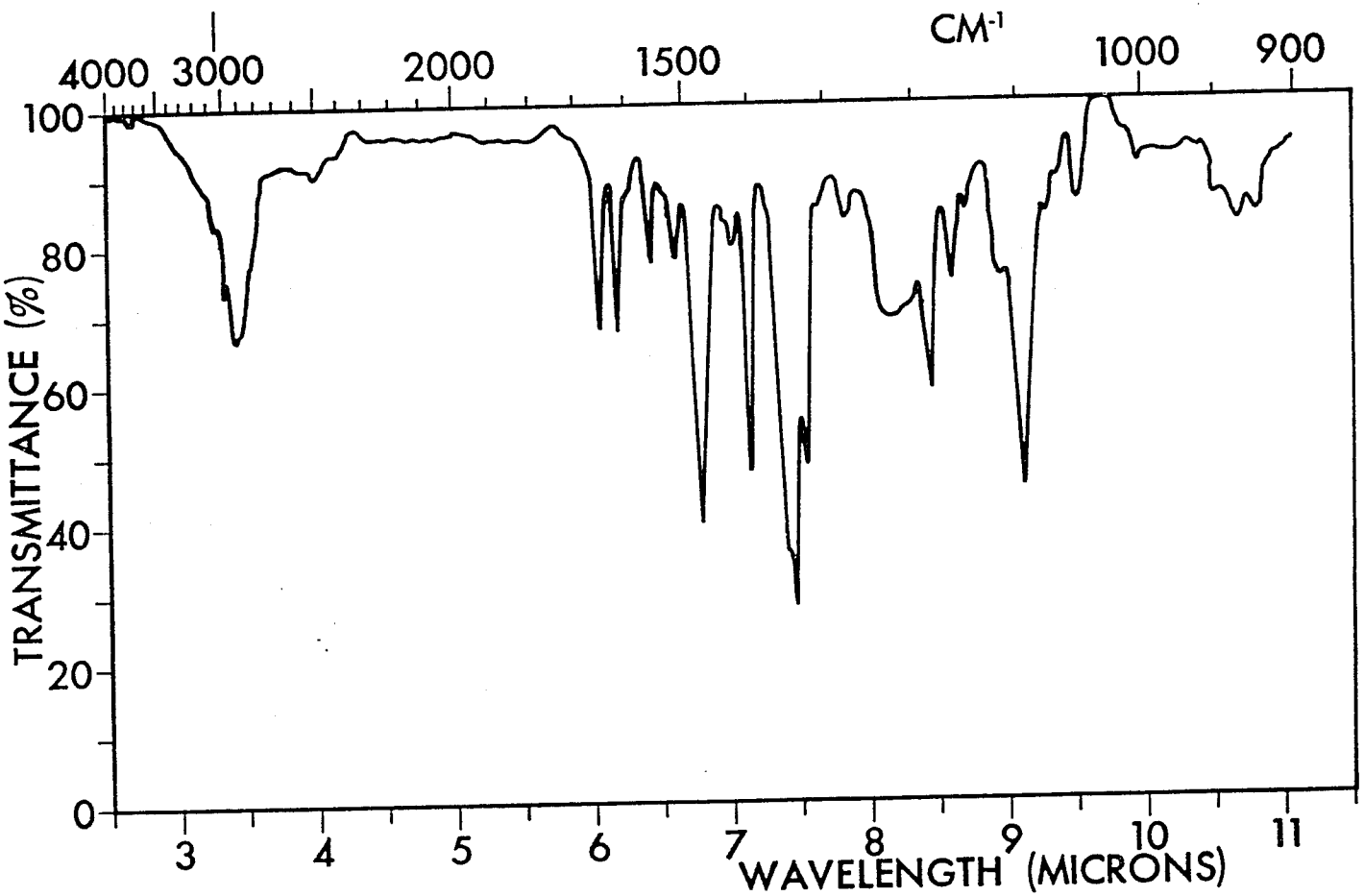


Fig. 6 - Infrared absorption spectrum of 18-methoxysempervirine in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

one hour. The acid solution was cooled, poured into 20 ml of water and made alkaline with dilute sodium hydroxide. The alkaline solution was extracted three times with 20 ml of chloroform, the chloroform solution washed twice with 15 ml of water, dried, and the solvent removed. The residue was chromatographed on alumina in chloroform. No 18-hydroxy-sempervirine or starting material was present. This reaction was run under a variety of concentration and reaction times but in no case was any 18-hydroxysempervirine obtained. Shorther reaction periods usually led to a partial recovery of starting material. Attempts to remove the 18-methoxyl group were also made using pyridine hydrochloride (41), aluminum bromide in benzene (42) and stannic chloride acetyl chloride. In no case was any 18-hydroxysempervirine obtained; the reactions usually gave tars with occasional partial recovery of starting material.

Preparation of 18-methoxyalloyohimbane

A mixture of 500 mg of 18-methoxysempervirine, 100 mg of Adams' catalyst (43) and 2 drops of 2 N methanolic potassium hydroxide in 30 ml methanol was hydrogenated under 75 lb of pressure for six hours. A crystalline precipitate had separated at the end of the reaction. The suspension was filtered and the residue digested with hot methanol. The combined extract and filtrate were concentrated, and cooled

to 0°. The solid was removed by filtration and crystallized twice from methanol to give 205 mg (40%) of 18-methoxy-alloyohimbane, m.p. 245-47°.

Calc. for $C_{20}H_{26}ON_2$: C, 77.38; H, 8.44; N, 9.03

Found: C, 77.57; H, 8.41; N, 9.02

The ultraviolet spectrum (Fig. 7) showed maxima at 283 mμ (Log ε 4.04) and 226 mμ (Log ε 4.60) and a shoulder at 290 mμ (Log ε 3.99). The infrared spectrum is given in Figure 8.

Attempted preparation of 18-hydroxyalloyohimbane

A solution of 200 mg of 18-methoxyalloyohimbane in 3 ml of 47% hydrobromic acid was refluxed for one hour under nitrogen. The acid solution was cooled, poured into 20 ml of water, the aqueous solution made alkaline with ammonium hydroxide, and extracted three times with 10 ml of chloroform. The chloroform extracts were washed twice with 10 ml of water, dried, and the solvent removed under reduced pressure. The residue was dissolved in 2:1 chloroform: 30-60° petroleum ether and chromatographed on alumina. The first fraction yielded 57 mg of starting material, but no other alloyohimbane was obtained.

This reaction was carried out under a variety of concentrations and reaction times but gone only tars and partial recovery of starting material.

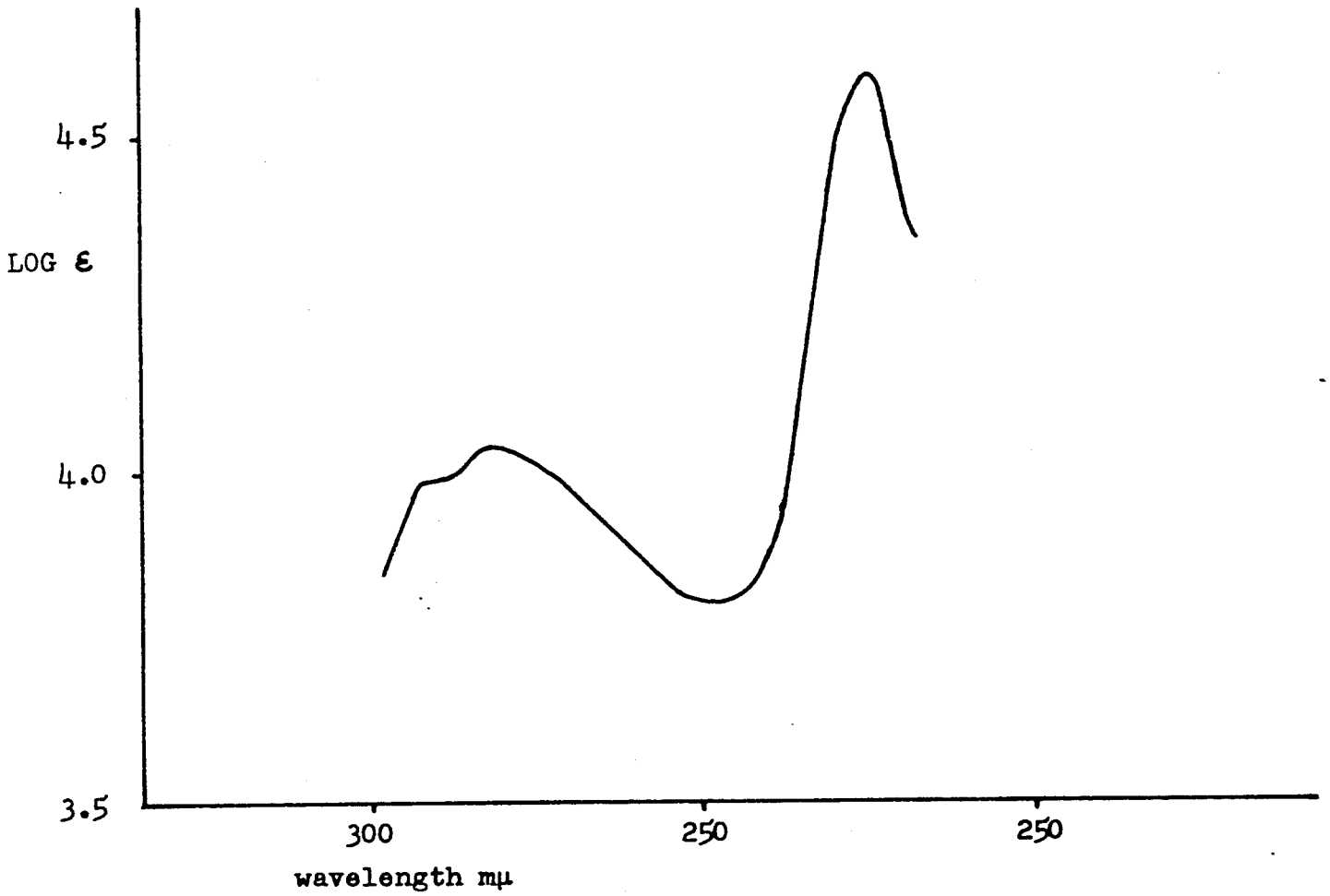


Fig. 7 - Ultraviolet spectrum of 18-methoxyalloyohimbane in ethanol.

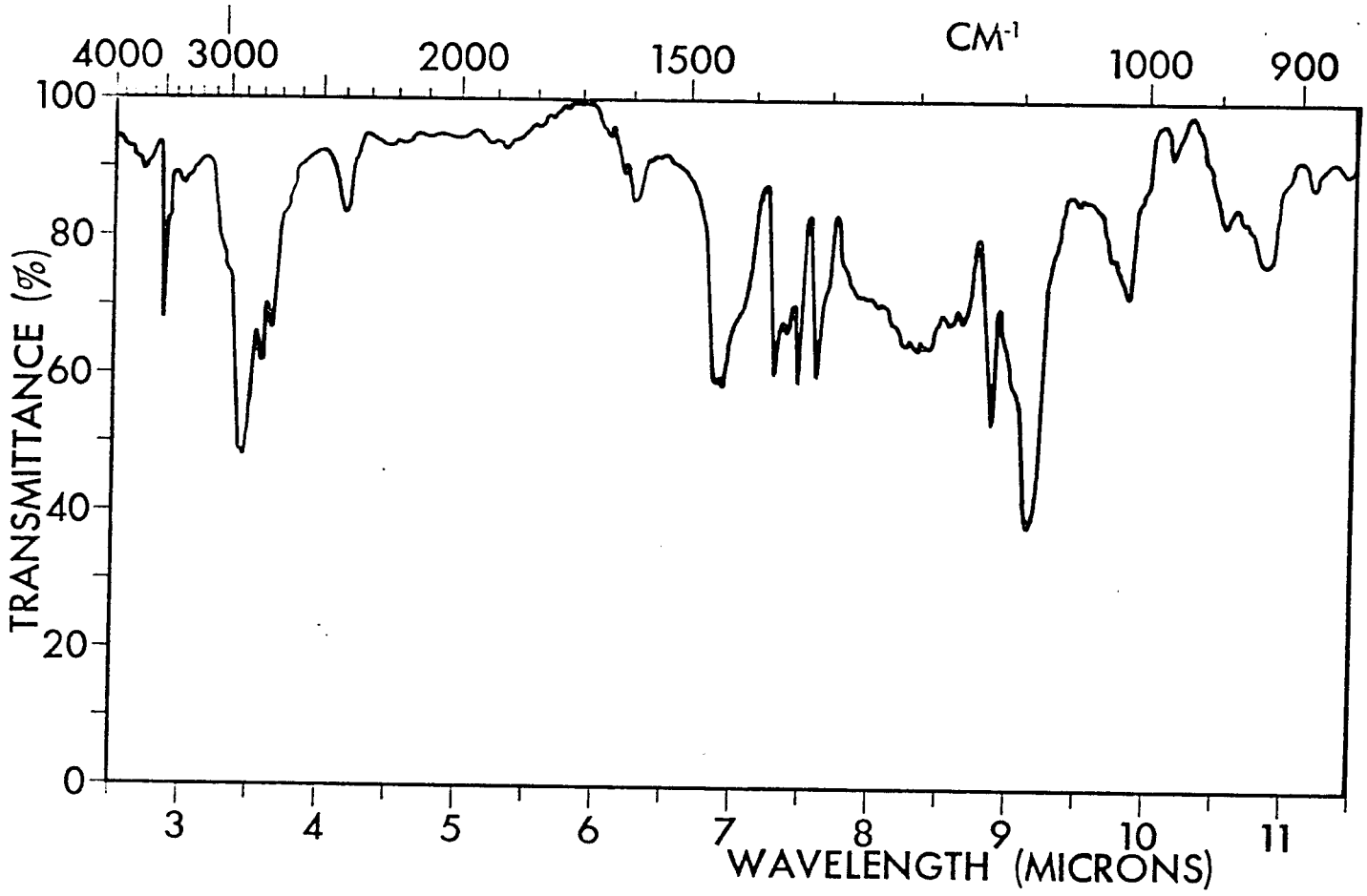


Fig. 8 - Infrared absorption spectrum of 18-methoxyalloyohimbane in chloroform (1.0 mm cell) measured on a Perkin-Elmer "infracord".

Preparation of 4-benzyloxycyclohexanol

This was prepared following the procedure of Prins (44).

To a solution of 50 gm of cis-trans quinitol in 400 ml of absolute dioxane was added 11.5 gm of sodium and the stirred solution refluxed overnight. The solution was cooled, 85 gm of benzyl bromide in 100 ml of dioxane added, and the reaction mixture refluxed for 24 hrs. The solution was cooled, 50 ml of methanol added carefully to destroy excess sodium, 350 ml of acetone added, and the mixture filtered. The filtrate was evaporated under reduced pressure, the residue taken up in ether and washed five times with 25 ml of water. The ether solution was dried, the solvent removed under reduced pressure, and the residue fractionated to give 38.6 gm of 4-benzyloxycyclohexanol, b.p. 103-105/0.02 mm.

The aqueous extracts from above were evaporated under reduced pressure, taken up in acetone, filtered, and evaporated to give 18.9 gm of quinitol. The yield of 4-benzyloxycyclohexanone based on unrecovered quinitol was 48%.

Preparation of 4-benzyloxycyclohexanone (44)

Following the procedure of Prins (44), a solution of 29.3 gm of chromium trioxide in 20 ml of water and 80 ml of glacial acetic acid was added over a period of 5 hrs to a

stirred, cooled solution of 66.5 gm of 4-benzyloxycyclohexanone in 125 ml of glacial acetic acid, the temperature being kept below 3°C. The reaction mixture was allowed to stand overnight, 500 ml of ether added and most of the acetic acid removed by repeated washings with water. The solution was then washed with excess cold 15% sodium hydroxide solution followed by water, dried, and the ether removed under reduced pressure. The residue was distilled to give 50 gm (76%) of 4-benzyloxycyclohexanone, b.p. 146-48°/0.45 mm; 2,4-dinitrophenylhydrazone, m.p. 122-123°; reported 126-28° (44).

Preparation of 2-hydroxymethylene-4-benzyloxycyclohexanone

Using Woodward's method (38) for the preparation of hydroxymethylene compounds, sodium methoxide was prepared from 12.5 gm of sodium and 175 ml of dry methanol and dried at 160° and 1 mm for one hour. It was cooled in nitrogen, the solid broken up and suspended in 150 ml of anhydrous benzene. The vigorously stirred suspension was kept under nitrogen and 68.9 gm of dry, freshly distilled ethyl formate added over thirty minutes. The mixture was stirred for a further one-half hour, and was then cooled to 0°C. A solution of 40.9 gm of 4-benzyloxycyclohexanone in 150 ml of dry benzene was added dropwise during forty minutes with stirring and ice

cooling. The ice bath was removed, 150 ml of dry benzene added, and stirring continued at room temperature overnight. The mixture was diluted with benzene and ice cold 10% aqueous sulfuric acid, and the aqueous layer washed twice with 100 ml of 1:1 ether:benzene. The combined organic extracts were shaken with excess ice cold 2% potassium hydroxide solution. The alkaline layer was washed with ether, acidified with dilute hydrochloric acid, and extracted twice with 250 ml of ether. The organic extract was washed twice with 250 ml water, dried, and the solvent evaporated under reduced pressure to give 34.4 gm of crude 2-hydroxymethylene-4-benzyloxycyclohexanone. Owing to its instability, the product was not purified further, but was used immediately in the succeeding reaction.

Preparation of 2-isopropoxymethylene-4-benzyloxycyclohexanone

This preparation was carried out using essentially the procedure of Johnson and Posvic (39).

To a stirred suspension of 37.9 gm of freshly ignited and finely powdered potassium carbonate in 250 ml of dry acetone was added 34.4 gm of 2-hydroxymethylene-4-benzyloxycyclohexanone and 38.3 gm of 2-iodopropane. The mixture was stirred and heated under reflux for six hours, cooled to room temperature, and the solvent removed under reduced

pressure. To the residue was added 400 ml of water and the organic material extracted twice with 150 ml of ether. The ether solution was washed twice with 100 ml of 10% sodium hydroxide, four times with 100 ml of saturated sodium chloride solution, dried over sodium sulfate and the solvent removed under reduced pressure. The residue was distilled under vacuum to give 17.4 gm (47.2%) of 2-isopropoxymethylene-4-benzyloxy cyclohexanone, b.p. 175-180°/0.1 mm.

Calc. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08

Found: C, 74.92; H, 8.32

The ultraviolet spectrum (Fig. 9) showed an absorption band at 277 mμ (Log ε 4.05); the infrared spectrum showed a strong carbonyl absorption band at 1677 cm^{-1}.

Preparation of 18-benzyloxysempervirine

To a stirred solution of 5.40 gm of harman in 75 ml of anhydrous tetrahydrofuran under an atmosphere of dry nitrogen was added 77.0 ml of a 0.793 N ethereal solution of phenyl lithium. After two hours, the reaction mixture was cooled to 0°, and a solution of 5.50 gm of 2-isopropoxymethylene-4-benzyloxycyclohexanone in 50 ml of dry tetrahydrofuran added dropwise over thirty minutes. Stirring was continued for a further seventy minutes, 45 ml of concentrated hydrochloric acid carefully added and the reaction stirred at room temperature overnight. The solvent was removedunder reduced pressure,

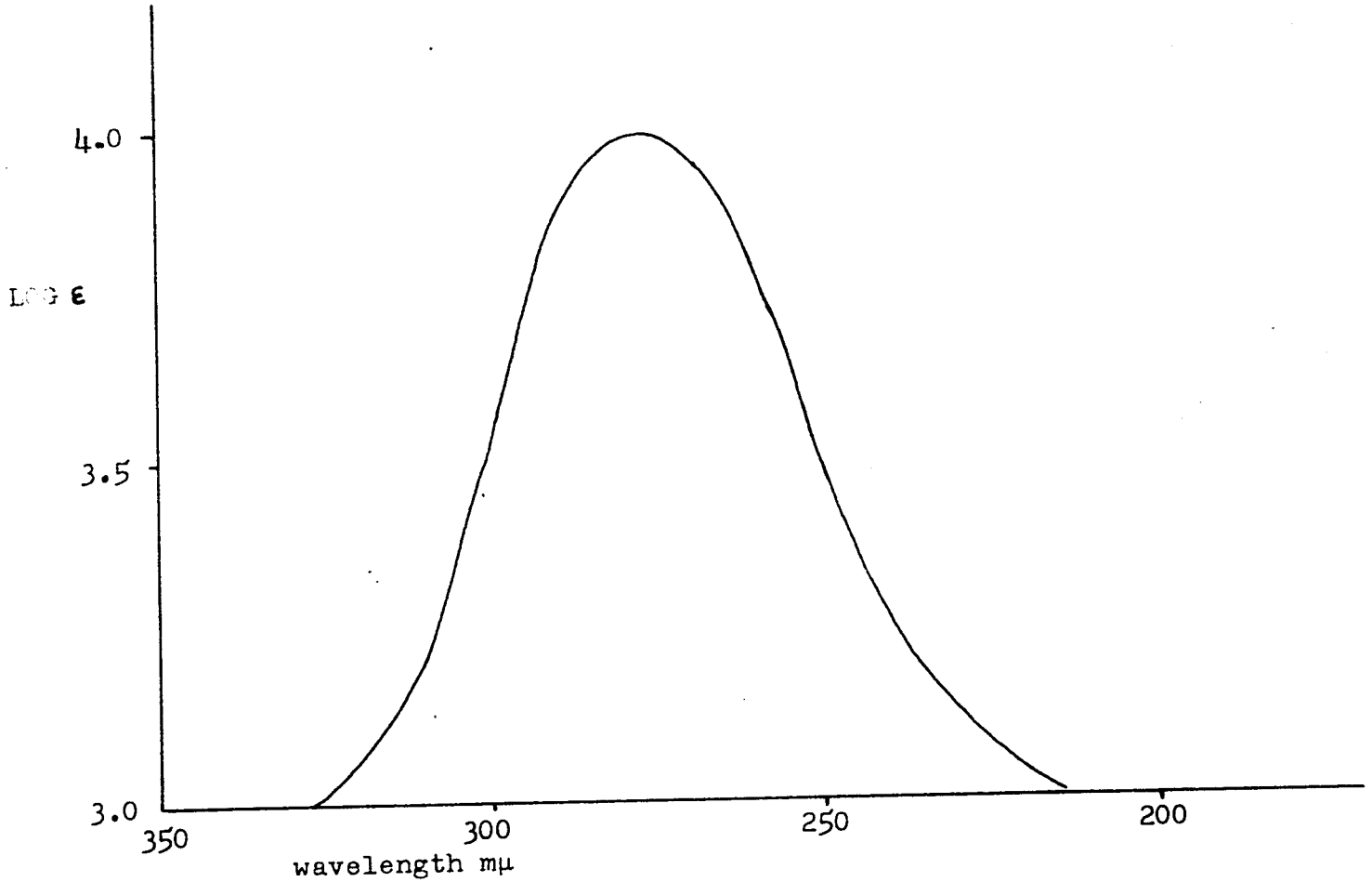


Fig. 9 - Ultraviolet spectrum of 2-isopropoxymethylene-4-benzyloxycyclohexanone in ethanol.

50 ml of water added, the solution made alkaline with ice cold 15% sodium hydroxide solution and extracted four times with 100 ml of chloroform. The chloroform extracts were washed twice with 100 ml of water and then shaken with 600 ml of disodium phosphate-citric acid buffer of pH 6. The chloroform phase slowly separated from the slurry of the insoluble sempervirine-citric acid salt in the aqueous phase. The chloroform was removed, and the aqueous suspension washed five times with 200 ml of chloroform. The aqueous phase was made alkaline, extracted five times with 100 ml of chloroform, the combined organic extracts washed twice with 100 ml of water, dried, and the solvent removed. The residue was dissolved in chloroform and chromatographed on alumina to give, after crystallization from methanol, 2.43 gm (42%) of 18-benzyloxysempervirine, m.p. 81-83° (decomp.)

Calc. for $C_{26}H_{23}ON_2.CH_3OH$: C, 78.99; H, 6.38; N, 6.83

Found: C, 79.20; H, 6.36; N, 6.80

The ultraviolet absorption spectrum (Fig. 10) showed the characteristic sempervirine absorption peaks at 243 mμ (Log ε 4.55), 295 mμ (Log ε 4.23), 344 mμ (Log ε 4.29) and 387 mμ (Log ε 4.26). The infrared spectrum is shown in Fig. 11.

Preparation of 18-hydroxysempervirine

A mixture of 378 mg of 18-benzyloxysempervirine, 150

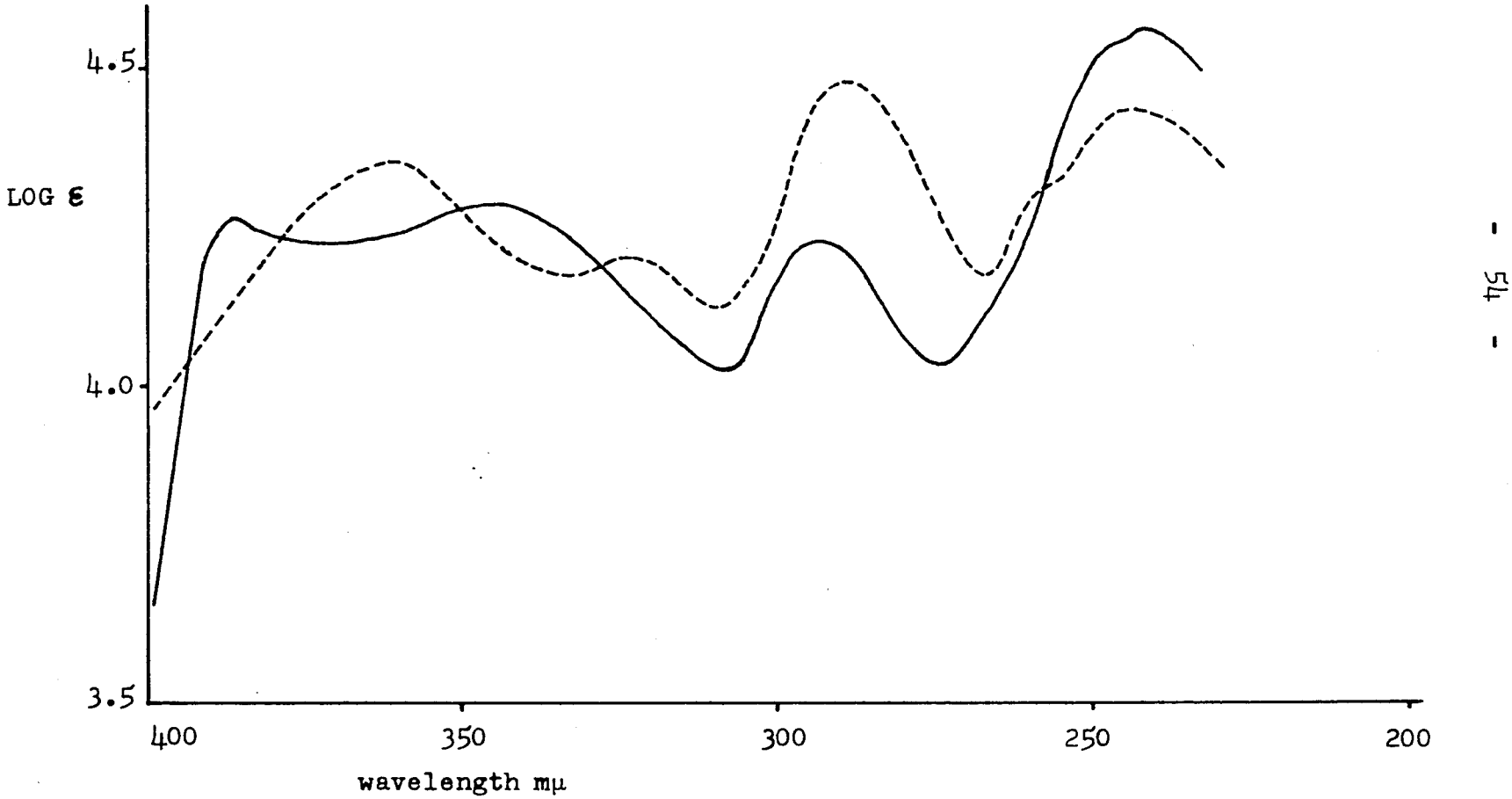


Fig. 10 - Ultraviolet spectrum of 18-benzyloxysempervirine in ethanol (-) and in alkaline ethanol (---).

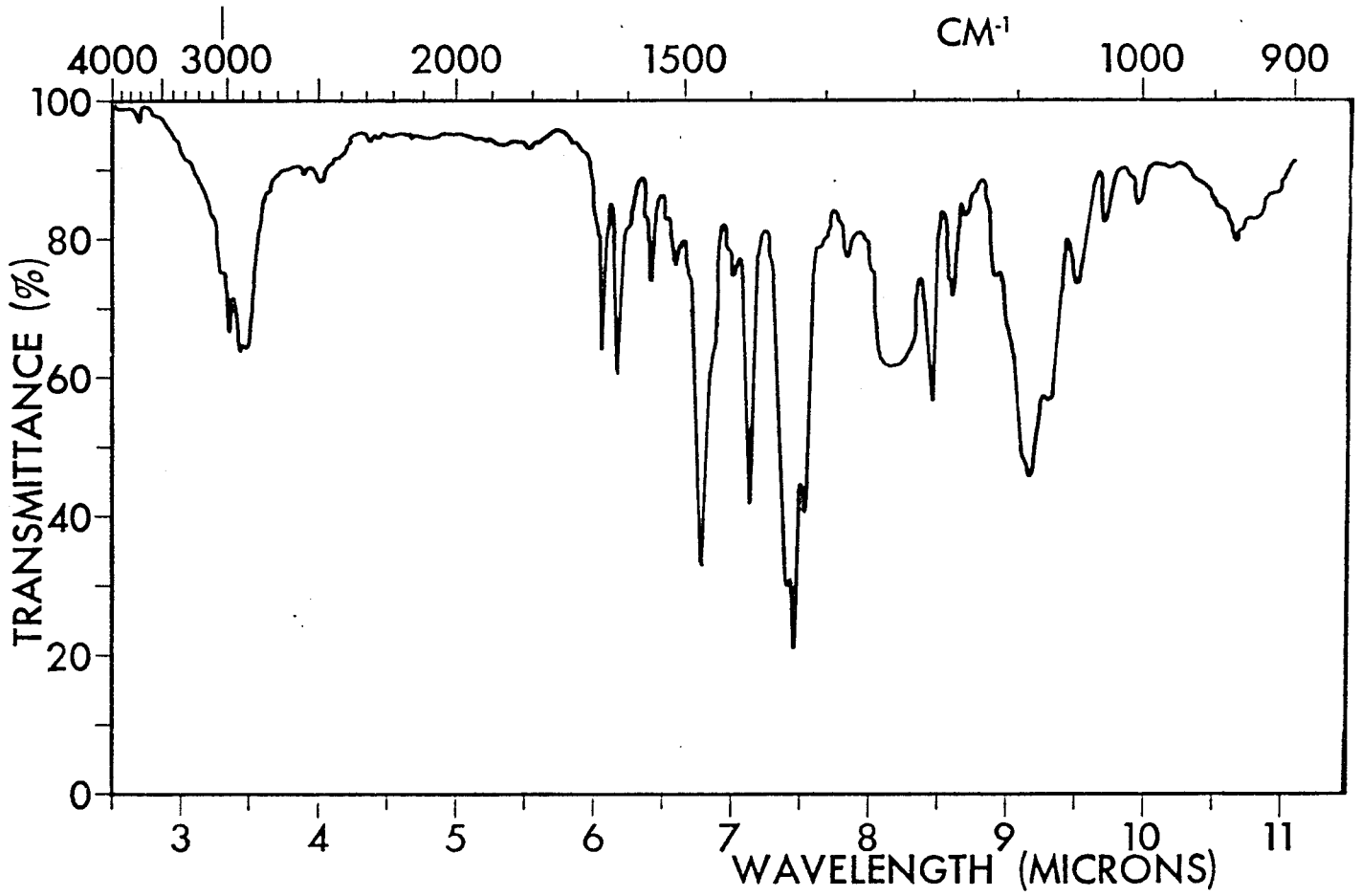


Fig. 11 - Infrared absorption spectrum of 18-benzyloxysempervirine in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

mg of palladium black (45) and 2 ml of concentrated hydrochloric acid in 20 ml of ethanol was hydrogenated at atmospheric pressure until the hydrogen uptake ceased. An additional 30 ml of ethanol was added, the solution removed, the palladium filtered off, and the solvent evaporated under reduced pressure. The residue was dissolved in 50 ml of disodium phosphate-citric acid buffer of pH 6, washed four times with 15 ml of chloroform, and made alkaline. After standing overnight in the cold, the gummy solid was filtered off, washed with water, and crystallized from warm methanol to give 181 mg (63%) of 18-hydroxy sempervirine, m.p. 210-215° (decomp.).

Calc. for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59

Found: C, 79.32; H, 5.67

The ultraviolet absorption spectrum (Fig. 12) was characteristic of sempervirine compounds, having absorption maxima at 243 mμ (Log ε 4.50), 296 mμ (Log ε 4.16), 845 mμ (Log ε 4.22) and 386 mμ (Log ε 4.20). The infrared spectrum is shown in Fig. 13.

Preparation of 18-hydroxyalloyohimbane

This was carried out following the procedure used by Wenkert (4) for the hydrogenation of sempervirine.

A mixture of 2.88 gm of 18-hydroxysempervirine, 400 mg of Adams catalyst (43) and 0.05 ml of 2 N alcoholic potassium hydroxide in 75 ml of methanol was hydrogenated under seventy

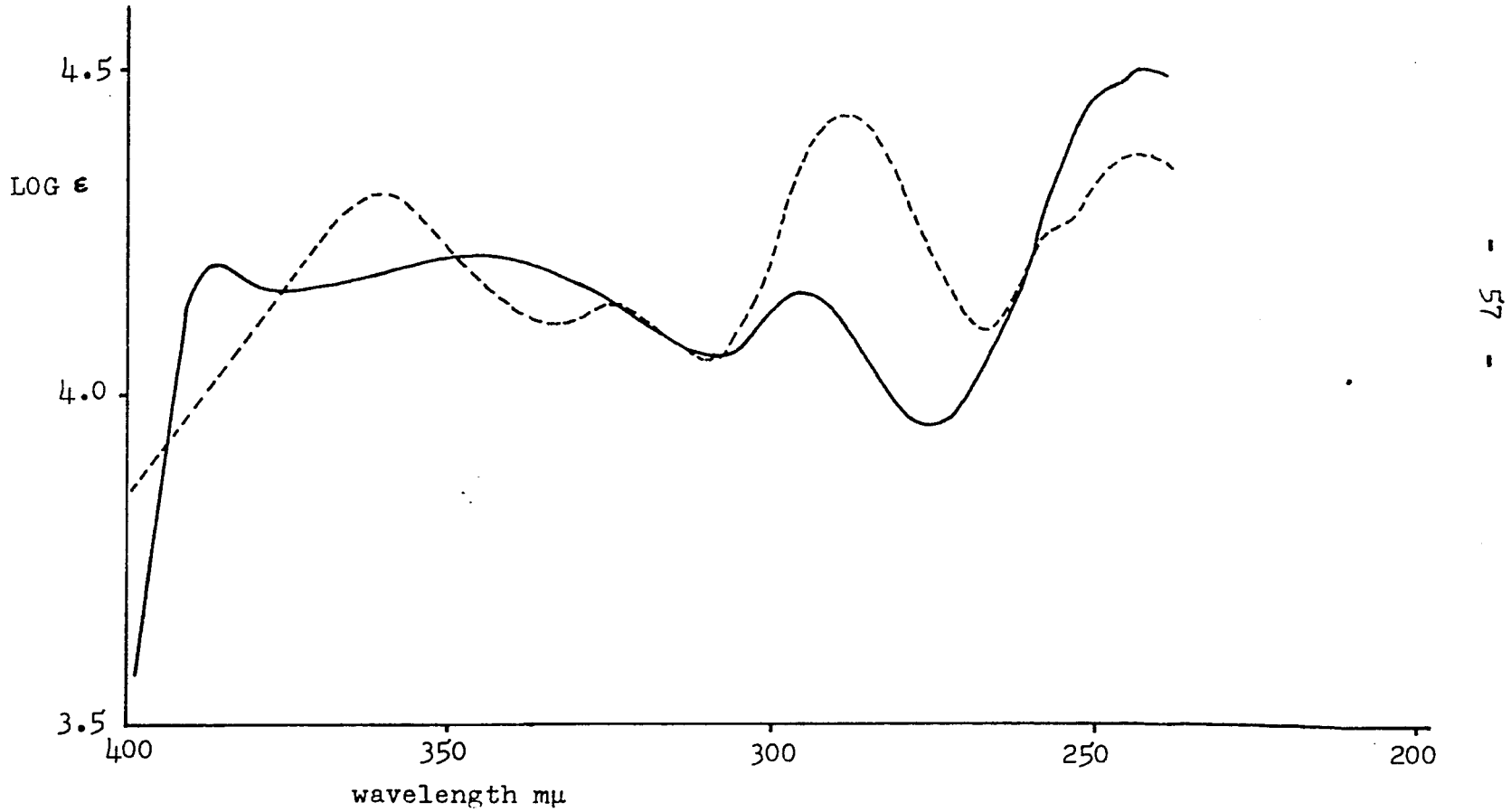


Fig. 12 - Ultraviolet absorption spectrum of 18-hydroxysempervirine in ethanol (-) and in alkaline ethanol (---).

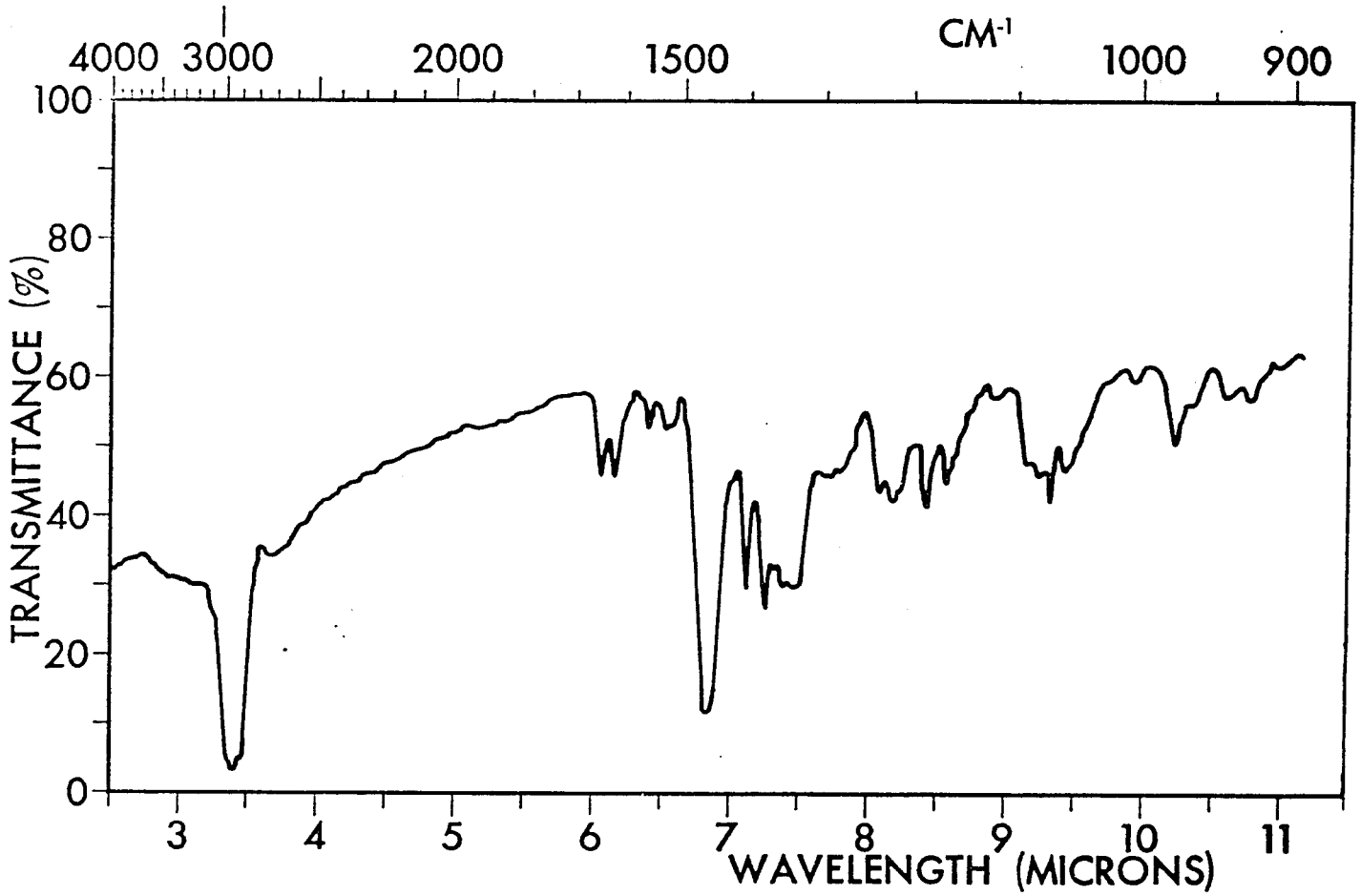


Fig. 13 - Infrared absorption spectrum of 18-hydroxysempervirine in nujol measured on a Perkin-Elmber "infracord".

five pounds of pressure for two hours. The solution was filtered, concentrated and cooled to give 1.30 gm of crystalline material, m.p. 215-220°. Two crystallizations from methanol gave d,l-18-β-hydroxyalloyohimbane m.p. 223-25°.

Calc. for $C_{19}H_{24}ON_2$: C, 76.99; H, 8.16

Found: C, 76.96; H, 8.10

The filtrate and mother liquors from the above crystallization were combined, the solvent removed and the residue chromatographed on alumina in 2:1 chloroform: 30-60° petroleum ether, 40 ml fractions being collected. The ultraviolet absorption spectrum of all the fractions was determined and the graph drawn of the absorption intensity of the 283 mμ band versus the fraction number (Fig. 14). The presence of three compounds was indicated. Fractions 27-53 were evaporated, and the residue crystallized from methanol to give an additional 600 mg of d,l-18-β-hydroxyalloyohimbane. The ultraviolet and infrared spectra of this compound are shown in Figs. 15 and Figs. 16 respectively.

Fractions 15-20, after two crystallizations from methanol, gave 22 mg of solid m.p. 210-215°. The infrared spectrum (Fig. 17) showed that it was an alloyohimbane, and hence most probably was 18-α-hydroxyalloyohimbane.

Calc. for $C_{19}H_{24}ON_2$: C, 76.99; H, 8.16

Found: C, 76.95; H, 8.06

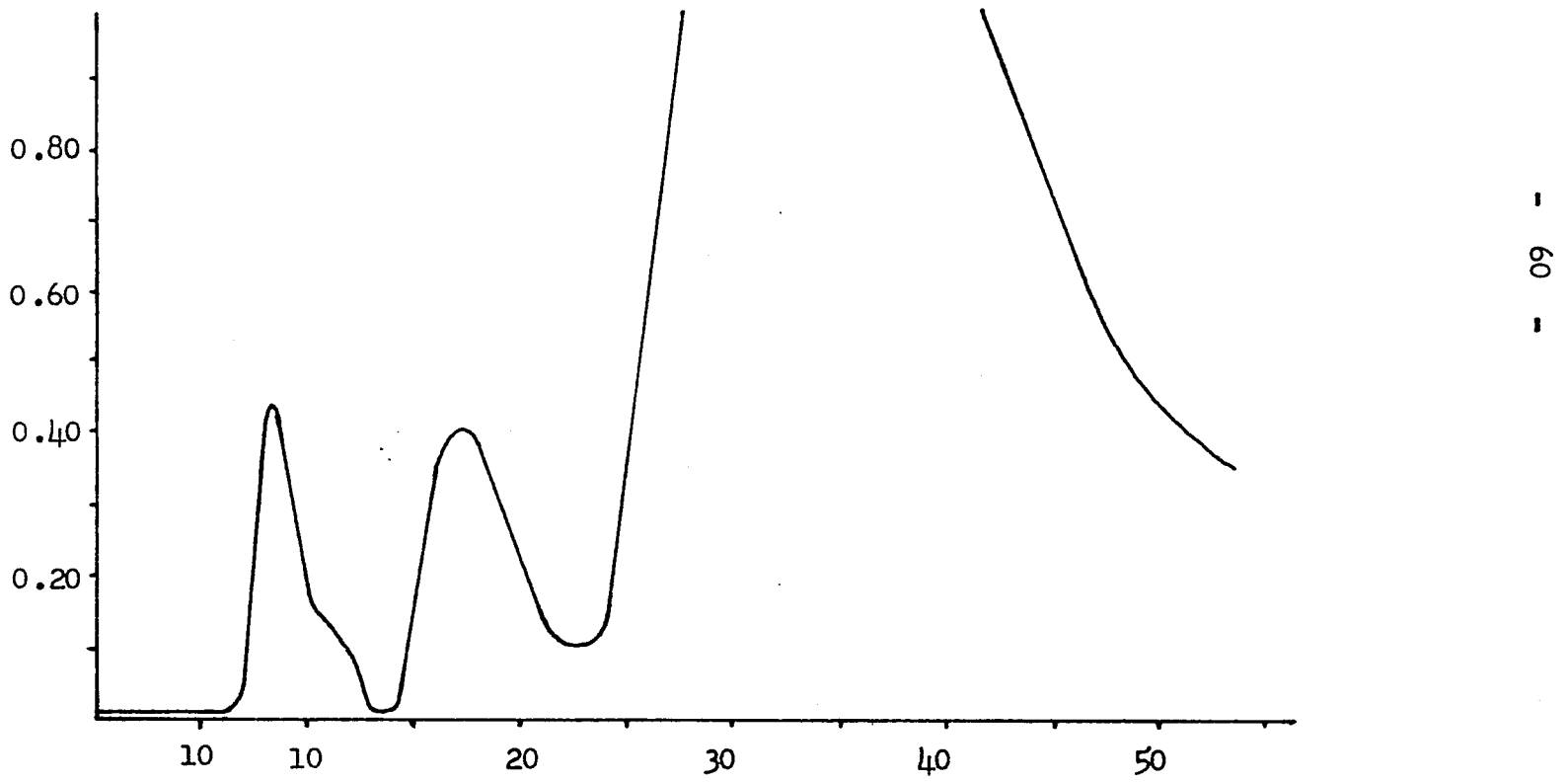


Fig. 14 - Elution diagram from alumina chromatogram of the mixture obtained by hydrogenation of 18-hydroxysempervirine (fraction vs ultraviolet

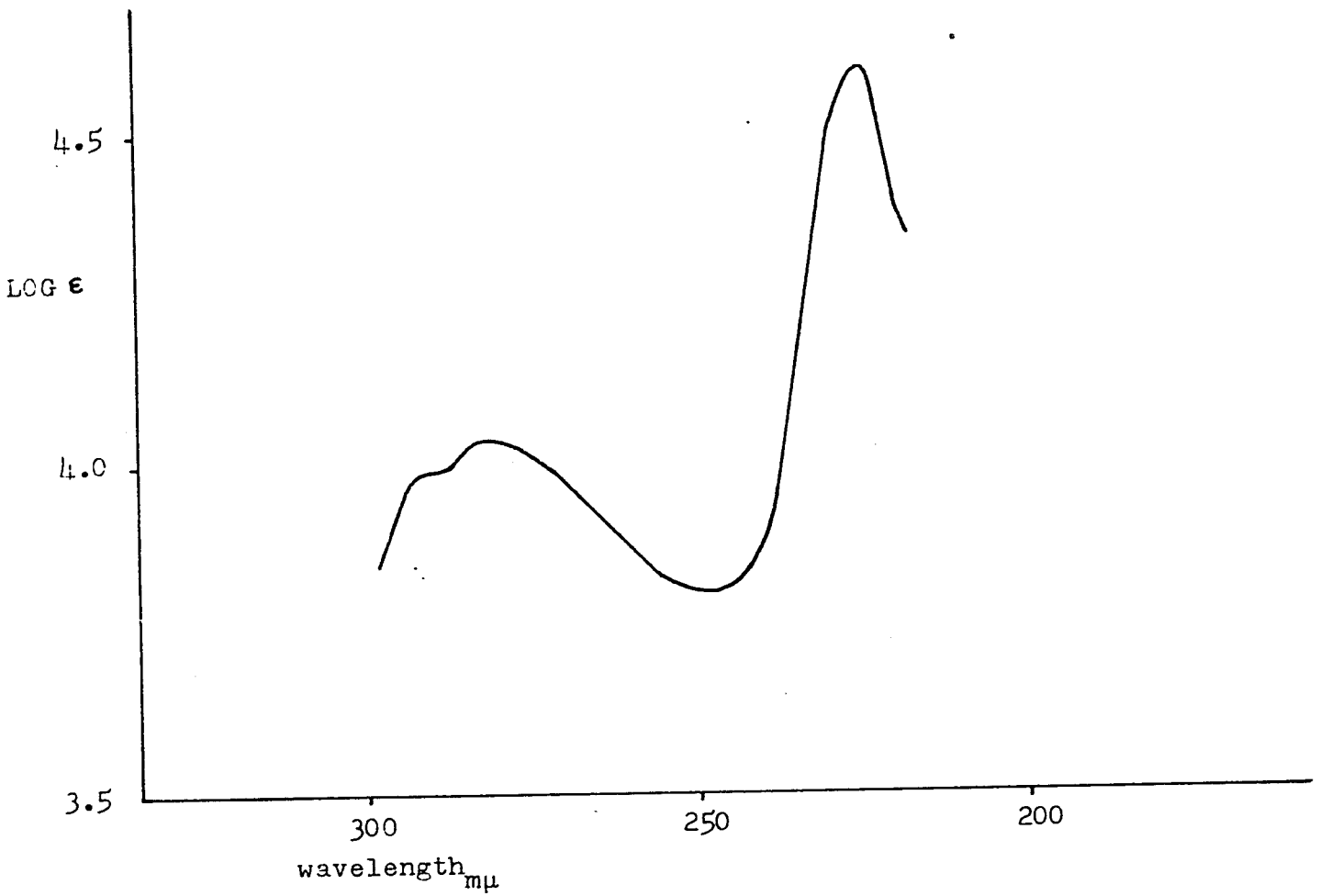


Fig. 15 - Ultraviolet absorption spectrum of 18-β-hydroxyallohohimbane in ethanol.

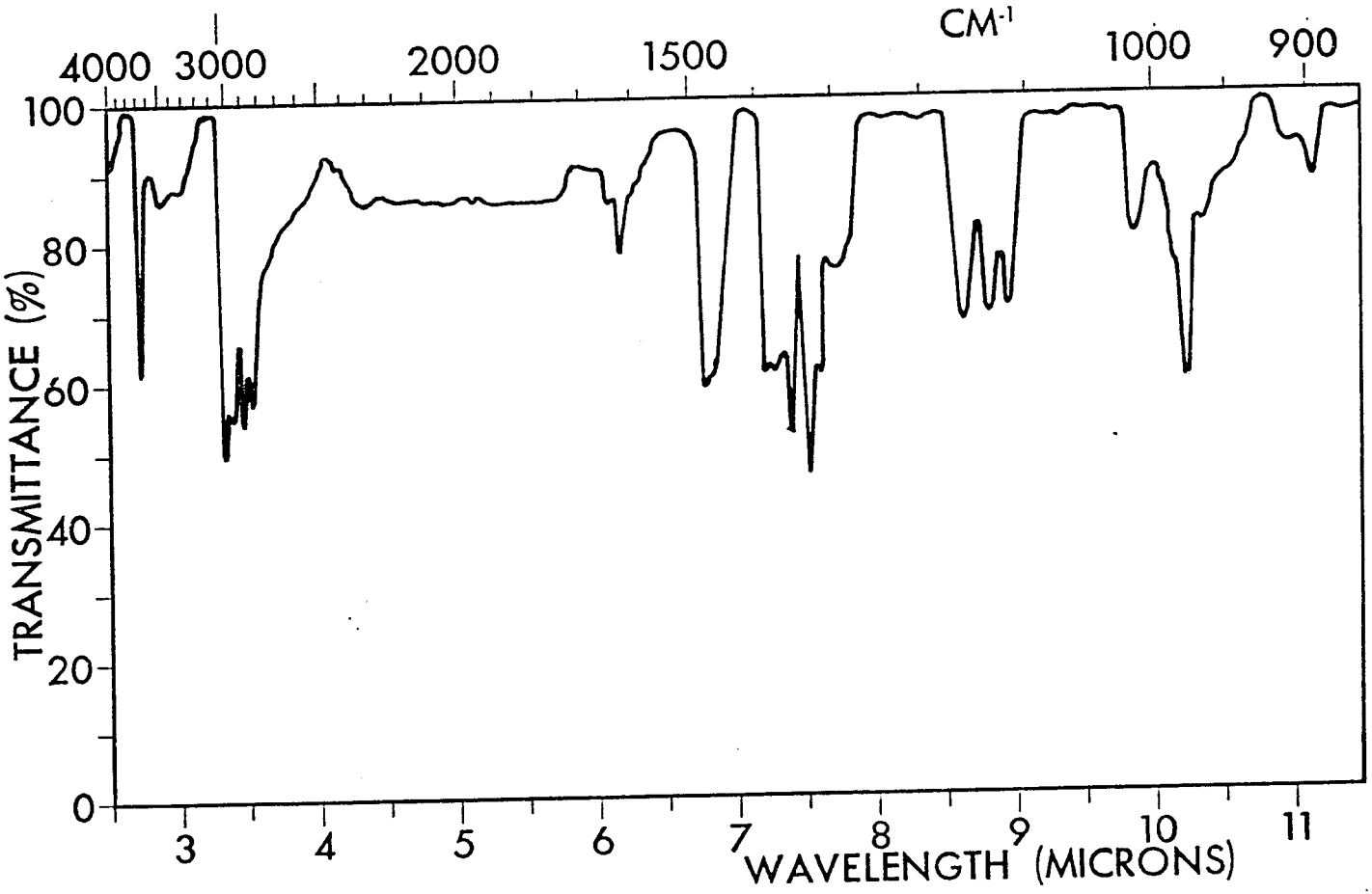


Fig. 16 - Infrared absorption spectrum of 18-β-hydroxyalloyohimbane in chloroform (1.0 mm cell) measured on a Perkin-Elmer "infracord.

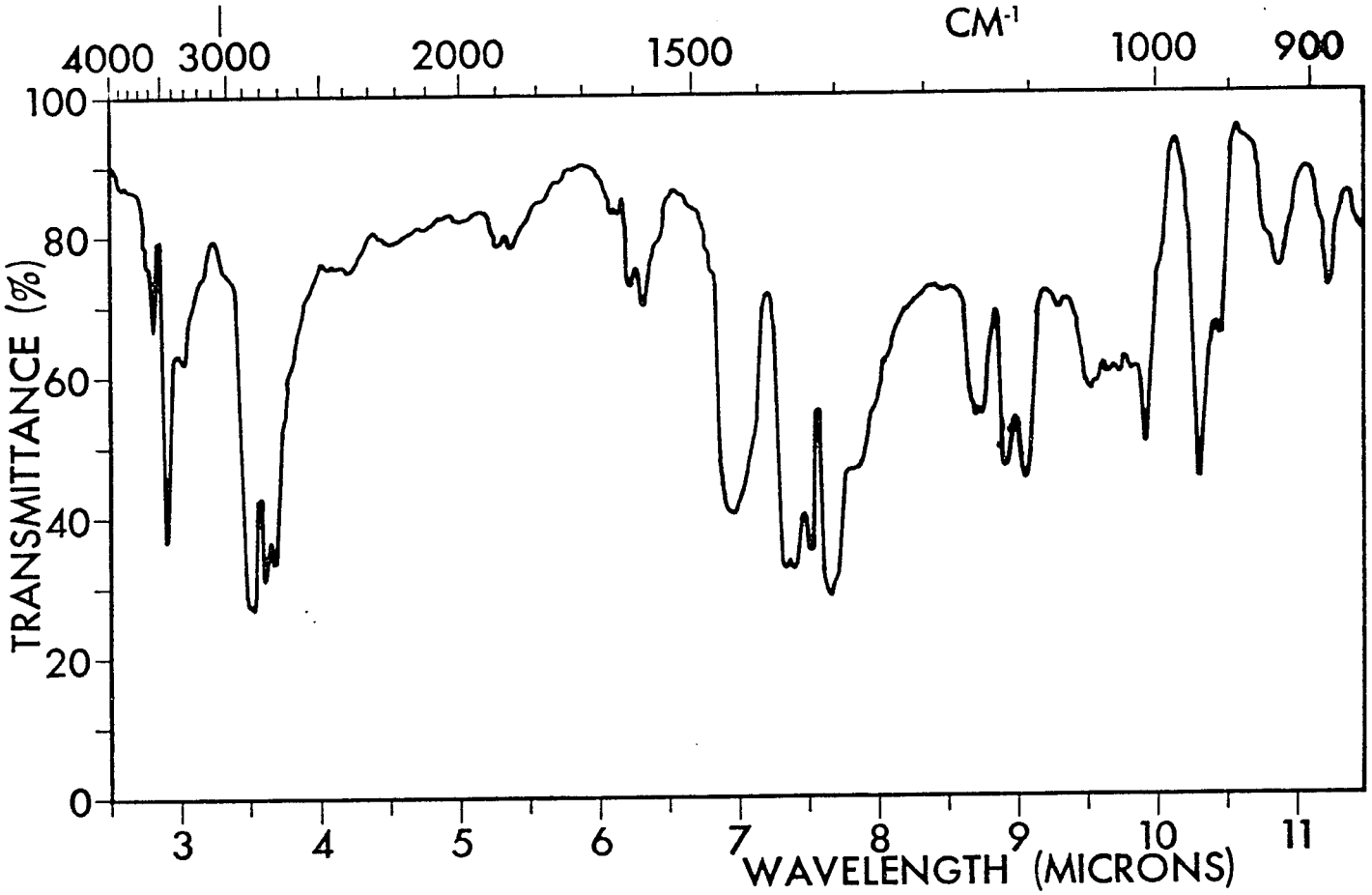


Fig. 17 - Infrared absorption spectrum in chloroform (1.0 mm cell) of the compound, m.p. 210-215°, isolated from chromatogram fractions 15-20, measured on a Perkin-Elmer "infracord".

Fraction 8-10, after removal of the solvent and two crystallizations from methanol, gave 4 mg of a crystalline solid m.p. 233-35°. The ultraviolet spectrum was characteristic of yohimbanes, having maxima at 227 mμ (Log ε 4.55), 281 mμ (Log ε 3.93) and 289 (Log ε 3.85), but the compound was not characterized further.

Preparation of alloyohimbane-18-one

A solution of 100 mg of 18-β-hydroxyalloyohimbane, 250 mg of aluminum isopropoxide and 750 mg of cyclohexanone in 5 ml of toluene was refluxed under nitrogen for three hours. The cooled solution was poured into 20 ml of 2 N sulfuric acid, the xyleneseparated and extracted with 10 ml of 2 N sulfuric acid. The combined acid extracts were washed three times with 10 ml of ether, made alkaline, and extracted three times with 15 ml of chloroform. The chloroform solution was washed with water, dried, and the solvent removed under reduced pressure. The residue was crystallized from methanol to give 34 mg of alloyohimbane-18-one, m.p. 215-17°.

Calc. for $C_{19}H_{22}ON_2$: C, 77.51; H, 7.53

Found: C, 77.45; H, 7.03

The infrared spectrum (Fig. 18) showed a strong carbonyl band at 1700 cm^{-1}.

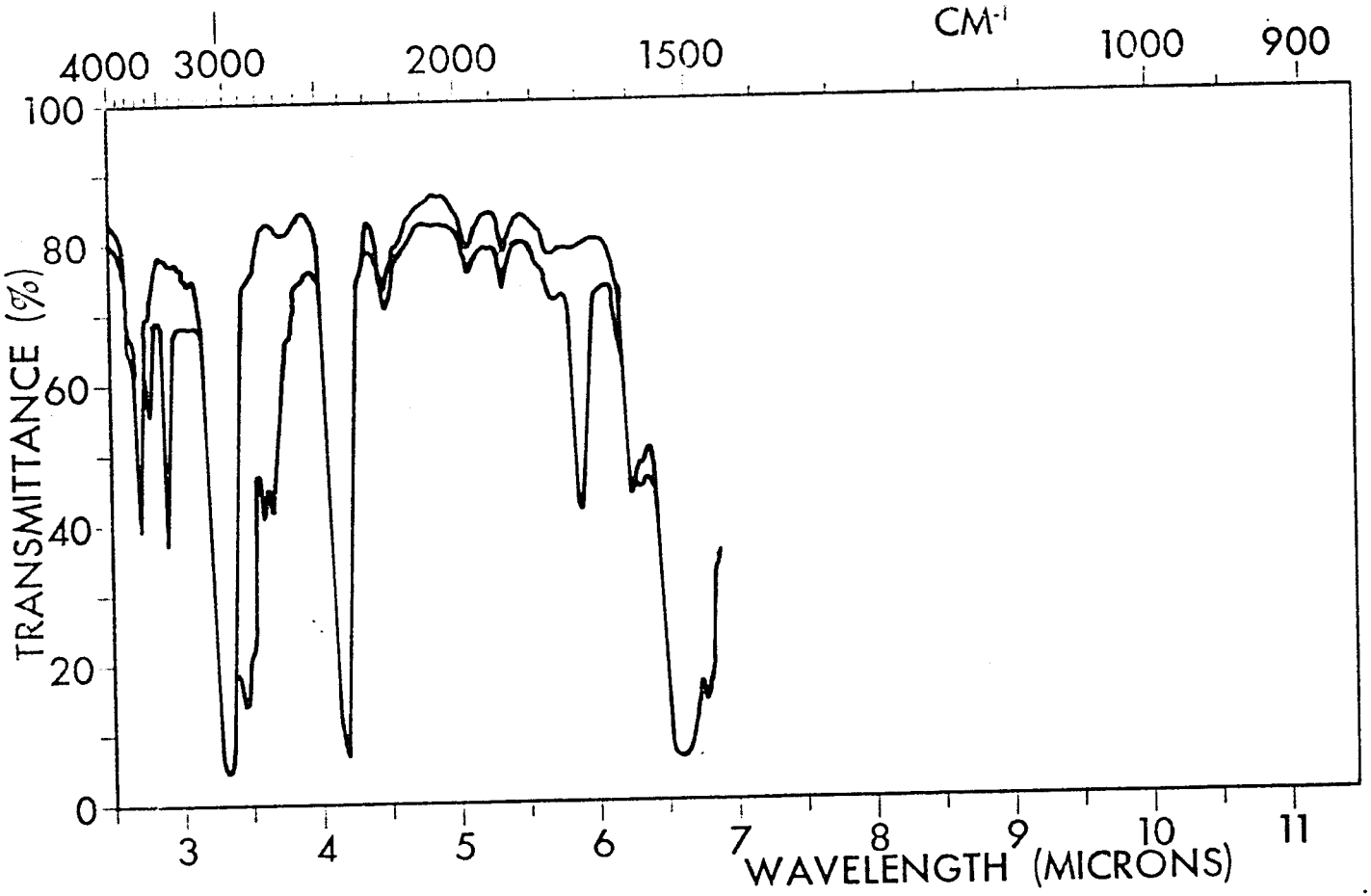


Fig. 18 - Infrared absorption spectrum of alloyohimbane-18-one in chloroform (1.0 mm cell) measured on a Perkin-Elmer "infracord". The background line is the solvent absorption.

Reduction of alloyohimbane-18-one

This reduction was done following the procedure used by Wheeler and Mateos (46).

To a solution of 20 mg of lithium aluminum hydride in 1.2 ml of dry tetrahydrofuran at 0° was slowly added 0.149 ml of dry tertiary butyl alcohol. A solution of 34 mg of alloyohimbane-18-one in 1.3 ml of dry tetrahydrofuran was added and the mixture allowed to stand at 0° for thirty minutes and at room temperature for one hour. The reaction was then poured into excess dilute hydrochloric acid, the acid solution made alkaline with dilute sodium hydroxide and extracted three times with 15 ml of chloroform.

The organic extracts were washed twice with 20 ml of water, the solvent removed, and the residue crystallized from methanol to give 22 mg of 18-β-hydroxyalloyohimbane, m.p. 221-23°. A mixture melting point with an authentic sample was not depressed.

Preparation of 3-dehydro-18-β-hydroxyalloyohimbane perchlorate

Following essentially the procedure used by Wenkert (26), a mixture of 593 mg of 18-β-hydroxyalloyohimbane and 2.55 gm of mercuric acetate in 60 ml of 5% aqueous acetic acid was heated at 85° for two hours. The precipitate of mercurous

acetate was filtered off, the filtrate heated to boiling and saturated with hydrogen sulfide. The solution was cooled, 1.25 ml of concentrated hydrochloric acid added, the solution boiled for twenty minutes, cooled, filtered, and 2 ml of concentrated perchloric acid added to the filtrate. The suspension was cooled to 0°, filtered, and the solid crystallized from methanol to give 527 mg (67%) of 3-dehydro-18-β-hydroxy-alloyohimbane perchlorate, m.p. 217-19°.

Calc. for $C_{19}H_{23}O_5N_2Cl$: C, 57.79; H, 5.87

Found: C, 57.69; H, 5.97

The ultraviolet spectrum is shown in Figure 19.

Reduction of 3-dehydro-18-β-hydroxyalloyohimbane perchlorate

a) With sodium borohydride (26)

A solution of 59 mg 3-dehydro-18-β-hydroxy alloyohimbane perchlorate and 400 mg of sodium borohydride in 15 ml of methanol was refluxed for 5 hours. The methanol was removed under reduced pressure, 50 ml of water added, and the solution extracted three times with 15 ml of chloroform. The organic extracts were washed twice with 15 ml of water, dried, and the solvent removed. The residue was crystallized from methanol to give 34 mg (76%) of 18-β-hydroxyalloyohimbane m.p. 221-24°. A mixture melting point with an authentic sample was not depressed.

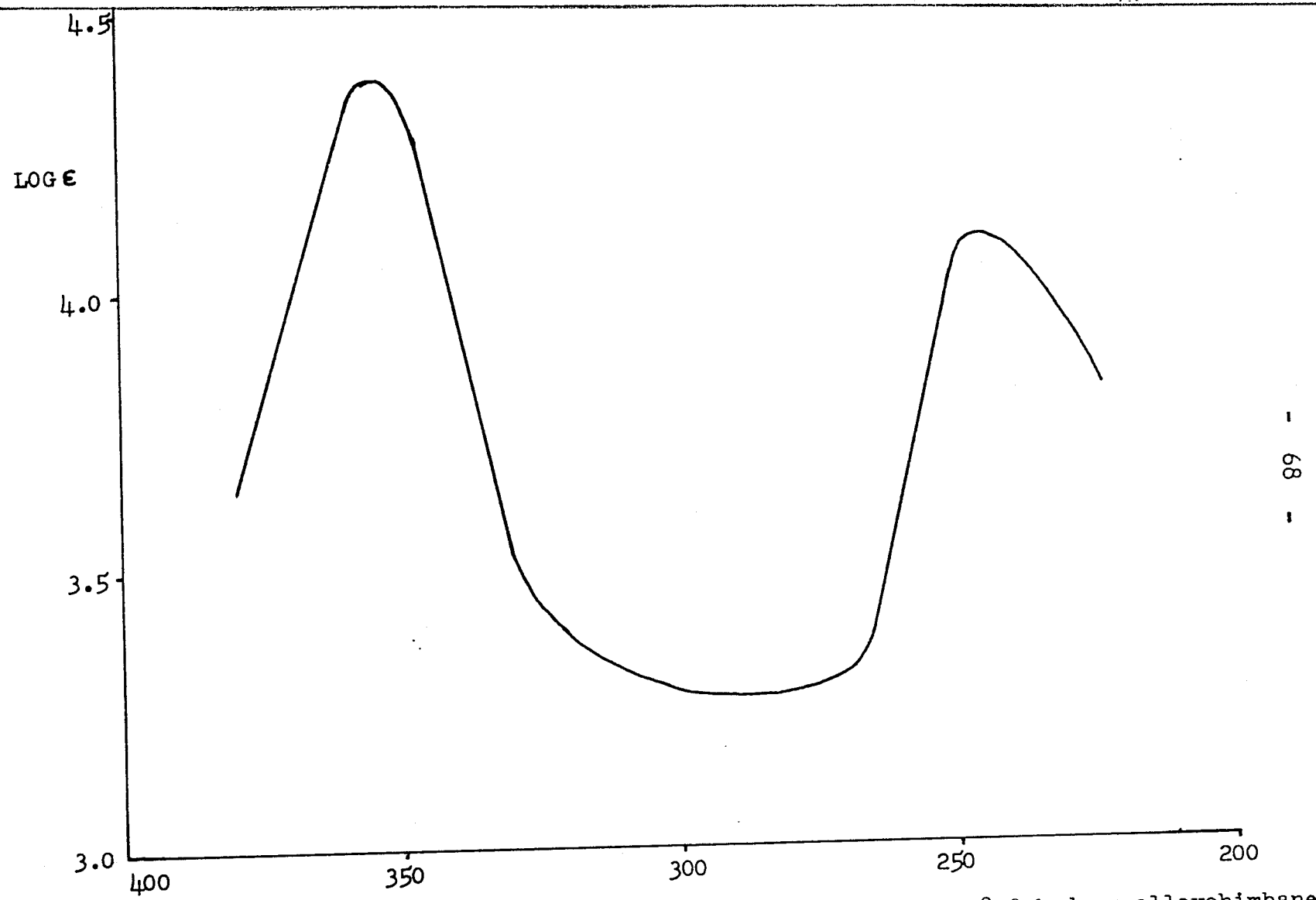


Fig. 19 - Ultraviolet absorption spectrum of 3-dehydro-18-β-hydroxyalloyohimbane perchlorate in ethanol.

b) With tin and hydrochloric acid (30)

A solution of 220 mg of 3-dehydro-18-β-hydroxy alloyohimbane perchlorate in 6 ml of ethanol and 3.75 ml of concentrated hydrochloric acid was gently refluxed and 750 mg of tin added over two hours. After refluxing for two more hours, 10 ml of water was added, and the alcohol removed under reduced pressure. To the residue was added 25 ml of 10% aqueous sodium hydroxide and the solution extracted three times with 15 ml of chloroform. The organic extracts were washed with water, dried, the solvent removed and the residue crystallized from methanol to give 33 mg (20%) of 18-β-hydroxy-alloyohimbane, m.p. 221-23°. A mixture melting point with an authentic sample was not depressed.

c) With zinc and acetic acid (27)

A mixture of 527 mg of 3-dehydro-18-α-hydroxy alloyohimbane perchlorate and 2.10 gm of zinc in 17 ml of 50% aqueous acetic acid was stirred at room temperature under nitrogen for twenty hours. The reaction mixture was poured into 150 ml of water, the aqueous suspension decanted from the zinc, made alkaline and extracted four times with thirty ml of chloroform. The chloroform solution was washed with water, the solvent removed, and the residue crystallized twice from methanol to give 217 mg (55%) of 18-β-hydroxyepialloyohimbane, m.p. 238-39°.

Calc. for $C_{19}H_{24}ON_2$: C, 76.99; H, 8.16

Found: C, 77.11; H, 8.05

The ultraviolet and infrared spectra are shown in Fig. 20 and 21 respectively.

Preparation of 18-β-acetoxyalloyohimbane

A mixture of 100 mg of 18-β-hydroxyalloyohimbane and 0.25 ml of acetic anhydride in 2.0 ml of dry pyridine was allowed to stand under nitrogen at room temperature for twenty hours. The reaction mixture was poured into 30 ml of cold water containing 1 ml of concentrated ammonium hydroxide and allowed to stand for thirty minutes. The precipitate was filtered off and crystallized twice from methanol to give 67 mg (59%) of 18-β-acetoxyalloyohimbane, m.p. 174-76°.

Calc. for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.74

Found: C, 74.45; H, 7.74

The infrared spectrum (Fig. 22) shows a strong carbonyl band at 1725 cm^{-1} and an acetate band at 1255 cm^{-1}. The nuclear magentic resonance (Fig. 23) spectra showed the presence of an axial proton at C_{18} and hence an equatorial acetoxy group.

Preparation of 18-β-acetoxyepialloyohimbane

A mixture of 90 mg of 18-β-hydroxyepialloyohimbane and 0.250 ml of acetic anhydride in 2.0 ml of pyridine were

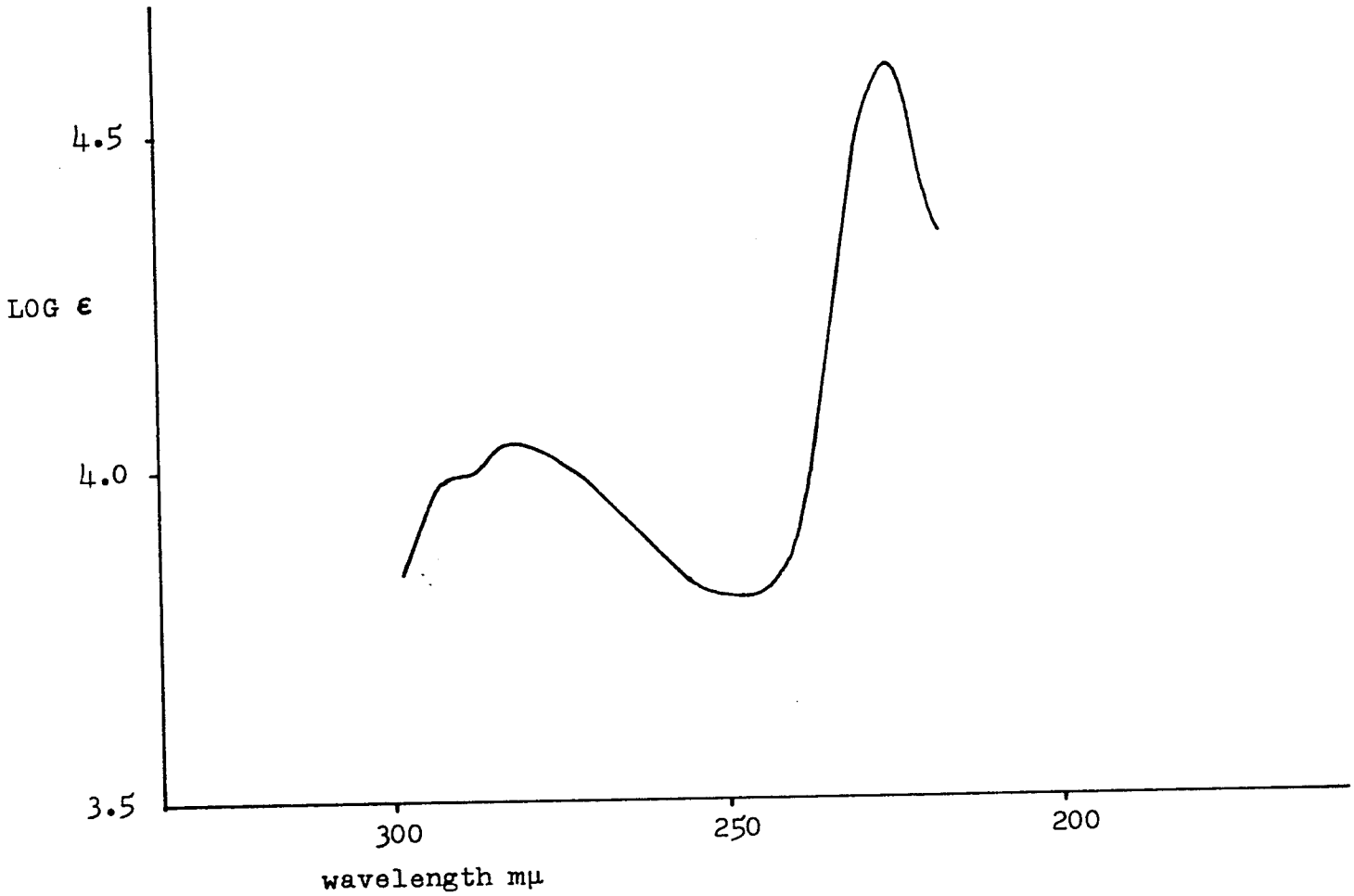


Fig. 20 - Ultraviolet absorption spectrum of 18-β-hydroxyepialloyohimbane in ethanol.

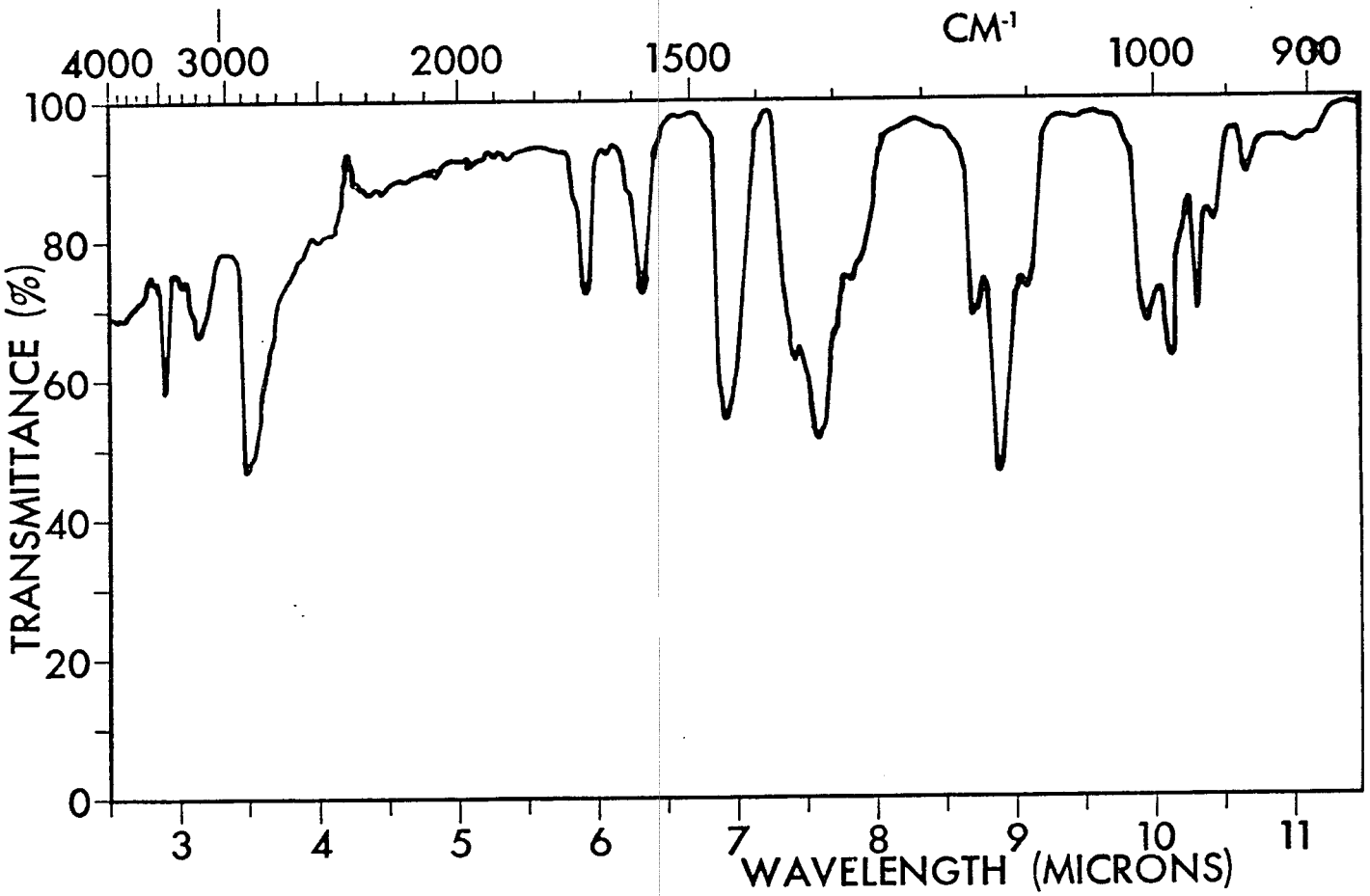


Fig. 21 - Infrared absorption spectrum of 18-β-hydroxyepialloyohimbane in chloroform (1.0 mm cell) measured on a Perkin-Elmer "infracord".

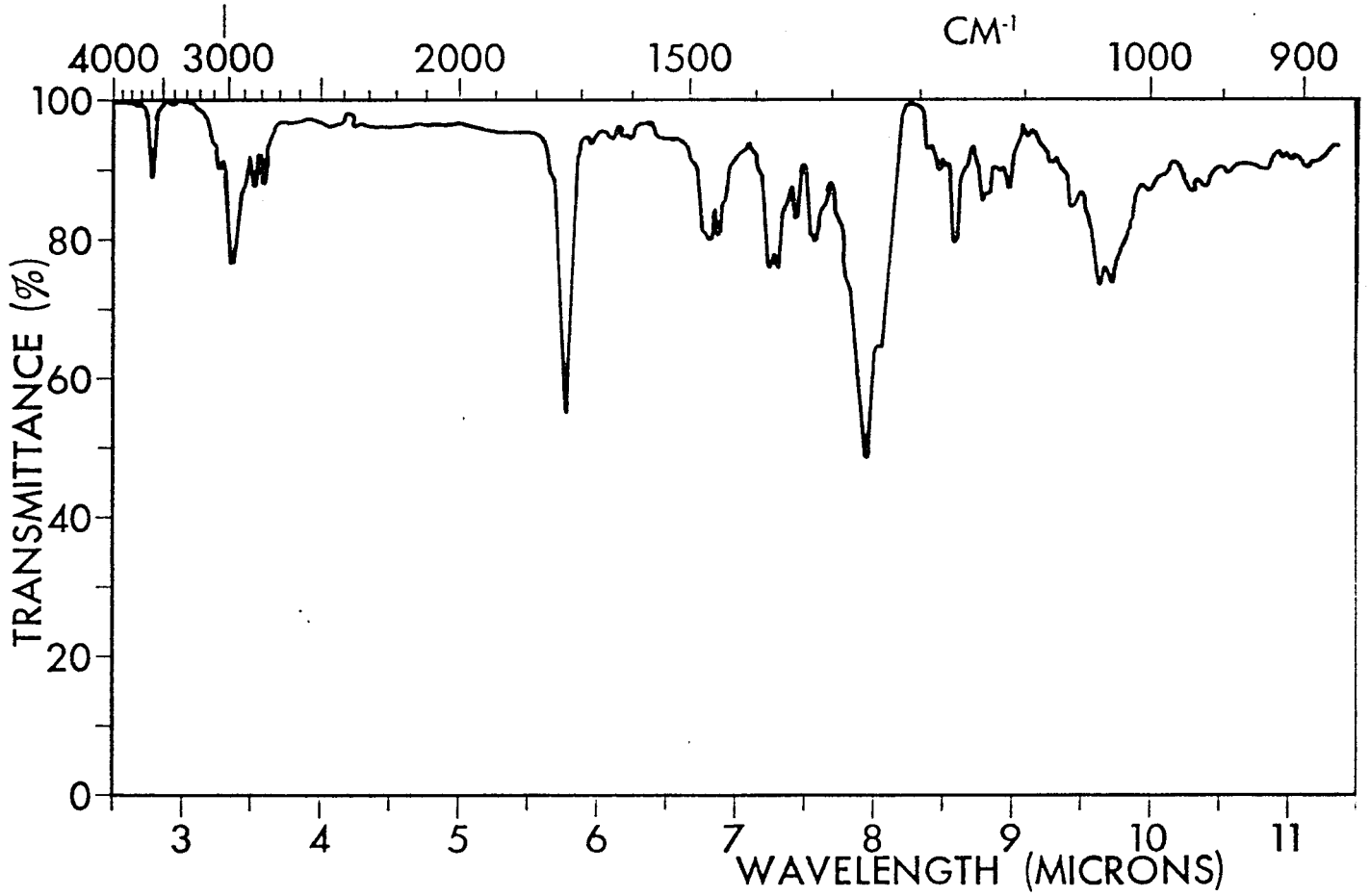


Fig. 22 - Infrared absorption spectrum of 18-β-acetoxyallovohimbane in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

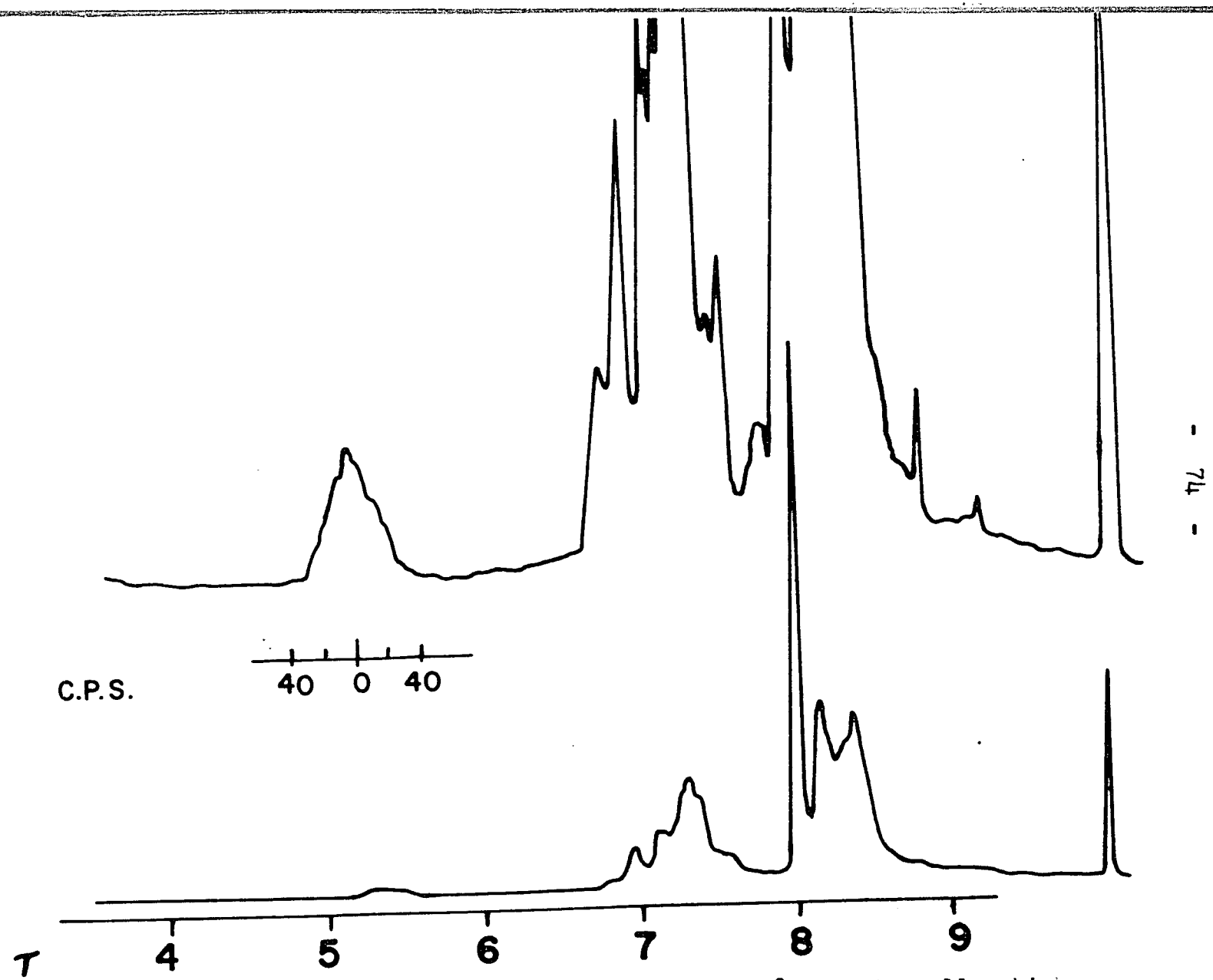


Fig. 23 - Nuclear magnetic resonance spectrum of 18-β-acetoxyvallovohimbane.

allowed to stand at room temperature for twenty hours under nitrogen. The solution was poured into 30 ml of water containing 2 ml of concentrated ammonium hydroxide and allowed to stand for thirty minutes. The precipitate was filtered off and crystallized twice from methanol to give 55 mg (54%) of 18-β-acetoxyepialloyohimbane.

Calc. for $C_{21}H_{26}O_2N_2$:	C, 74.52;	H, 7.74
Found:	C, 73.91;	H, 7.77
	C, 75.24;	H, 8.21

The infrared spectrum (Fig. 24) shows a strong carbonyl band at 1720 cm^{-1} and an acetate ester band at 1255 cm^{-1}. The nuclear magnetic resonance spectrum (Fig. 25) shows the presence of an equatorial proton at C_{18}, which indicates that the C_{18} acetoxyl group must be in the axial position.

Preparation of 18-β-(3,4,5-trimethoxy)benzoyloxy-alloyohimbane

Following the procedure used by Lucas and coworkers for the preparation of reserpine C_{18} derivatives, a mixture of 90 mg of 18-β-hydroxyalloyohimbane, and 170 mg of 3,4,5-trimethoxybenzoyl chloride in 4 ml of dry pyridine was kept under nitrogen at room temperature for twenty four hours. The reaction was poured into 30 ml of water containing 1 ml of ammonium hydroxide, the precipitate filtered off and crystallized from methanol to give 96 mg (64%) of 18-β-(3,4,5-trimethoxy)-

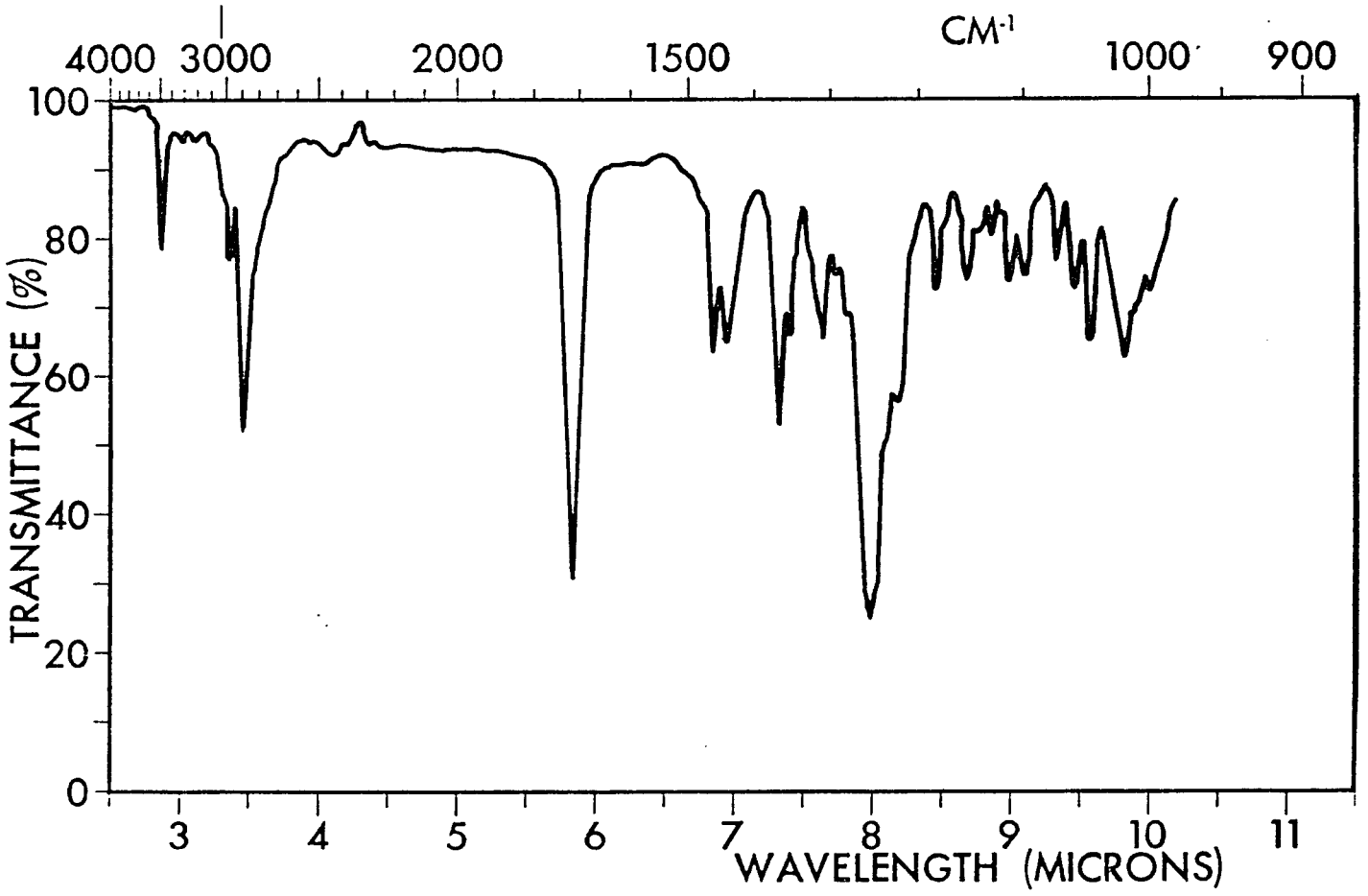


Fig. 24 - Infrared absorption spectrum of 18-β-acetoxyepialloyohimbane in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

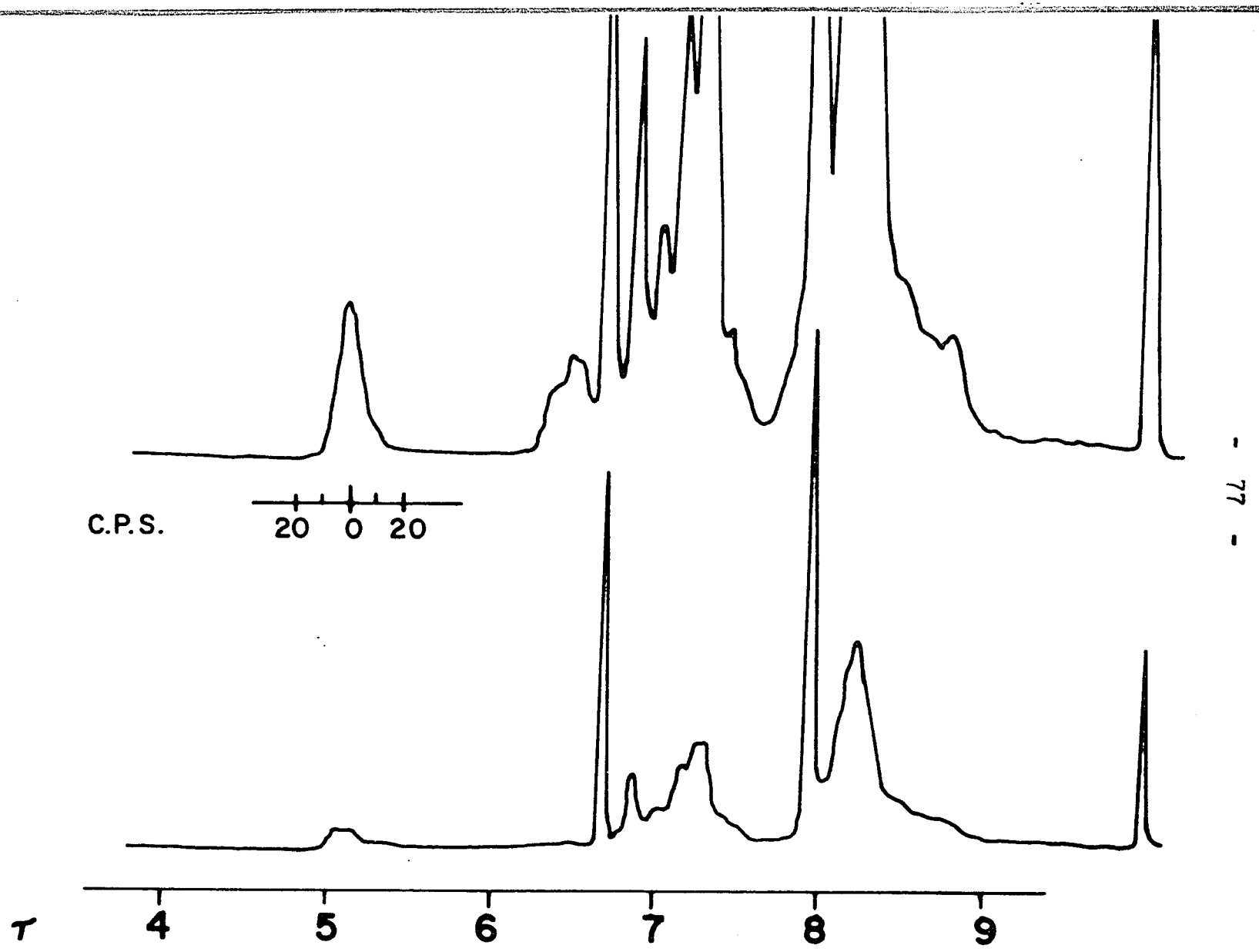


Fig. 25 - Nuclear magnetic resonance spectrum of 18-β-acetoxyepialloyohimbane.

benzoyloxyalloyohimbane, m.p. 187-90°.

Calc. for $C_{29}H_{34}O_5N_2$: C, 70.99; H, 6.99

Found: C, 70.80; H, 7.31

The infrared spectrum (Fig. 26) showed a strong carbonyl band at 1710 cm^{-1}.

Preparation of 18-β-(3,4,5-trimethoxy)benzoyloxy-epialloyohimbane

Using the procedure due to Lucas et al, a mixture of 90 mg of 18-β-hydroxyepialloyohimbane, 170 mg of 3,4,5-trimethoxybenzoyl chloride in 4 ml of dry pyridine was allowed to stand at room temperature under nitrogen for twenty hours. The solution was poured into 30 ml of water containing 1 ml of ammonium hydroxide and the precipitate filtered off. The solid was digested with hot methanol, the insoluble position filtered off, washed with hot methanol and dried to give 35 mg (24%) of 18-β-(3,4,5-trimethoxy)benzoyloxyepialloyohimbane, m.p. 227-29°.

Calc. for $C_{29}H_{34}O_5N_2.CH_3OH$: C, 68.93; H, 7.32

Found: C, 68.66; H, 7.05

The infrared spectrum (Fig. 27) shows a strong carbonyl band at 1720 cm^{-1}.

Preparation of epialloyohimbane-18-one

A solution of 100 mg of 18-β-hydroxyepialloyohimbane,

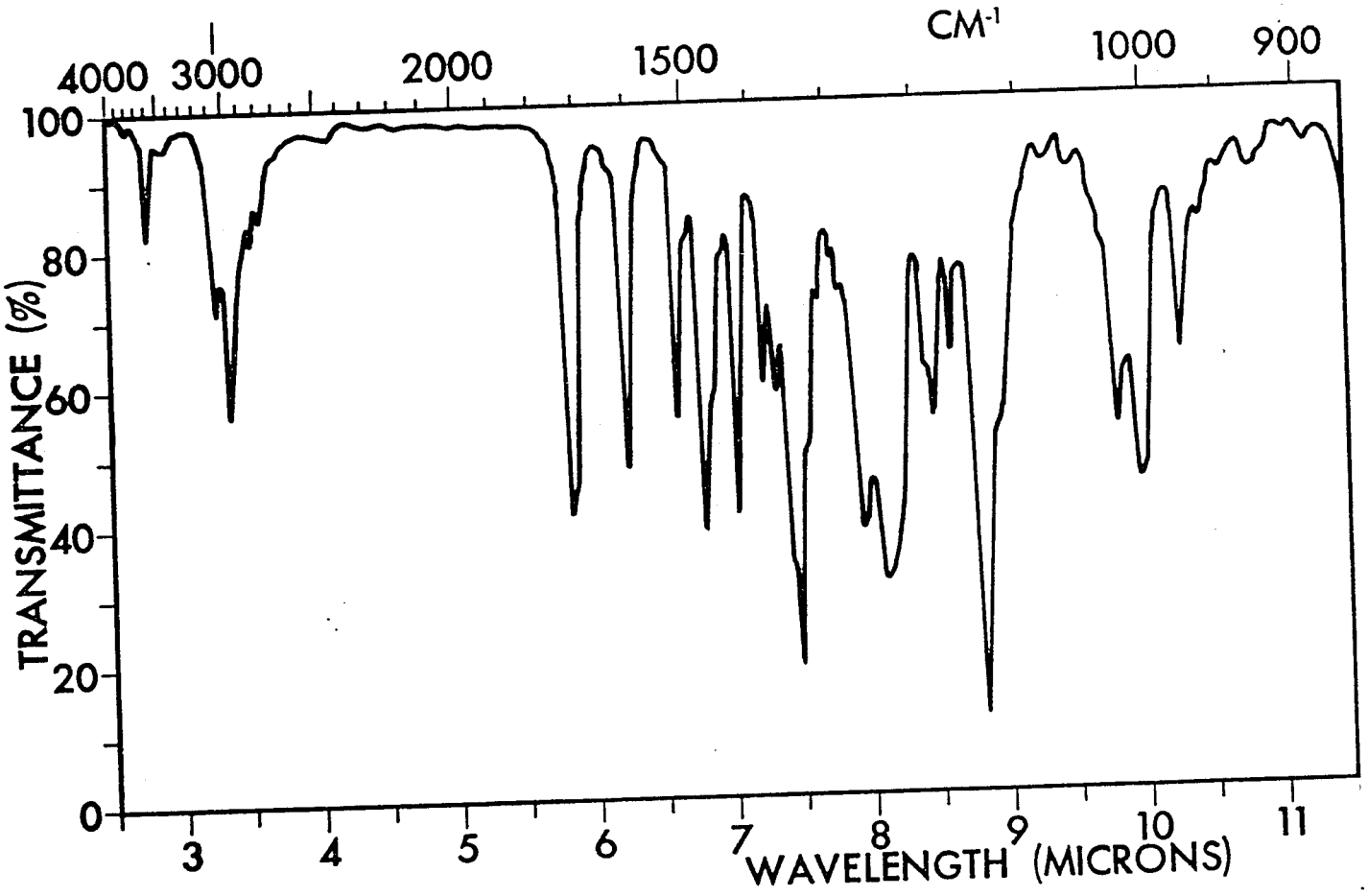


Fig. 26 - Infrared absorption spectrum of 18-β-(3,4,5-trimethoxy)benzoyloxy-alloyohimbane in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

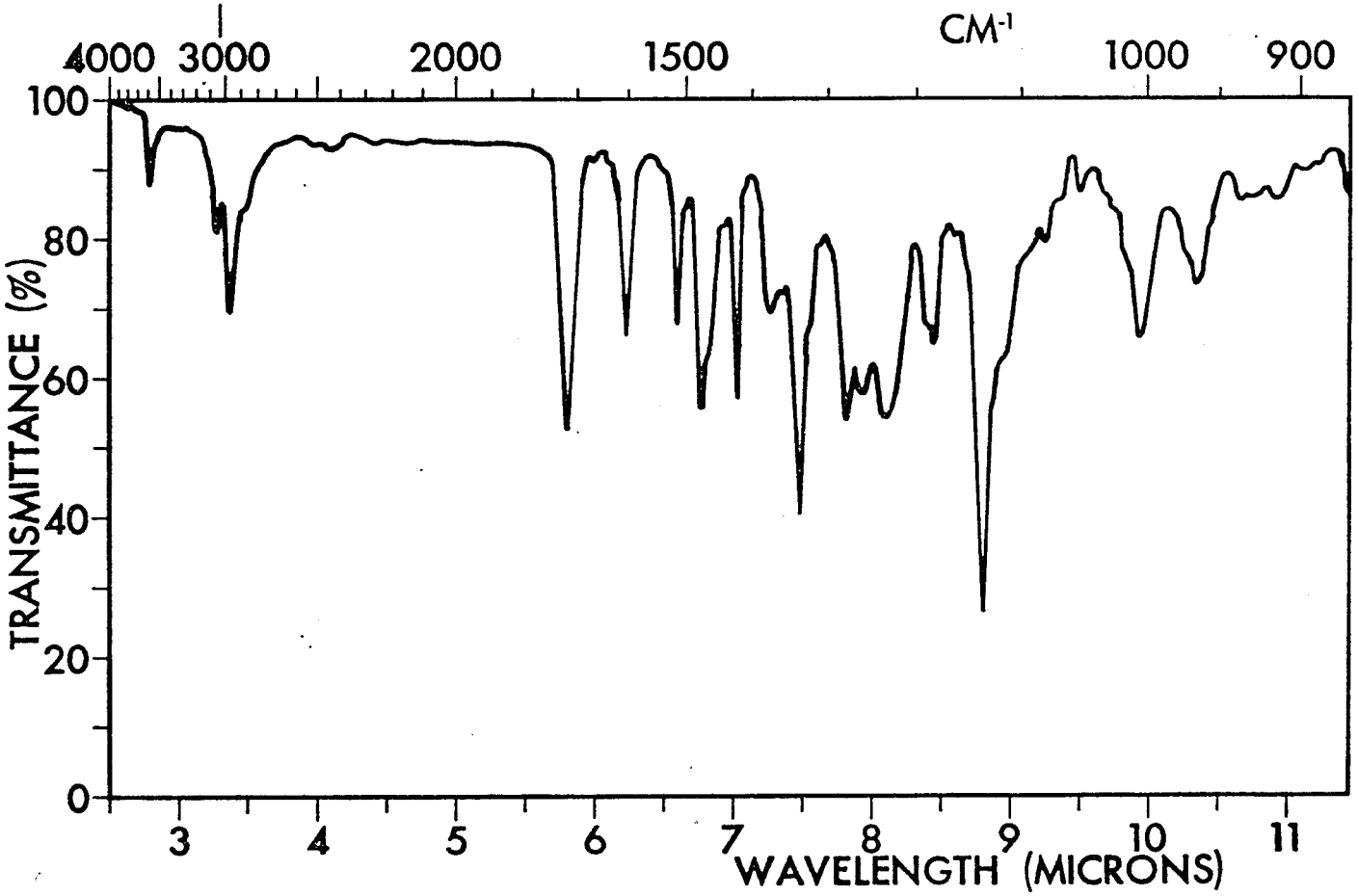


Fig. 27 - Infrared absorption spectrum of 18-β-(3,4,5-trimethoxy)benzoyloxy-epialloyohimbane in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

250 mg of aluminum isopropoxide and 750 mg of cyclohexanone in 5 ml of dry toluene were refluxed under nitrogen for two hours. The cooled solution was poured into 20 ml of 2 N sulfuric acid, the xylene separated and extracted with 10 ml of 2 N sulfuric acid. The combined acid extracts were washed three times with 20 ml of ether, made alkaline and extracted three times with 15 ml of chloroform. The chloroform solution was washed with water, dried, the solvent removed under reduced pressure and the residue crystallized from methanol to give 36 mg (37%) of epialloyohimbane-18-one, m.p. 224-27°.

Calc. for $C_{19}H_{22}ON_2$: C, 77.51; H, 7.53

Found: C, 77.31; H, 8.08

The infrared spectrum (Fig. 28) showed a strong carbonyl band at 1705 cm^{-1}.

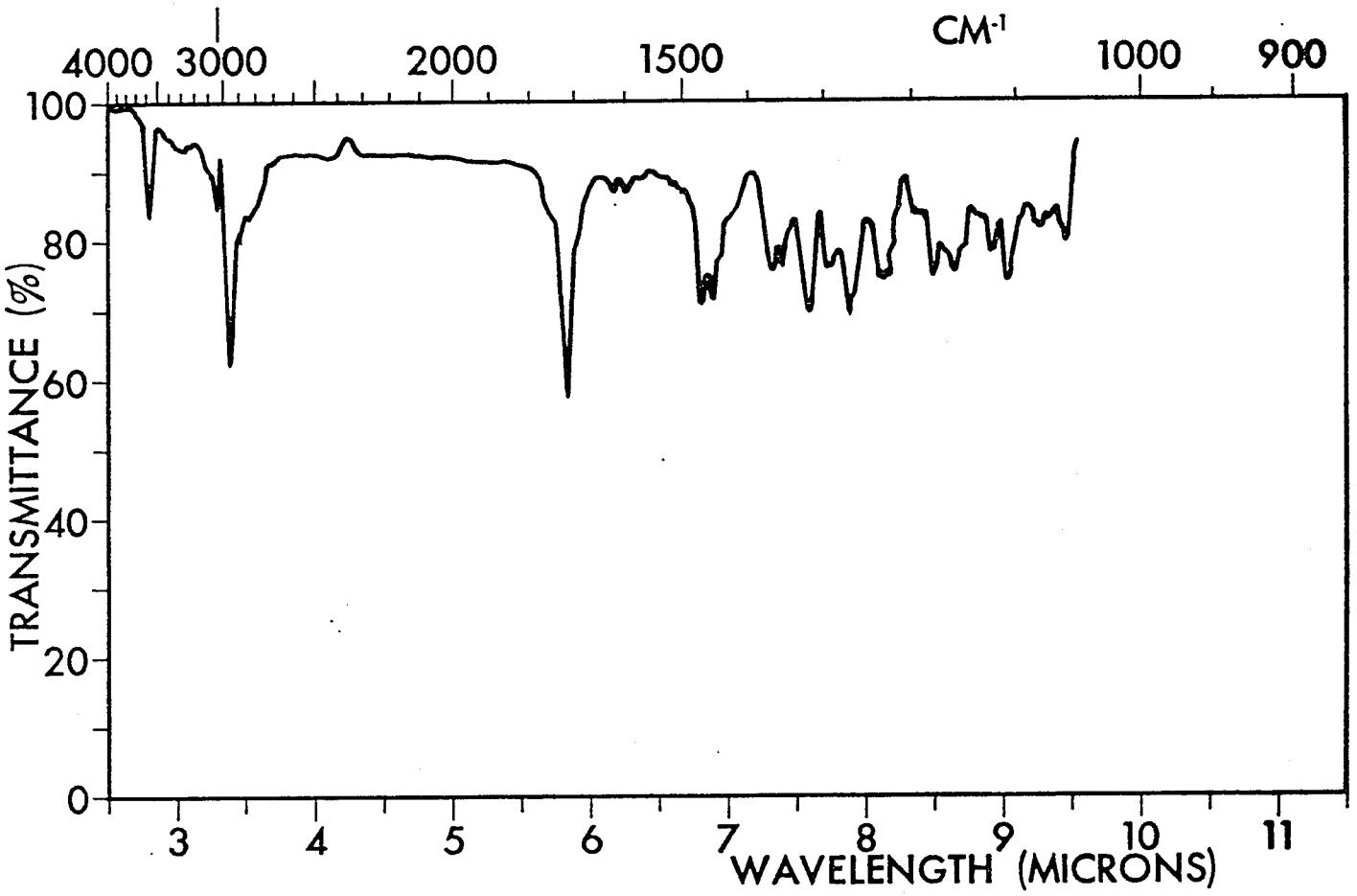
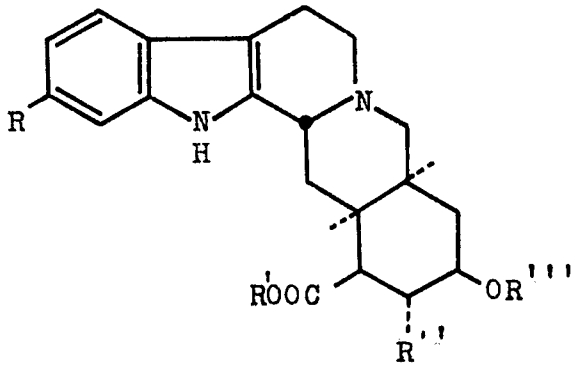
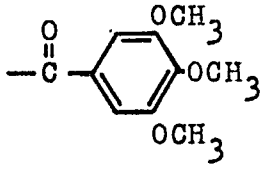
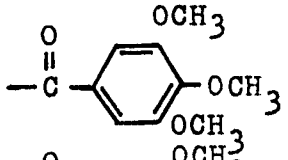
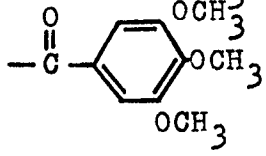


Fig. 28 - Infrared absorption spectrum of epialloyohimbane-18-one in chloroform (0.1 mm cell) measured on a Perkin-Elmer "infracord".

7. DISCUSSION OF RESULTS

The structural features of reserpine (I) which are necessary for the hypotensive and sedative effects



	R	R'	R''	R'''
I	OCH_3	CH_3	OCH_3	
II	OCH_3	CH_3	OCH_3	H
III	H	CH_3	H	
IV	OCH_3	H	OCH_3	

have not as yet been completely defined.

Nevertheless, from the existing knowledge, some conclusions can be drawn as to how the presence, withdrawal, introduction, or spatial orientations of certain atoms or

groups in the molecule affect the drug action. Regarding the minimum structural and steric requirements for activity, three facts are of particular interest:

1) if reserpine is epimerized to 3-isoreserpine the tranquilizing and hypotensive properties are lost (2). This would infer that for the alkaloid to possess these properties the basic skeleton must have an epiallo configuration at C_3, C_{15} and C_{20}.

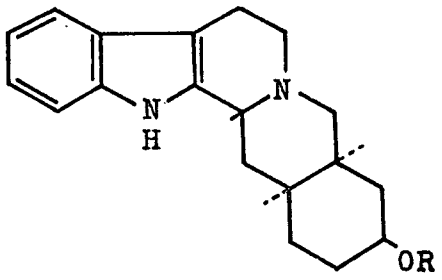
2) methyl reserpate (II) is inactive and therefore for a reserpine-like response the alkaloid cannot have the C_{18} position present as a free hydroxyl group. The presence of an ester grouping such as 3,4,5-trimethoxybenzoyl in the case of reserpine, appears to be necessary for physiological activity. The ester group does not necessarily have to be 3,4,5-trimethoxybenzoyl; in fact virtually any ester group at the C_{18} position shows to some degree a reserpine-like response. It was observed by Lucas and coworkers (17) in their studies of the effect of replacement of the trimethoxybenzoyl group in reserpine with a number of other acyl derivatives, that the action of reserpine can be markedly separated into it's components. Thus the carbethoxyl syringate ester and the 3-dimethylaminobenzoate ester of methyl reserpate are predominantly hypotensive and fast-

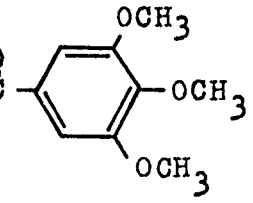
acting sedatives respectively.

3) the 11,17-didesmethoxy analogue (III) of reserpine was found to have essentially the same activity as reserpine. From this, it is apparent that the methoxyl functions at C_{11} and C_{17} are unnecessary for the pharmacodynamic activity of reserpine.

The structural requirements for the position at C_{16} have not yet been determined. It has been shown by Weisenborn (20) that the C_{16} epimer of 11,17-didesmethoxy reserpine (III) has no activity, but the actual necessity of having substitution at this position has been neither proven nor disproven. Lucas and coworkers prepared (18) O-(3,4,5-trimethoxybenzoyl)-reserpic acid (IV) and stated that the biological activity "is very low, thus indicating that both the C_{16} and C_{18} positions of reserpic acid must be substituted in order to elicit reserpine-like activity". Their conclusion however, seems unjustified, since their evidence does not indicate that a compound having no substitution at C_{16} would therefore be devoid of physiological activity, but only that the C_{16} substituent cannot be a free carboxyl group. It was therefore of interest to synthesize a reserpine analogue (V) having no substituents at C_{11}, C_{16} or C_{17}, but having the same skeletal structure and β oriented substituent at C_{18} as are found in reserpine.

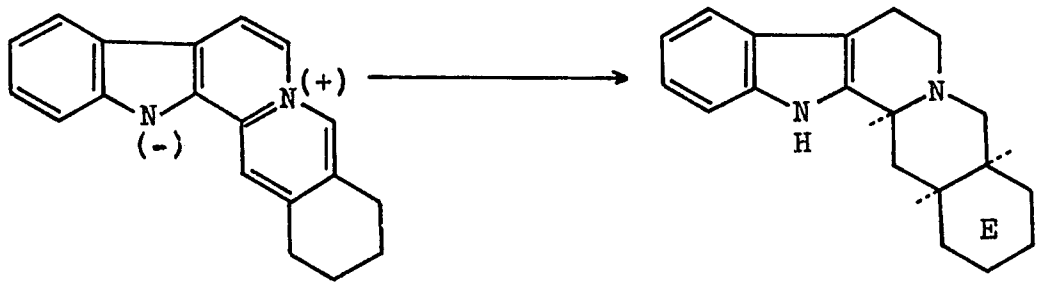
Since alloyohimbanes can readily be converted to



V R = 

VI R = H

epialloyohimbanes, it was thought that the synthesis of 18-β-hydroxyepialloyohimbane (VI) could possibly be carried out via the corresponding alloyohimbane. The method used by Goutarel and coworkers for the synthesis of alloyohimbane (VIII) itself (21,22), namely the hydrogenation of sempervirine (VII), has not been used, with the exception of the work presented in



VII VIII

this thesis, for the preparation of compounds containing ring E substituents. In fact, it had been stated by Stork (30) that this method "is not readily applicable to substances substituted in ring E". Since no reports had been recorded in the literature of attempts to prepare ring E substituted alloyohimbanes via this route, it was felt that this statement was not necessarily correct, and that on asymmetric synthesis of a ring E substituted alloyohimbane could indeed be carried out following this procedure.

The problem can then logically be divided into three parts: first, the synthesis of an appropriately substituted sempervirine; second, the hydrogenation of this sempervirine to the corresponding alloyohimbane and the determination of its stereochemistry; third, the conversion of this to the desired epialloyohimbane.

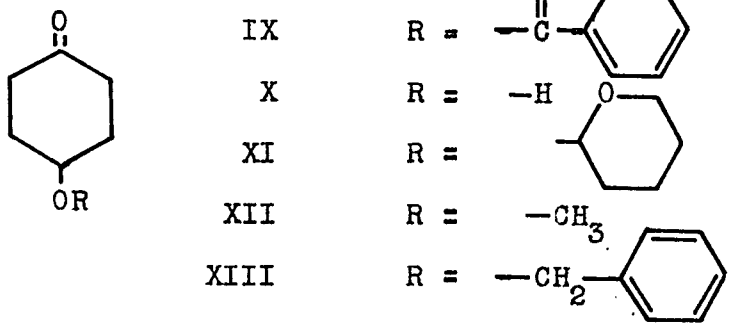
As outlined in the introduction, the procedure used by Woodward and MacLamore for the synthesis of sempervirine was the condensation of 2-isopropoxymethylenecyclohexanone with the dilithium salt of harman. It was thought that through the use of a 2-isopropoxymethylenecyclohexanone containing a suitably protected hydroxyl function, that it would be possible to prepare a sempervirine having a hydroxyl group in ring E.

The use of a 4-substituted cyclohexanone is particularly attractive for two reasons:

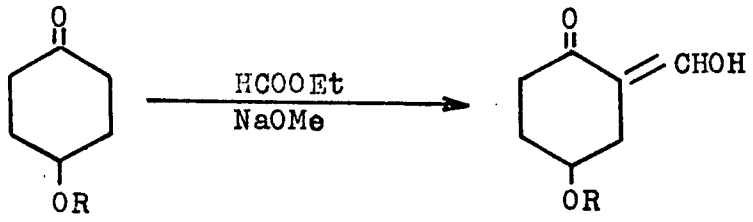
a) the preparation of a 2-hydroxymethylene compound from a 4-substituted cyclohexanone could not lead to positional isomers as might be the case if the cyclohexanone were substituted in the 3-position.

b) the use of a 2-isopropoxymethylenecyclohexanone having a suitably protected hydroxylic function at C_4, would give a sempervirine having a substituent in ring E at C_{18}, which is the position where the hydroxyl group occurs in reserpine.

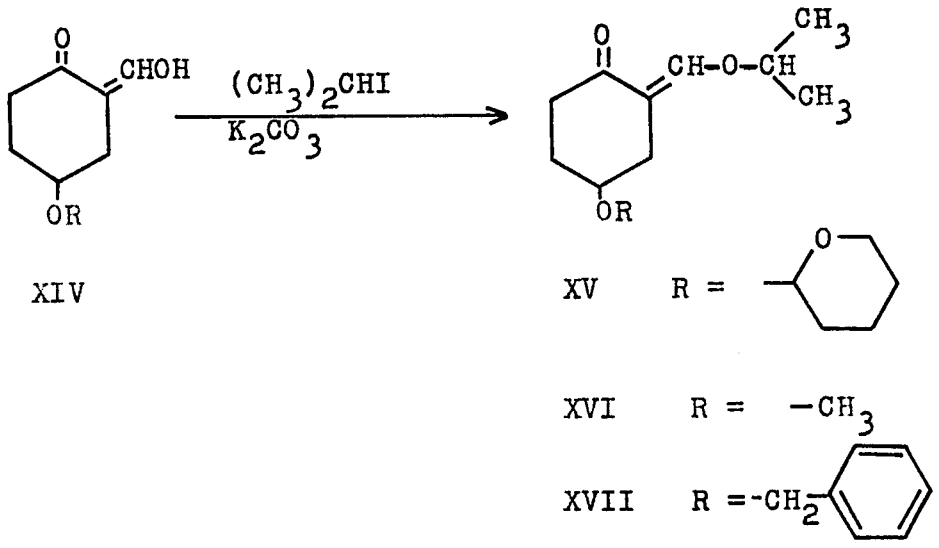
Accordingly, a number of substituted cyclohexanones were prepared, which ultimately included all of the following compounds:



It was hoped that the condensation of one of these with ethyl formate to give the



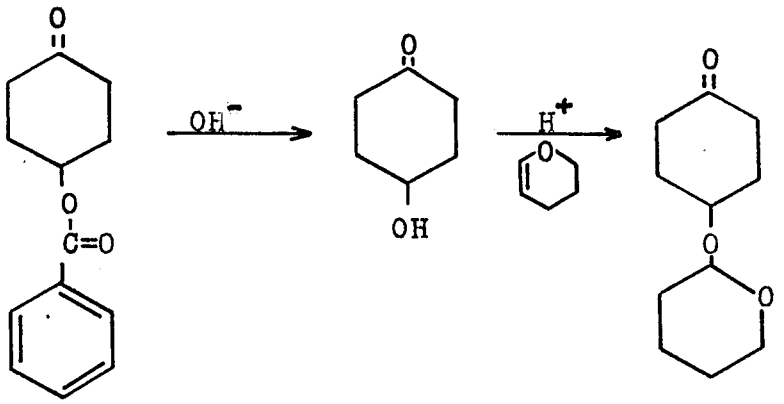
XIV



enol (XIV) followed by etherification would give a 2-isopropoxymethylenecyclohexanone having a suitable substituent at C_4.

The first attempt to prepare a substituted 2-hydroxymethylenecyclohexanone were made using 4-benzoyloxycyclohexanone (IX) prepared by the procedure of Jones and Sondheimer (36). It was found, however, that reaction times as short as fifteen minutes in the cold led to almost complete alcoholysis of the benzoyl group.

It was then decided that it would be preferable to protect the C_4 oxygen function with a group that was more stable under alkaline conditions. One such group commonly used is the tetrahydropyranyl group (47,48,49), and so 4-tetrahydropyranyloxycyclohexanone (XI), b.p. 116-18°/0.05 mm. was prepared.



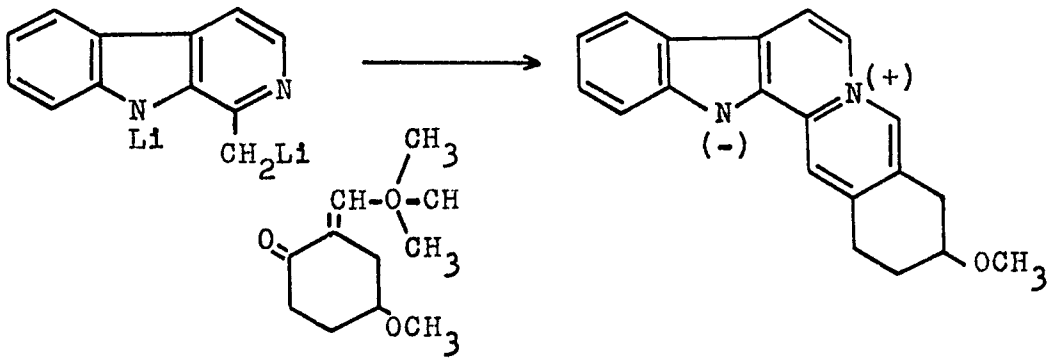
XI

Condensation of this with ethyl formate gave 2-hydroxymethylene-4-tetrahydropyranyloxycyclohexanone and treatment of this gave the desired 2-isopropoxymethylene-4-tetrahydropyranyloxycyclohexanone (XV), b.p. 152-56°/0.05 mm.

However, the condensation of this with the dilithium salt of harman, which it was hoped would lead to the substituted sempervirine, was unsatisfactory. A wide variation in reaction times, temperatures, and methods of working up the crude product led only to yield of 18-hydroxysempervirine in the range of 0-1%. The reasons for this are not readily apparent, especially as condensation of this type involving protecting groups other than tetrahydropyranyl were later found to be quite satisfactory. One possible explanation stems from the fact that dihydropyran under acid conditions hydrolyses to γ-hydroxyvaleraldehyde, and this aldehyde could possibly condense with the aldehyde formed by cleavage of the isopropoxy

enol ether.

Since the tetrahypropyranyl ether did not appear to be overly useful as a protecting group, it was decided to use a more stable ether. Accordingly, using the same reaction scheme as before, 2-isopropoxymethylene-4-methoxycyclohexanone (XVI), b.p. 95-100°/0.08 mm. was prepared from 4-methoxycyclohexanone (XII). This upon condensation with the dilithium salt of harman gave 18-methoxysempervirine (XVIII), m.p. 170-75°, in 46% yield.

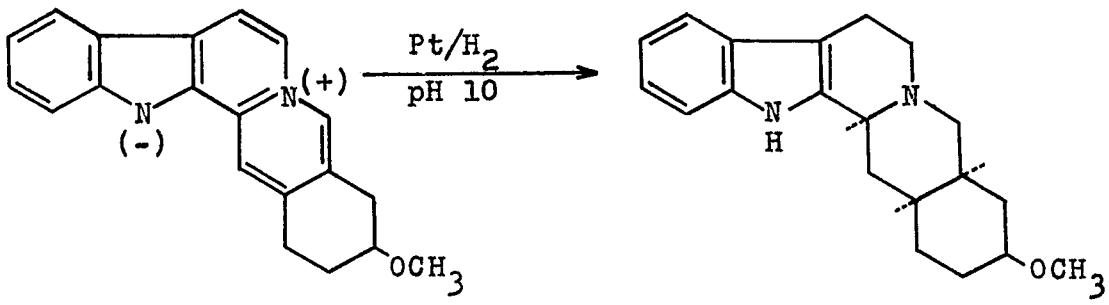


XVI XVIII

Attempts to demethylate this to the desired 18-hydroxysempervirine were not successful. Concentrated hydrobromic acid over a wide range of reaction times and temperatures

gave only tars or partial recovery of the starting material. Similiar results were obtained using molten pyridine hydrochloride, aluminum bromide in benzene, or stannic chloride-acetyl chloride.

It was felt that these demethylation attempts might be more successful if applied to the saturated compound rather than the sempervirine, so the 18-methoxysempervirine was hydrogenated under the conditions used by Goutarel and coworkers (21,22) to give 18-methoxyalloyohimbane (XIX).

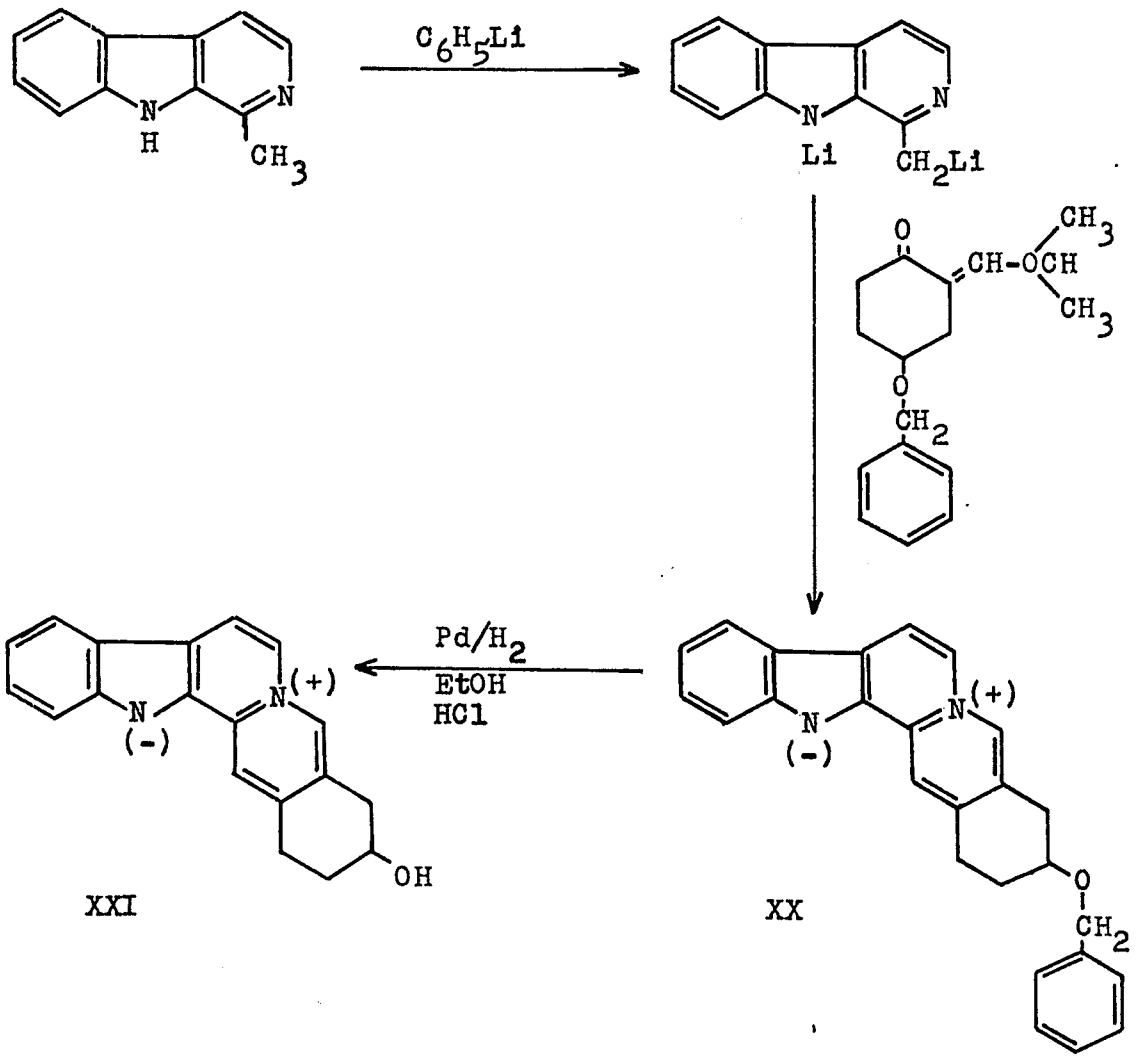


XVII XIX

Demethylation attempts on this with concentrated hydrobromic acid again gave no hydroxyl containing compound. Variations in reaction temperatures and times gave only partial or no recovery of starting material.

At this time, a suitable procedure for the preparation of 4-benzyloxycyclohexanone was described (44), so it was decided to begin again using the benzyl group as a means of

protection for the C_4 function, since it should be removeable under less stringent conditions. Accordingly, 4-benzyloxy-cyclohexanone (XIII) was prepared following the procedure of Prins (44). The 2-isopropoxymethylene-4-benzyloxycyclohexanone (XVII) prepared from this was then condensed with the dilithium salt of harman to give 18-benzyloxysempervirine (XX), m.p. 81-83°.



Hydrogenolysis of this over palladium black in acidic ethanol gave the desired 18-hydroxysempervirine (XXI), m.p. 210-215°.

The second part of the projected synthesis involved the hydrogenation of this sempervirine to the corresponding alloyohimbane.

The hydrogenation of sempervirine itself with Adams' catalyst in alkaline medium over a period of twenty four hours had been found (4) to give 55-65% of alloyohimbane and 2-6% of epialloyohimbane. Since it was known (20) that the asymmetric centre at C_3 could undergo epimerization while in contact with the platinum catalyst, it is suggested that the epialloyohimbane obtained in this reaction was probably not a direct hydrogenation product, but more likely the result of equilibration under the reaction conditions. Because of the obvious desirability of obtaining as pure a reaction product as possible, the hydrogenation of 18-hydroxysempervirine was carried out under the same conditions, but the reaction time shortened from twenty four to two hours. Chromatography of the hydrogenation product on alumina gave mainly one compound (64% yield) m.p. 223-25°, with small amounts of a second of m.p. 210-215° (0.75%), and trace amounts of a third (0.1%) m.p. 233-35°. The high stereospecificity of this reaction, involving the introduction of three new centres of asymmetry, is readily apparent.

It had been shown by Wenkert and Roychaudhuri (50)

that the infrared spectrum of all compounds of this type possessing an α-hydrogen at C_3, i.e. normal and allo products such as d,l-alloyohimbane exhibited two or more distinct and characteristic peaks of medium intensity on the high side of the 3.46 mμ carbon-hydrogen stretching band. The infrared spectrum of the main hydrogenation product showed these bands (Fig. 16) confirming that it was an alloyohimbane and not an epialloyohimbane. The only question then remaining was the configuration of the hydroxyl group at C_{18}, which could be either α or β*.

The conformations of the epimeric 18-hydroxyalloyohimbanes, where R represents the indole moiety, are:

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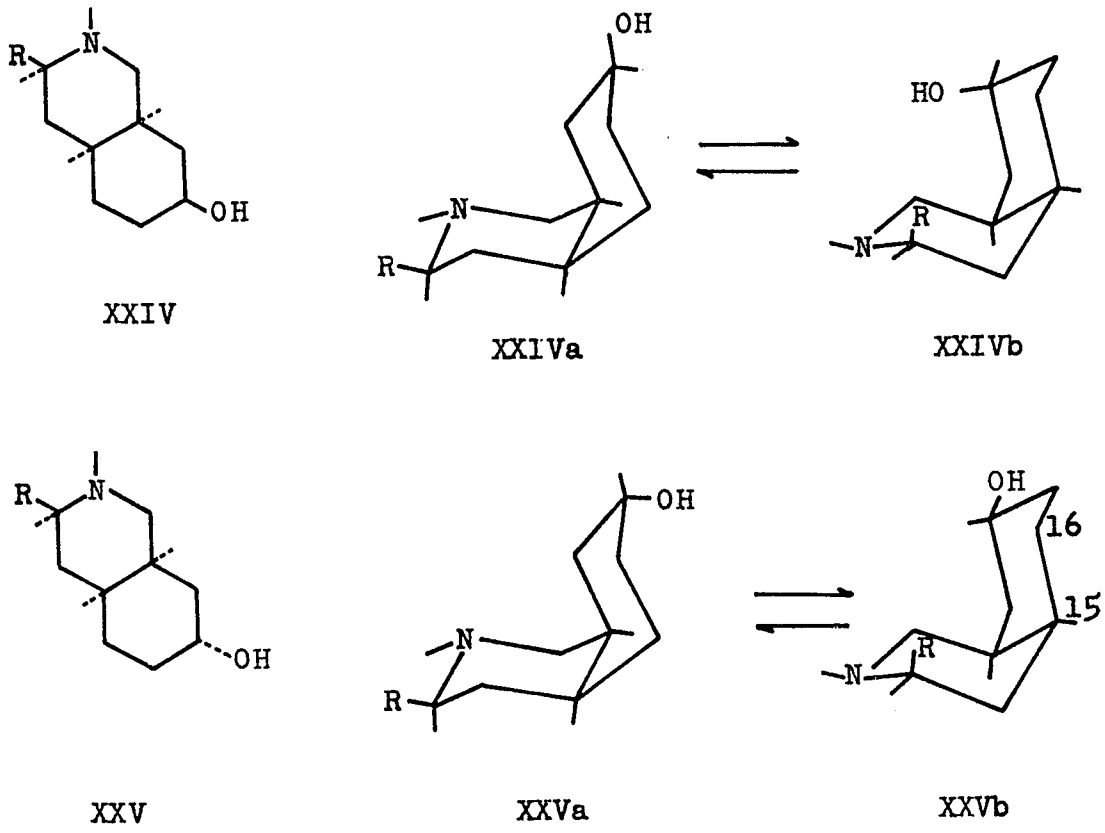
* It should be born in mind that the designations α and β are used with indole alkaloids in the same manner as with steroids. Substituents are α or β with respect to the absolute configuration, which is the configuration used for the diagrams in this thesis. Substituents projecting to the front of the molecule are described as β-oriented and represented by full-line bonds; substituents projecting to the rear or underside of the molecule are described as α-oriented and are indicated by dotted bands.

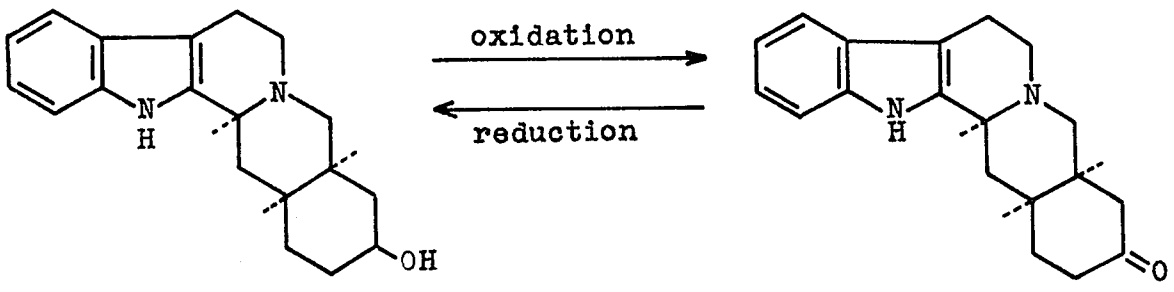


For 18-β-hydroxyalloyohimbane (XXIV), the two possible conformations are XXIVa and XXIVb. Of these two, XXIVa would clearly be the preferred one since it has both the large indole group (R) and the C_{18} hydroxyl group in the equatorial conformation..

For 18-α-hydroxyalloyohimbane (XXV), the two possible conformations, XXVa and XXVb, both have one axial and one equatorial substituent. Pickering and Price (51)

have recently calculated that the energy difference for an equatorial vs axial hydroxyl on a cyclohexane ring is 0.3-0.4 kcal/mole. The energy difference for the axial vs equatorial indole group at C_3 is not known, but it might be expected to approximate that of an isopropyl group, which Winstein and Holness(52) have found to be 3.3 kcal/mole. In addition to this, conformation XXVb has a 1,3 diaxial interaction between the indole group (R) and the C_{15}-C_{16} bond of ring E whereas in XXVa, the axial hydroxyl group has no 1,3 diaxial interactions with groups other than hydrogen. The indole group (R) at C_3 would therefore occupy the equatorial position rather than the axial one, and the preferred conformation for 18-α-hydroxy-alloyohimbane would be XXVa. If this argument is correct, the β-isomer would have the C_{18} hydroxyl group equatorial and the α-isomer would have it axial.

Evidence that the C_{18} hydroxyl group in the hydrogenation product was very probably equatorial, and therefore β, was found in the following manner:



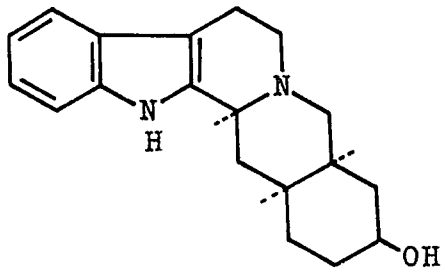
XXIV XXVI

Oppenauer oxidation of the alcohol gave alloyohimbane-18-one (XXVI), and this ketone on reduction with lithium tri-tert-butoxyaluminum hydride returned the original alcohol. It was shown by Wheeler and Mateos (46) that reduction with this reagent generally gave almost exclusively the equatorial isomer; in the particular case of coprostan-3-one, in which the position of the ketone group is reasonably similiar to XXVI, the reduction gave 96.5% of the equatorial isomer. It was therefore highly probable that the hydroxyl group in the starting alcohol was equatorial, and the compound would then be 18-β-hydroxyalloyohimbane.

Since it has been shown by Lemieux and coworkers (53) from their nuclear magnetic resonance studies that there is stronger coupling between axial hydrogens on neighboring carbons that between neighboring hydrogens in the other orientations, and on this basis, axially and equatorially oriented hydroxyl groups could be distinguished by their nuclear magnetic resonance spectra, it was thought that this could be used as a means of confirming the stereochemistry of the hydrogenation product. Because of the low solubility of the hydroxyl compound and as a means of avoiding the signal due to the proton of the hydroxyl group, the acetate was prepared, and the nuclear magnetic resonance spectrum determined. The bond due to the C_{18} proton occurred at τ-5.45 and had a

half-width of about 20 c.p.s. (Fig. 23). In the case of trans-4-t-butylcyclohexanol or it's acetate, the signal for the axial proton at C_1 was found to have a half-band width of 22 c.p.s.; the half-band width of the signal for an equatorial proton at C_1, as determined from cis-4-t-butylcyclohexanol or it's acetate, was found to be 7 c.p.s. (53). The proton at C_{18} of the alloyohimbane must therefore be axially oriented, and the acetoxyl group at this position must then be equatorial.

The structure of the main product from the hydrogenation of 18-hydroxysempervirine must therefore be d,l-18-β-hydroxyalloyohimbane (XXIV).

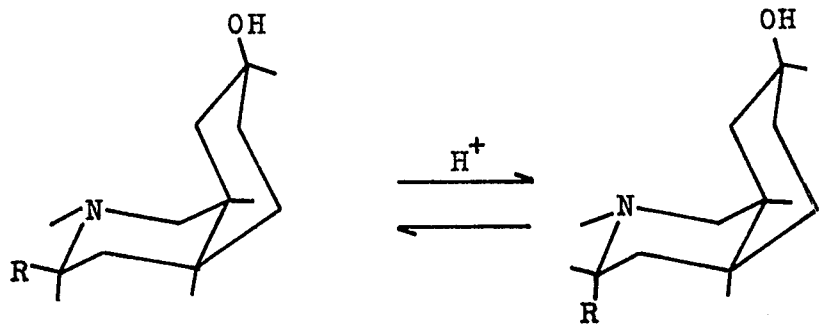


XXIV

Of the remaining two compounds isolated from the hydrogenation, the infrared spectrum of the one melting at 210-215° identified it as an alloyohimbane, and it is therefore most probably 18-α-hydroxyalloyohimbane. Insufficient of the third compound m.p. 233-35° was obtained to characterize it.

Since the hydroxyl group in 18-β-hydroxyalloyohimbane

is in the same orientation as in reserpine, the remaining problem was the conversion of this compound to the corresponding epialloyohimbane. Of the two methods available for this, equilibration would probably not be satisfactory, since the equilibrium would be



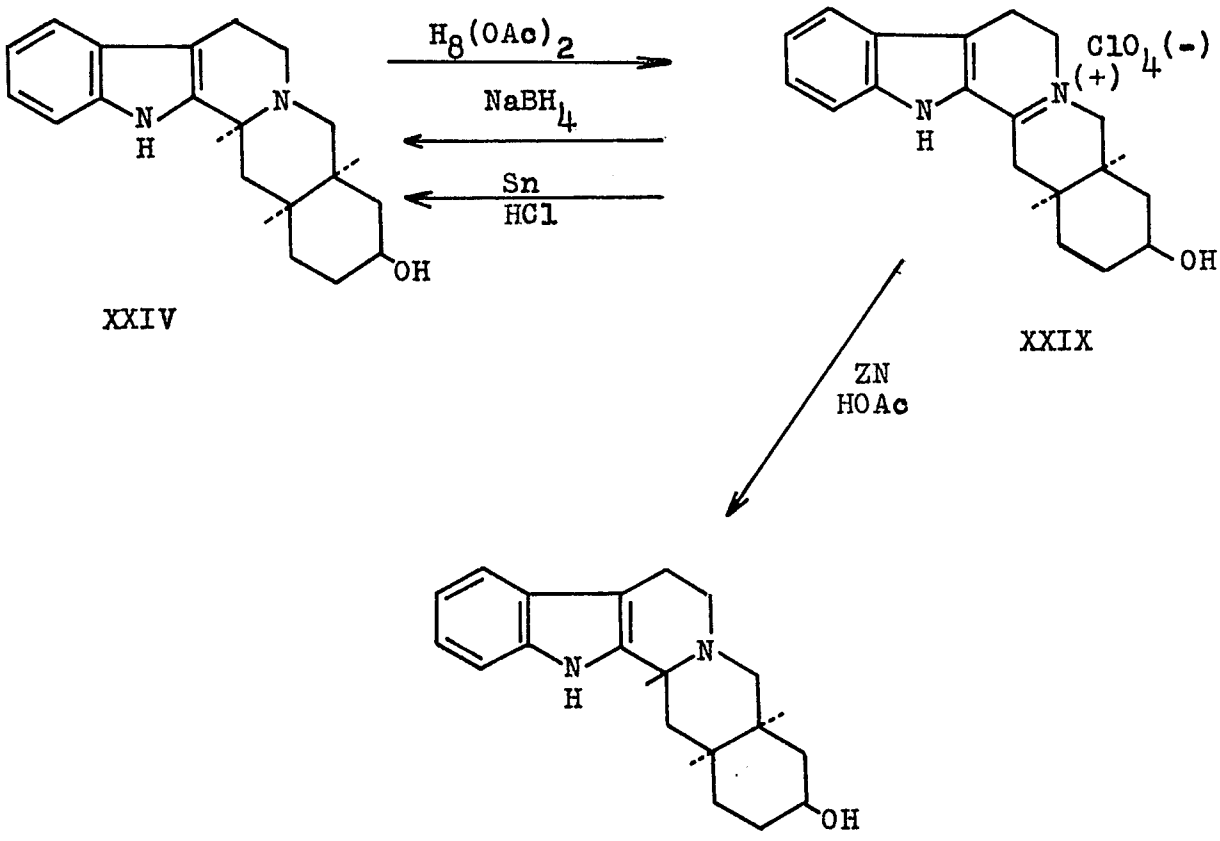
XXVII XXVIII

expected to be far to the side of the 18-β-hydroxyalloyohimbane (XXVII) which has the two substituents in the equatorial orientation, rather than to the side of the 18-β-hydroxy-epialloyohimbane (XXVIII) which has one group axial, and the other equatorial.

The second method involved the oxidation of the alloyohimbane to the 3-dehydro compound and reduction of this with the appropriate reagent to give the epialloyohimbane (26,27,28).

In this way 18-β-hydroxyalloyohimbane was oxidized

by mercuric acetate to the 3-dehydro compound (XXVIII) (isolated as the perchlorate salt)



XXIV

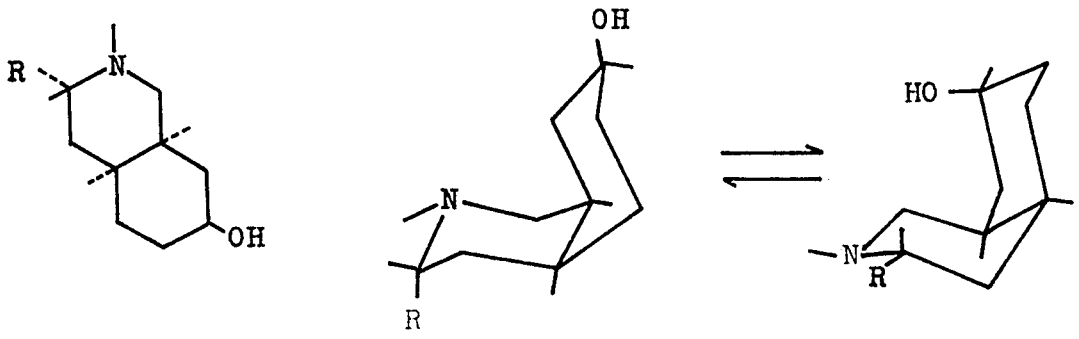
XXIX

XXX

Sodium borohydride (26) or tin and hydrochloric acid (30) reduction of the 3-dehydro-18-β-alloyohimbane returned the

original compound, but reduction with zinc in 50% aqueous acetic acid (27) gave a new compound, 18-β-hydroxyepialloyohimbane, (XXX) m.p. 238-39°.

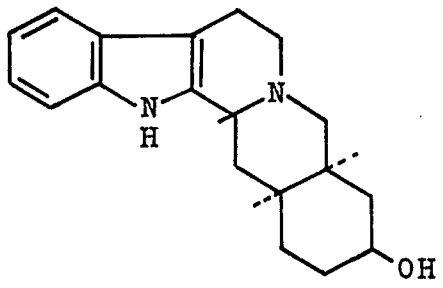
The possible conformations for this compound would be:



XXX XXXa XXXb

Both of these conformations contain one axial and one equatorial substituent; applying the same argument as used for the corresponding 18-hydroxyalloyohimbane, the conformation having the large indole group (R) in the equatorial orientation (XXXb) would be the preferred one. If this were the case, the hydroxyl group at C_{18} would be axially oriented, and the proton at this position would be equatorial. The nuclear magnetic resonance spectrum should therefore show, for this proton, a single signal at low field with a half-band width at approximately 7 c.p.s. (53). This in fact was the case;

the spectrum of 18-β-acetoxyepialloyohimbane showed a single proton signal at T-5.04 having a half-width of 9 c.p.s. (Fig. 25). This confirmed the structural assignment of this compound as 18-β-hydroxyepialloyohimbane (XXX).



XXX

The 3,4,5-trimethoxy benzoate of this compound, which has the same stereochemistry at C_3, C_{15}, C_{18} and C_{20} as reserpine, has been prepared for pharmacological testing.

8. CLAIMS TO ORIGINAL RESEARCH

1. The synthesis of the following new compounds
   a) 4-tetrahydropyranyloxycyclohexanone
   b) 2-hydroxymethylene-4-tetrahydropyranyloxycyclohexanone
   c) 2-isopropoxymethylene-4-tetrahydropyranyloxycyclohexanone
   d) 2-isopropoxymethylene-4-methoxycyclohexanone
   e) 2-hydroxymethylene-4-benzyloxycyclohexanone
   f) 2-isopropoxymethylene-4-benzyloxycyclohexanone
2. Satisfactory reaction conditions, which had not previously been published, were determined for the sempervirine synthesis of Woodward and MacLamore.
3. The synthesis via the procedure of Woodward and MacLamore of the following new sempervirines:
   a) 18-methoxysempervirine
   b) 18-benzyloxysempervirine
4. The synthesis and characterization of the previously unknown 18-hydroxysempervirine.
5. The stereospecific reduction of 18-hydroxysempervirine to 18-β-hydroxyalloyohimbane.
6. The proof of the stereochemistry of 18-β-hydroxyalloyohimbane by means of the infrared spectrum, nuclear magnetic resonance spectrum, and reduction studies on the previously unknown alloyohimbane-18-one.

7. The preparation of the acetate and 3,4,5-trimethoxy benzoate of 18-β-hydroxyalloyohimbane.
8. The synthesis of 3-dehydro-18-β-hydroxyalloyohimbane perchlorate.
9. The synthesis of 18-β-hydroxyepialloyohimbane.
10. The proof of the stereochemistry of 18-β-hydroxyepialloyohimbane by means of its infrared spectrum and nuclear magnetic resonance spectrum.
11. The preparation of the acetate and 3,4,5-trimethoxybenzoate of 18-β-hydroxyepialloyohimbane.

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