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Structure studies on gelsemine

John Holmes Hansen
Iowa State University

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STRUCTURE STUDIES ON GELSEMINE

by

John Holmes Hansen

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Dean of Graduate College

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TABLE OF CONTENTS

HISTORICAL

General

Gelsemine is the major oxindole alkaloid found in the roots and rhizomes of Gelsemium sempervirens Aiton, a flowering woody vine of the family Loganiaceae. This vine is native to the southern United States from Virginia southward into Mexico and is commonly known as yellow jasmine or Carolina jessamine. It is the state flower of South Carolina.

A crude extract of G. sempervirens Ait., Tincture Gelsemium, has been used in the United States as a medicine. It seems to act on the nervous system and has a sedative-like action. The drug was prescribed for neuralgic pains of the face, tooth-ache, and fevers of an intermittent nature. It has also been used in the treatment of headache, hangover, pneumonia, pleurisy, rheumatism, hysteria, epilepsy, gonorrhea, spasmodic croup, influenza and other diseases (2, Sect. 181). The medicinal extract is known to be toxic, and can cause paralysis of the respiratory centers and convulsions, probably because of the alkaloids present. Moore (31) showed that one milligram of the mixed alkaloid hydrochlorides injected into rabbits caused death in one-half hour. One-tenth gram of gelsemine, however, had no effect on rabbits when injected intravenously. It is of interest to note that Wormley's (53) investigation of gelsemium extracts was undertaken in an at-

tempt to discover if gelsemium had been administered to a woman who died suddenly.

An extract of a related species, G. elegans Benth., has been used medicinally in China and is known as "Ta-Ch'a-Yeh" (7, 42). Gelsemine has been isolated from this species also (7).

Constituents of G. sempervirens Ait.

Five alkaloids, including gelsemine, have been isolated from G. sempervirens Ait. Sempervirene, a partially dehydrogenated yohimbane, was first isolated by Stevenson and Sayre (45) who showed that it was one of the toxic principles of the crude Gelsemium extract, one milligram causing the death of a ninety-gram guinea pig in two days. The isolation was confirmed by Chou (4) in 1931.

Chou (3) also isolated a third alkaloid which he named gelsemicine. Later investigators showed that gelsemicine, $C_{20}H_{26}O_4N_2$, (40) is probably a 1,2,3-trisubstituted indole (39) and contains a secondary amino group (5, 21). Janot *et al.* (22) isolated an alkaloid which they believed to be gelsemicine although it had slightly different properties. Schwarz and Marion (40) showed, however, that Janot's "gelsemicine" was indeed a fourth alkaloid, which they named gelsedine. Gelsedine, $C_{19}H_{24}O_3N_2$, contains a secondary amino

group and is probably a 1,3-disubstituted oxindole.

Schwarz and Marion (40, 41) have also obtained a fifth alkaloid from the crude Gelsemium extract which they have named gelsevirene. Still not completely characterized, gelsevirene seems to be a 1,3,3-trisubstituted oxindole with the probable formula, $C_{21}H_{24-26}O_3N_2$. It is a tertiary amine. Schwarz and Marion also report that basic residues remaining after separation of the five known alkaloids from the crude extract still have not been purified further.

Several other alkaloids, such as Wormley's "gelseminine" (53) and Sayre's "gelsemoidine" (39), have been reported. However, later investigations have shown these to be mixtures of the known alkaloids and still unidentified materials.

Moore (31) investigated the dried rhizomes of G. sempervirens Ait. for non-alkaloidal constituents. He identified glucose and palmitic, oleic, stearic and linoleic acids, commonly found in plants. He also isolated pentatriacontane ($n\text{-}C_{35}H_{72}$), scopoletin, which was first isolated by Wormley (53), and a scopoletin glucoside. Among the poorly identified compounds isolated were an "emodin monomethyl ether", "ipuranol" and a phytosterol, supposedly $C_{27}H_{46}O$.

Power and Salway (35) later proved that "ipuranol" is actually a glucoside of a phytosterol, the properties of which

agree closely with those of Moore's phytosterol. Although the identity of this sterol has not been proved, it seems probable that it is a mixture of sitosterols, often found in plant material.

Formula

The determination of the correct formula of gelsemine was hampered by the inability of investigators to obtain the alkaloid in a crystalline state. Two early workers (10, 26) failed to isolate any alkaloidal principles from the crude gelsemium extract, but Wormley (53) succeeded in isolating an amorphous mixture of alkaloids in 1870 which he assumed to be a single compound. Sonnenschein's (43) analysis of this mixture led him to propose the formula, $C_{22}H_{38}O_4N_2$. Gerrard (13) purified Wormley's amorphous material to some extent, obtaining gelsemine as a low melting solid and several of its salts as crystalline solids. After analyzing these solids, he proposed the formula $C_{24}H_{28}O_4N_2$. Analyses by later investigators led to proposals of $C_{54}H_{69}O_{12}N_4$, (46), $C_{49}H_{63}O_{14}N_5$, (9), and $C_{22}H_{26}O_3N_2$, (14, 44).

The formula now believed to be correct, $C_{20}H_{22}O_2N_2$, was first proposed by Moore (31), who discovered that gelsemine crystallized readily from acetone in the form of a 1:1 adduct with the solvent. Recently (16), analyses of a highly puri-

fied sample of the alkaloid and several of its salts have confirmed Moore's proposal.

Oxindole

The presence of an aromatic system in gelsemine was first shown by Chou and Chu (6), who formed a dinitro derivative of dihydrogelsemine which gave a Janovsky test characteristic of a polynitro aromatic system. Later (25), an oxidation of gelsemine with nitric acid gave picric acid as the only isolatable product, and fusion of gelsemine with potassium hydroxide produced anthranilic acid.

Marion (29) heated gelsemine with soda lime and identified the neutral product as 2,3-dimethyl indole. Two unidentified basic products were also isolated. Selenium degradation by the same investigator produced the supposed 2,3-dimethyl indole and an unidentified neutral oil. (Later investigations (25) indicated that the supposed 2,3-dimethyl indole might be 3-ethyl indole.) These results led Marion to suggest that gelsemine could be a 2,3-disubstituted indole.

Some doubt was cast upon this suggestion, however, by Witkop's (50) experiments with zinc dust distillation of gelsemine. He obtained an unidentified phenol; skatole; a weak base, $C_{14}H_{11}N$, with an isoquinoline-like odor; and a strong base, $C_{11}H_{11}N$, which was not 1-ethyl-, 1,3-dimethyl-,

1,4-dimethyl- or 3,4-dimethyl isoquinoline. The formation of skatole indicated that the indole nucleus proposed earlier might not be substituted at the 2-position. Witkop also suggested that both skatole, C_9H_9N, and the strong base, $C_{11}H_{11}N$, might have been formed by a simple fission of gelsemine, $C_{20}H_{22}O_2N_2$.

In 1950, Kates and Marion (24) proposed that gelsemine is a 3,3-disubstituted oxindole on the basis of its infrared spectrum (absorption at 3443 cm^{-1} and 1720 cm^{-1}) and its ultraviolet spectrum which is very similar to that of 3,3-dimethyloxindole. Chemical evidence for this proposal was obtained by the reduction of dihydrogelsemine with lithium aluminum hydride to a tetrahydrodesoxo derivative (16,24) which showed no absorption in the 1700 cm^{-1} region of the infrared, had a pK value, 3.4, attributable to an aniline and formed an acetyl derivative showing no N-H absorption in the infrared. Finally, zinc dust distillation of gelsemine at reduced pressure (16) formed both skatole and 3-methyloxindole, which probably had been destroyed during the earlier experiments (50).

It is of interest that Moore (32) had formed the N-acetyl derivative of the oxindole during his early investigations, but that later investigators (7, 12, 25) could not repeat the preparation. Recently however, the derivative has

been produced again (16), by the use of fereic salts as catalysts.

Double bond

The presence of a double bond in gelsemine was first demonstrated by Chu and Chou (7), who reduced the alkaloid catalytically to a dihydro derivative. Since dihydrogelsemine has one C-methyl group (16, 17), shown by Kuhn-Roth analysis, while gelsemine has none (17), the double bond was considered to be in an exocyclic terminal position. Both ozonization of gelsemine (16) and oxidation of the alkaloid with sodium periodate and a catalytic amount of potassium permanganate produced formaldehyde (27), confirming the presence of the terminal methylene function. Marion and Sargeant (30), in 1956, proved that the terminal methylene was actually a vinyl group by a mild oxidation of the function to an aldehyde with the loss of one carbon atom.

Attempted bromination of the vinyl group gave a high-melting, polar dibromo derivative, which on treatment with sodium bicarbonate lost hydrogen bromide (6). The same dibromo compound is formed by the action of N-bromosuccinimide on gelsemine (23). Goutarel *et al.* (16) showed that the derivative is the hydrobromide salt of a bromo-imino ether, formed by interaction of the oxindole oxygen and the inter-

mediate bromonium ion, and that it may be reconverted to gelsemine by reduction with zinc and acetic acid.

Interaction of the oxindole and double bond probably occurs during hydration of the double bond also. Moore (32) obtained two hydrated products, apogelsemine and isoapogelsemine, and a hydrochlorinated product, chloroisoapogelsemine, by treatment of gelsemine with concentrated hydrochloric acid. Treatments of gelsemine with hydrobromic acid (32) and hydriodic acid (12) produce the analogous bromoisoapogelsemine and iodoisoapogelsemine, respectively, as well as the two hydrated products. Mild hydrolysis of the haloisoapogelsemines converts them to isoapogelsemine (12, 32) and reduction of the iodo-compound with zinc and acetic acid produces dihydrogelsemine (12).

Elimination of hydrohalide from the haloisoapogelsemines with N,N-diethylaniline produces an isomer of gelsemine (12, 32). Chu and Chou (7) also isomerized gelsemine with zinc, platinum and dilute hydrochloric acid to a product which may be the same as Moore's isomer and can be reduced catalytically to dihydrogelsemine. Since the imino double bond of bromoallogelsemine is reduced catalytically without cleavage of the adjoining ether (16), it would seem that the isomer of gelsemine is not an imino ether but a double bond isomer. However, Marion attempted to equilibrate the aldehyde obtained

by oxidation of the vinyl group (30) with deuterium oxide and obtained a product which contains no deuterium[1]. This indicates that the vinyl group of gelsemine is attached to a carbon atom which does not have a hydrogen atom bonded to it and precludes the possibility that a double bond isomer of gelsemine could be formed without skeletal rearrangement.

Amine

Gelsemine was shown to be a tertiary amine by Moore (32) who converted it to a quaternary methiodide which contained only one carbon atom more than the alkaloid. Spiegel's earlier work (44) with impure gelsemine had produced the same results, but these results were not supported by good analyses. In 1943, an analysis by Marion (29) showed that one N-methyl group was present in gelsemine and, since dehydrogenation produced an indole with no substituent on the nitrogen, he concluded that the methyl group must be on the tertiary amino function.

Standard degradative procedures for tertiary amines gave anomalous results. An Emde reduction of dihydrogelsemine methiodide produced, in one instance (12), an amorphous solid which was possibly an organomercuric compound. In another attempt (23), gelsemine methosulfate under Emde Conditions produced no characterizable product while catalytic reduction of the same compound produced no non-quaternary product. Re-

[1]Marion, L., Ottawa, Canada. Data from National Research Council. Private communication to Dr. E. Wenkert. 1957.

duction of gelsemine methiodide with sodium in liquid ammonia removed the extra methyl group giving gelsemine as the only product (23). Moore (32) reported that Hofmann degradation of either gelsemine methiodide with potassium hydroxide or gelsemine methohydroxide with water also removed the methyl group and produced only gelsemine. The same demethylation occurred during an attempted Hofmann degradation of apogelsemine methohydroxide (32).

In 1951, it was reported (15) that gelsemine methohydroxide did undergo the Hofmann reaction. The new double bond supposedly introduced into the product, however, could not be reduced catalytically. Attempted Hofmann degradation of the methylated Hofmann product caused demethylation and the original product was recovered. Lithium aluminum hydride reduction of the methylated Hofmann product effected removal of the methyl group also, as well as the expected reduction of the oxindole.

Several investigators (20, 37, 51) soon proved, however, that Hofmann treatment of gelsemine methiodide does not cause the usual elimination of the ammonium function, but caused transfer of a methyl group to the oxindole nitrogen atom with no further rearrangement. Further, it was shown that the oxindole nitrogen could be methylated in almost quantitative yield by heating gelsemine with tetramethylammonium hydroxide

(37). In a final examination of the Hofmann treatment of gelsemine methohydroxide, Jones and Stevens (23) showed that transmethylation occurs at about 240° while demethylation, such as observed by Moore (32), occurs at about 190°.

Demethylation of gelsemine has been accomplished by the von Braun procedure. A first attempt (12) produced a poorly-characterized compound, probably a cyanoamine, which was hydrolyzed to an amorphous amine. Jones and Stevens (23) treated dihydrogelsemine with cyanogen bromide, obtaining a cyanodesmethyl product which was hydrolyzed to a solid secondary amine. Acylation of this amine produced amorphous material which was not degraded further. Habgood and Marion (18) finally obtained the secondary amine and its benzoyl derivative in a crystalline state. Treatment of the benzamide with phosphorus pentachloride did not cleave the amide as expected, but caused monochlorination of the aromatic ring of the oxindole. The position of substitution was not determined. Hydrolysis of the chlorobenzamide, followed by methylation of the amine, produced the same chloro-dihydrogelsemine produced by treatment of dihydrogelsemine with phosphorus pentachloride, indicating that probably no rearrangement occurred.

Attempted demethylation of dihydrogelsemine with ethyl azodicarboxylate (19) gave an adduct which, without isolation, was hydrolyzed to a carbinol amine with the same number of

carbon atoms as dihydrogelsemine. The carbinol amine could be reduced with sodium borohydride to dihydrogelsemine or oxidized with chromium trioxide to a lactam which could not be hydrolyzed. Absorption at 1693 cm^{-1} in the infrared indicated that this lactam was a five-membered ring. Reduction of the lactam with lithium aluminum hydride produced the known (24) tetrahydrodesoxogelsemine.

Ether

Attempts to identify the remaining oxygen function chemically have failed. Moore's (32) early preparation of an acetyl derivative of gelsemine, later shown to be the N-acetyl oxindole (16), led later investigators (7, 12, 29) to believe that a hydroxyl group was present. Attempts to prepare acetate (7, 12) or benzoate (12) derivatives failed. Infrared studies by Kates and Marion (24) finally showed that no hydroxyl group is present in gelsemine.

Forsythe, Marrian and Stevens (12) found that gelsemine does not react with either hydroxylamine or excess butylmagnesium bromide. The same investigators found that dihydrogelsemine is likewise unreactive when treated with excess methylmagnesium iodide. Further evidence that a carbonyl group, besides that of the oxindole, is not present was given by the infrared spectrum of tetrahydrodesoxogelsemine, $C_{20}H_{26}ON_2$, which shows no absorption in the carbonyl and

hydroxyl regions (24).

Infrared spectra of gelsemine and its derivatives (15, 16, 24) show strong absorption at about 1100 cm^{-1}, typical of the carbon-oxygen stretching vibration of cyclic ethers (1, p. 104). On this evidence, ether linkages have been included in the structural formulae thus far proposed (15, 16, 17). The proposed ether linkage is very stable, however, being unaffected by boiling in concentrated hydrochloric and hydriodic acids, or by red phosphorus in boiling acetic acid (7). The linkage is also stable toward phosphorus in boiling hydriodic acid (12).

Structure

Thus far, it has been shown that gelsemine contains an oxindole system, a methyl tertiary amine, an ether and a vinyl group. Considering the formula, $C_{20}H_{22}O_2N_2$, the alkaloid must contain six rings (17).

The presence of a second, non-aromatic double bond and resulting five-ring system in gelsemine has not been disproved. Gelsemine has been hydrogenated with Adams' catalyst in glacial acetic acid to an octahydro compound (12, 16) in which the aromatic ring and vinyl group are saturated. A tetrasubstituted double bond might resist hydrogenation under these conditions, but bromoallogelsemine hydrobromide shows very little absorp-

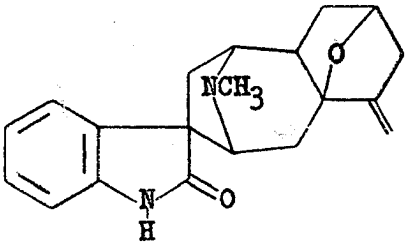
tion in the 1690 cm^{-1} to 1670 cm^{-1} region of the infrared (16), an area in which tetrasubstituted double bonds absorb. Bellamy (1, p. 33) has pointed out that this absorption is always low, however, and may disappear completely as symmetry increases. More evidence against the presence of a second double bond was obtained during the oxidation of the vinyl group to an aldehyde. Marion and Sargeant (30) reported no other products formed.

Several structures for gelsemine have been suggested since 1950. Gibson and Robinson (17) proposed structure I on the basis of a biogenetic relationship to sempervirene.

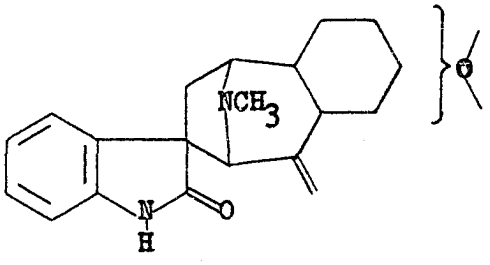
Goutarel *et al.* (16), presented structures II and IIA, modifications of the Robinson-type structure.

All of the structures proposed have been shown to be wrong by the experiments of Marion and Sargeant (30) which proved that a vinyl group, rather than a terminal methylene group, was present in gelsemine. The oxidation of gelsemine with ethyl azodicarboxylate has shown also that the amino nitrogen is adjacent to a methylene group and in a five-membered ring (19). Structures I and II lack the methylene group and structure IIA, while including the methylene group, has the nitrogen in a six-membered ring. In addition, all of the proposed structures have methylene groups in such relationship to the amino nitrogen that Hofmann elimination should

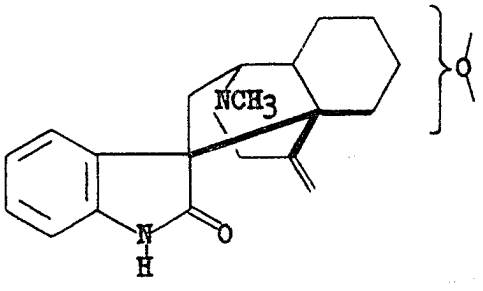
Plate 1. Diagram



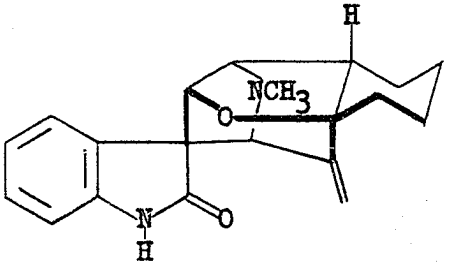
I



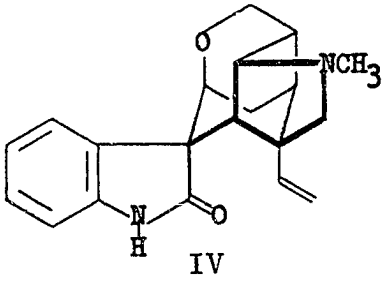
II



IIA



III



IV

occur, although Moore's early work (32) indicated that this elimination does not occur.

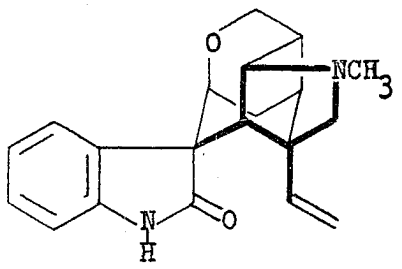
After their supposedly successful Hofmann elimination, Goutarel *et al.* (15), modified structure II to structure III. This structure, of course, has the same deficiencies as were noted for structure II.

The ether linkages in structures I and III have been placed in positions which are allyl to the double bond. However, acid hydrolysis which would be expected to cleave an allyl ether causes, instead, hydration of the double bond (32). Both structures also show the ether linkage on a quaternary carbon atom although dihydrogelsemine is unaffected by boiling, concentrated hydriodic acid (7).

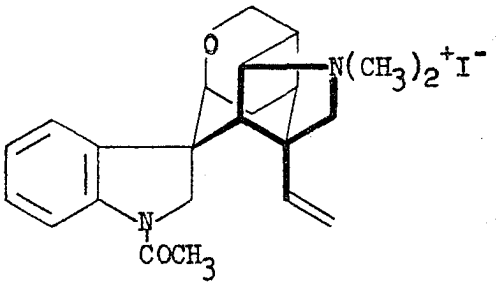
Since completion of the experimental work described in this report, a new structure has been presented by two independent groups. On the basis of X-ray analyses of hydrohalides of gelsemine, Lovell *et al.* (28) have proposed structure IV. Simultaneously, Conroy and Chakrabarti (8) proposed the same structure on the bases of biogenetic considerations and NMR spectra.

In addition, Conroy and Chakrabarti partially degraded gelsemine to produce chemical evidence which supported their proposed structure. Gelsemine was reduced, acetylated and

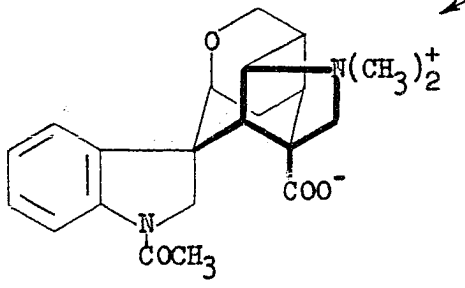
Plate 2. Diagram

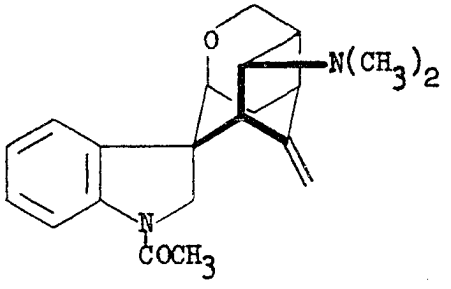


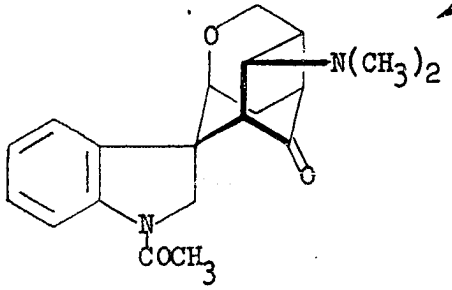
Gelsemine



N_a-acetyldesoxodihydrogelsemine-
N_b-methiodide







methylated to form N_a-acetyldesoxogelsemine-N_b-methohydroxide. Oxidation of this compound with alkaline permanganate produced a betaine which was decarboxylated in a dilute solution, with concerted β-elimination, to a basic pentacyclic olefin. (When decarboxylation was attempted in the absence of solvent, transmethylation, similar to that first observed by Moore, was the favored reaction and the methyl ester of the corresponding tertiary amine was formed.) Oxidation of the olefin with osmium tetroxide caused formation of a ketone, shown by its infrared spectrum to be in a five-membered ring. This oxidation also yielded a neutral fraction which was believed to have been formed via reverse Mannich decomposition of the pentacyclic keto-base.

DISCUSSION

The work discussed in this report was completed prior to publication of the results of Lovell *et al.* (28) and Conroy and Chakrabarti (8). Therefore, the degradative approaches described were made in an attempt to elucidate the structure of gelsemine, and not to prove the proposed structure IV.

Oxindole

Since the oxindole portion of the gelsemine molecule had been well-characterized and is connected to the rest of the molecule only at the 3-position, complete or partial removal of the oxindole portion would provide a new point of attack for further degradation of gelsemine. If it is assumed that gelsemine is formed from a tryptamine-type precursor, then only two carbon atoms separate the C-3 atom and the amino-nitrogen atom. Further, if gelsemine contains a spiro, five-membered Ring C, such as Robinson's (17) proposed structure I, then the C-3 atom also is separated from the amino-nitrogen atom by only one carbon atom. Examination of the proposed structure IV shows that the ether linkage is separated from the C-3 atom by only one carbon atom. Thus, the C-3 atom would provide not only a novel, but possibly effective point for degradation of the non-aromatic portion of the alkaloid.

Several methods for removal of the oxindole to free the C-3 atom were considered. Complete oxidation of the oxindole

to a substituted malonic acid, followed by decarboxylation, would produce a compound which could be degraded further by standard reactions. Moore (32) pointed out, however, that gelsemine is sensitive to oxidizing agents and only recently have definite oxidation products of the alkaloid been obtained (19, 31), by the use of very mild oxidizing agents. Oxidation of the benzenoid structure would necessitate use of a powerful oxidizing agent, possibly leading to decomposition of the entire molecule. Therefore, a method of degradation which avoided the use of powerful oxidizing agents was indicated.

Gelsemine can be reduced catalytically to an octahydro compound in which both the aromatic ring and the vinyl group are completely reduced (16). If the lactam of octahydrogelsemine could be hydrolyzed and a double bond, β to the resulting carboxyl group, be introduced simultaneously, then pyrolytic decarboxylation would produce a compound which could be oxidized with mild reagents to remove the residue of the original oxindole group. Alternatively, the unsaturated acid might be first oxidized, then decarboxylated to a compound which could be degraded further.

Huisgen and Reinertshofer (21) have pyrolyzed N-nitroso pyrrolidone, forming butyrolactone. They also reported that treatment of N-nitroso pyrrolidone with potassium carbonate

in methanol caused formation of both butyrolactone and methyl γ-methoxybutyrate, but no unsaturated ester. However, White (49) showed that pyrolysis of acyclic N-nitroso secondary amides produced not only the expected ester, but also the corresponding acid and alkene. Since octahydrogelsemine probably has a cis A/B ring junction and the lactam nitrogen atom is probably in an axial position, it was felt that a modification of Huisgen's experiments might be useful in the degradation of gelsemine.

Octahydrogelsemine, VI, would not undergo nitrosation when treated with ethyl nitrite in the presence of potassium t-butoxide. The nitroso compound was formed, however, by treatment of a carbon tetrachloride solution of octahydrogelsemine with sodium acetate and a solution of nitrogen tetroxide in chloroform, a method used by White (49). N-nitroso-octahydrogelsemine, VII, was obtained as a yellow, non-crystalline solid and was identified by its infrared spectrum. Pyrolysis of the compound in nitrobenzene, by the method of Huisgen (21), caused formation of tars which could not be purified.

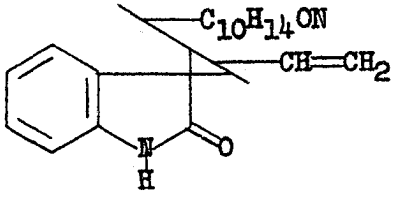
The nitroso compound was refluxed with sodium methoxide in methanol, a more drastic treatment than that employed by Huisgen, and was converted to a gummy material. The gummy material could not be purified by chromatography but was

separated into several fractions, the major of which were shown by infrared spectra (Figure 5) to be mixtures of a small amount of lactone, VIII, 5.68μ, and a large amount of ester IX, 5.83μ. The mixtures showed only a small amount of absorption in the 6.0 to 6.1μ region of the infrared and no absorption in the 12.0μ region, indicating that the desired trisubstituted double bond had not been formed. Since the mixtures showed no absorption in the 3.0μ region, indicating the absence of the amino group, and strong absorption at both 8.2μ and 8.3μ, a region of the infrared in which both esters and ethers absorb, it is probable that the ester formed was a γ-methoxyl ester analogous to that reported by Huisgen (21), although the unsaturated ester also shown is not ruled out as a possible co-product.

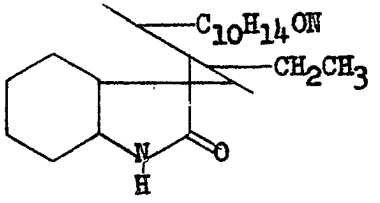
Pyrolysis of the ester-lactone mixture in phenyl ether produced a dark-colored residue, which could not be purified by chromatography.

Treatment of the ester-lactone mixture with hydrochloric acid in refluxing glacial acetic acid, or with p-toluenesulfonic acid in refluxing benzene, caused no appreciable change in the infrared spectrum of the mixture. Refluxing the ester-lactone mixture with hydrochloric acid in water-dioxane solution, however, produced a gummy product. The infrared spectrum of this product was very similar to that of the starting material except for minor absorptions at 6.05μ and 6.17μ, probably

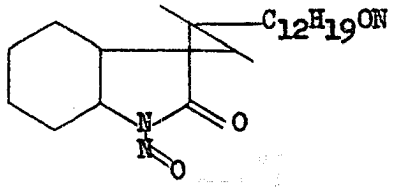
Plate 3. Diagram



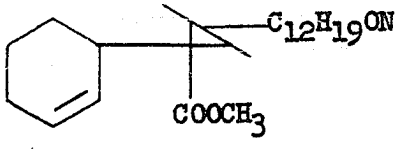
Gelsemine, V



Octahydrogelsemine, VI



N-Nitroso Octahydrogelsemine, VII



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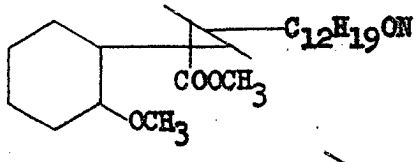
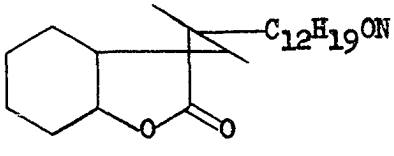
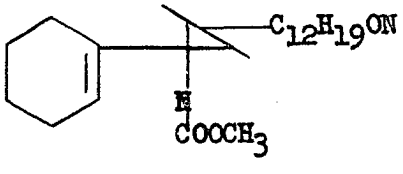


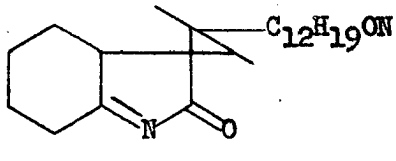
IX



VIII



X



XI

due to a double bond formed by removal of the methoxyl group. The product showed no appreciable absorption near the 12.0 μ region of the infrared, indicating that the desired trisubstituted double bond had not been formed. This result supports the assumption made earlier that the ester of the mixture is probably the γ-methoxyl ester. In a final acid treatment, the ester-lactone mixture was refluxed with concentrated hydrobromic acid, which converted the ester IX almost completely to the lactone VIII.

The previously described products were obtained in low yield in all cases. They were difficult to separate and were never obtained in crystalline form, making positive identification of them almost impossible. In addition, the product most suitable for further degradation, the lactone VIII, would require several more steps before the proposed decarboxylation could be accomplished. For these reasons, no further experiments on this approach were attempted.

In an attempt to avoid formation of the lactone, a method involving decarboxylation with introduction of oxidizable groups was sought. It was felt that a modification of the Hofmann amide rearrangement, utilizing elimination instead of proton abstraction to form the rearrangeable intermediate, would produce the carbamate X, which could be degraded further. When octahydrogelsemine was treated with sodium methoxide and bromine in methanol, however, no carbamate was formed. Most

of the octahydrogelsemine was recovered, but a minor tar-like residue was tentatively identified as the lactim XI. The infrared spectrum of this fraction was very similar to that of octahydrogelsemine (16) except that the N-H absorption at 2.96μ was less intense and that a new band at 6.07μ, possibly indicating the presence of a lactim had appeared. Because of the very low yield and the tarry nature of the product, this approach was not pursued further.

Since the attempts to free the C-3 atom by degradation of octahydrogelsemine proved to be fruitless, another approach was considered. If the oxindole nucleus could be hydrolyzed, then the resulting phenyl-acetic acid might be decarboxylated and oxidized. Alternatively, the freed carboxyl group might be converted to some other functional group which would allow further degradation to be accomplished readily without complete removal of the phenyl group.

Lactams, however, are difficult to hydrolyze and, if hydrolyzed, reform under very mild conditions. Therefore, it was necessary to modify gelsemine in some manner so as to facilitate hydrolysis and to stabilize the hydrolysis product. The toluenesulfonamide group, being both electron-withdrawing and relatively resistant to hydrolysis itself, seemed to fit the requirements well.

p-Toluenesulfonimidogelsemine, XII, hereafter referred to as tosylgelsemine, was formed by treatment of the potassium salt of the amide anion of gelsemine with p-toluenesulfonyl chloride, a method of synthesis analogous to that used by Witkop and Patrick (51) for the synthesis of N-methylgelsemine. Tosylgelsemine is a colorless, crystalline compound, $C_{27}H_{28}O_4N_2S$, and forms a crystalline methiodide, $C_{28}H_{31}O_4N_2SI$. The compound was not hydrolyzed by refluxing in dilute sulfuric acid, nor was the toluenesulfonimide group cleaved by lithium in liquid ammonia. The ultraviolet spectrum (Figure 1) and infrared spectrum (Figure 6) of tosylgelsemine are included in this report.

Tosylgelsemine was hydrolyzed in ethanolic sodium hydroxide solution, however, to form the zwitterionic carboxylate compound, XIII, hereafter referred to as the tosyl-acid. The tosyl-acid, $C_{27}H_{30}O_5N_2S$, formed colorless crystals in methanol, with inclusion of one molecule of the solvent. The zwitterionic nature of the tosyl-acid XIII was confirmed by the infrared spectrum (Figure 6) of the compound, which showed little absorption in the 3.0μ region, strong absorption from 3.8μ to 4.6μ, indicative of the ammonium N-H group, and strong absorption at 6.22μ, typical of the carboxylate ion. The ultraviolet spectrum (Figure 1) was similar to that of tosylgelsemine.

Since the tosyl-acid reverted to tosylgelsemine at room

temperature in 50% sulfuric acid it seemed probable that decarboxylation of the tosyl-acid would be accomplished only under basic conditions. The sodium salt of the tosyl-acid was not decarboxylated, however, by pyrolysis at 190°. Attempted decarboxylation of the tosyl-acid with a solution of sodium hydroxide in refluxing ethylene glycol caused cleavage of the toluenesulfonamide and formation of gelsemine, V. The latter was identified by its infrared spectrum and its melting point. Although no attempt was made to clarify the course of this reaction, it possibly was initiated by attack of the carboxylate anion at the sulfur atom of the toluenesulfonamide. After transfer of the tosyl group from the nitrogen atom to the oxygen atom, forming a mixed anhydride, gelsemine was formed, either by a direct attack of the nitrogen atom on the anhydride or by hydrolysis of the anhydride, with ring closure occurring during isolation of the product.

Although decarboxylation of the type originally envisioned would not occur, it was felt that decarboxylation with introduction of a double bond might be favorable if a suitable leaving group were situated β to the carboxyl group. The tertiary amino group could have been in such a position, as was shown in the proposed structures I, II, and III, and, when converted to the quaternary ammonium salt, should be a good leaving group. Therefore, tosylgelsemine methiodide was refluxed at 120° with sodium hydroxide in aqueous ethylene

glycol. No non-quaternary product could be isolated. The reaction also was attempted in a sealed tube at 150°C, but the desired unsaturated amine could not be isolated.

Consideration of the proposed structure IV indicates that elimination of the ammonium group could not have occurred. Thus, the experimental result supports this structure. At the time of the experiments, however, it was assumed that the amino and carboxyl groups were vicinal and several factors which could have prevented decarboxylation were considered. If the carboxyl and ammonium groups had a cis relationship, the desired reaction was improbable. The temperature necessary for decarboxylation could have been greater than the temperature used in the experiments. However, the loss of a methyl group from the ammonium salt under Hofmann conditions, as was reported by Moore (32), or transfer of a methyl group, as was reported by Goutarel et al. (15), indicated that higher temperatures might well have caused undesired side reactions. Finally, the sulfonamide-carboxylate proton bond may have been so strong that decarboxylation was not favored. The tosyl-acid was treated with diazomethane in an attempt either to esterify the acid or to methylate the sulfonamide, thus breaking the proton bond and allowing the functional groups to be treated separately. However, no reaction was observed.

The vinyl group of gelsemine is relatively near the oxindole oxygen atom since halogenation of the double bond yields

a monohalo-imino ether, rather than a dihalo derivative (6, 16). It seemed that lactonization of the tosyl-acid also might occur when the double bond was halogenated, possibly giving some information on the size of the lactone ring formed and the number of carbon atoms between the oxindole and vinyl groups. When a chloroform solution of the tosyl-acid was treated with iodine and sodium bicarbonate, a non-crystalline solid was produced. Absorption at 5.77μ in the infrared spectrum (Figure 7) showed that an unstrained lactone had been formed, indicating that the newly-formed ring contained six or more atoms. Since the size of the ring could not be determined definitely and, as will be shown later, the lactonization might have occurred at the terminal carbon atom of the double bond, the question of the relative positions of the oxindole and vinyl groups was not clarified. However, the result of this lactonization is consistent with the proposed structure IV.

Although decarboxylation of the tosyl acid had not been accomplished, there remained the possibility of converting the carboxyl group to some other functional group which could then be degraded. Replacement of the carboxyl group with an amino group *via* the Schmidt reaction (52, p. 307) was attempted. The gummy product obtained was not the expected amine, but seemed to be a mixture of tosylgelsemine and a substituted urea, XIV. The supposed urea could not be purified further,

did not rearrange under the influence of iodine and base, and produced no clear product upon acidic hydrolysis.

Beta-trisubstituted ethanols rearrange and dehydrate under acidic conditions to form trisubstituted ethylenes. If the tosyl-acid could be reduced to the tosyl-alcohol, XVa, migration of the phenyl group would lead to the formation of a styrene which could be oxidized to a compound in which the oxindole residue has been removed completely. Migration of either of the other groups attached to C-3 would lead to a styrene also, but oxidation of such a styrene probably would not remove the aromatic residue.

Lithium aluminum hydride failed to reduce the tosyl-acid. However, reduction of tosylgelsemine with lithium aluminum hydride produced the desired tosyl-alcohol, XVa, $C_{27}H_{32}O_4N_2S$. The infrared spectrum of the tosyl-alcohol (Figure 6) showed absorption at 2.82μ and 3.05μ but no absorption in the carbonyl region, features expected from consideration of the partial structure proposed. The ultraviolet spectrum is shown in Figure 1. This reductive cleavage of the toluenesulfonimido group is similar to the reduction of saccharin with lithium aluminum hydride, and almost identical with the reductive cleavage of 1-toluenesulfonyl-4-carboxyamidopyrrolidone with lithium borohydride (36).

When the tosyl-alcohol was refluxed with aqueous formic

acid to effect rearrangement, a gummy, brown product which could not be crystallized was obtained. The infrared spectrum (Figure 7) of this product showed strong absorption at 5.83μ, a region in which ketones absorb, and lessened absorption at 9.2μ. The ultraviolet spectrum (Figure 2) showed strong absorption at 317 mμ, log ε 3.98. The formation of a ketone might occur if the ether linkage of gelsemine had been at C-3. Rearrangement of the phenyl group would form an enol ether, hydrolysis of which would produce an unconjugated ketone.

It was felt that rearrangement might be facilitated and the product obtained in higher yield if the hydroxyl group of the tosyl-alcohol could be replaced with a better leaving group. Therefore, tosyl gelsemine was reduced with two equivalents of lithium aluminum hydride, then treated with an excess of tosyl chloride before hydrolysis of the reduction mixture. The product was crystalline but could not be purified further for analysis. It was assigned the structure XVb on the basis of its ultraviolet spectrum (Figure 3) which shows a peak at 222 mμ, logε 4.39. As shown in Figure 3, this is very similar to the spectrum calculated, 225 mμ (logε 4.41), for the sum of the tosyl-alcohol and one-half equivalent of glycol bistosylate. The infrared spectrum (Figure 7) was also consistent with the assigned structure,

showing no absorption in the 2.8μ region and intensified absorption in the 8.6μ region.

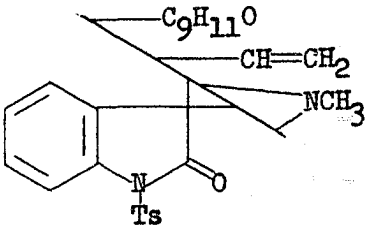
The crystalline product was pyrolyzed in glacial acetic acid for two days and a gummy brown product was obtained. The infrared spectrum of this product was similar to that of the pyrolysis product of the tosyl-alcohol, but the carbonyl band was less intense. The ultraviolet spectra (Figure 2) of the two products were different, however. The spectrum of the di-tosyl pyrolysis product was intermediate to the spectra of the di-tosyl compound and the tosyl-alcohol rearrangement product, indicating that the di-tosyl pyrolysis product was probably a mixture.

In an attempt to obtain crystalline products, dihydrotosylgelsemine was prepared by tosylation of dihydrogelsemine. Although dihydrotosylgelsemine was crystalline, it could not be purified for analysis. The crude, crystalline material was converted to a gummy derivative by the lithium aluminum hydride-tosyl chloride procedure used with tosylgelsemine, and the derivative pyrolyzed in formic acid. The rearrangement product was a brown gum with an ultraviolet spectrum similar to that of the tosyl-alcohol pyrolysis product, although the intensity was lower (Figure 2).

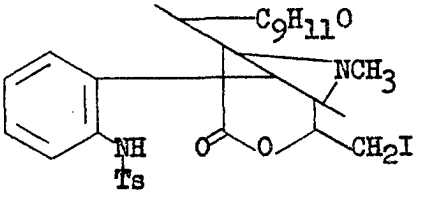
Although the rearrangement of the tosyl-alcohol and related compounds had produced no definite products, it was

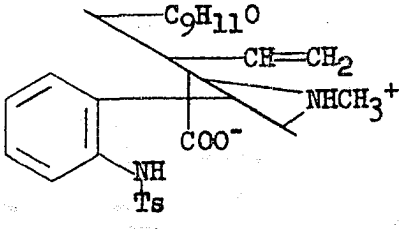
Plate 4. Diagram

Gelsemine, V

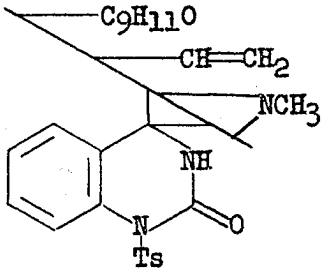


Tosylgelsemine, XII

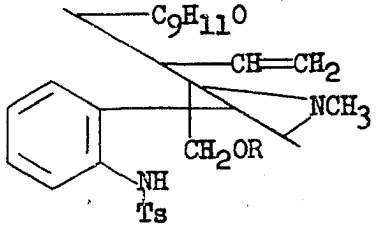




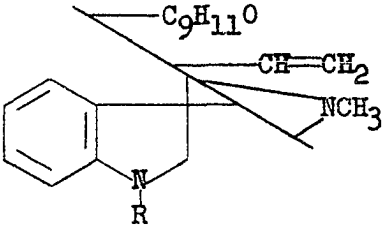
Tosyl-acid, XIII



XIV



XV a) R = H
b) R = Ts



XVI a) R = Ts
b) R = H

felt that dihydrodesoxotosylgelsemine, XVIa, could have been formed. In order to determine the infrared and ultraviolet spectra of this derivative, the compound was prepared by tosylation of dihydrodesoxogelsemine, XVIb. The colorless, crystalline derivative, $C_{27}H_{30}O_3N_2S$, was shown by its ultraviolet spectrum (Figure 1) to be different than the pyrolysis products. Tetrahydrodesoxotosylgelsemine, the dihydro analogue of XVa was prepared also, but could not be crystallized.

Double bond

Many of the earlier investigations of gelsemine involved modification of the vinyl group by reduction, addition or oxidation. Although none of these modifications had led to deep, controlled penetration into the unknown portion of the gelsemine molecule, the vinyl group nevertheless provided a reactive site for beginning degradative studies.

Preliminary attempts to oxidize the vinyl group with a permanganate-periodate reagent (27) under a variety of conditions caused formation of tars which could not be purified. The later, successful oxidation of the vinyl group to an aldehyde by Marion and Sargeant (30) was accomplished by first methylating the oxindole nitrogen atom, then oxidizing with an osmium tetroxide-periodate reagent to avoid undesirable side reactions.

Since oxidation of unmodified gelsemine seemed to be

fruitless, hydrolysis of the vinyl group to allow the use of more specific oxidizing agents was attempted. In his early work, Moore (32) hydrated gelsemine in hydrochloric acid, obtaining two hydrated and one hydrochlorinated products. To avoid formation of halogenated product, gelsemine was hydrated by refluxing in 20% sulfuric acid for 19 hours. The amorphous product, designated hydrogelsemine A, was converted to a second product, designated hydrogelsemine B, by sublimation or by aluminum phenoxide. Hydrogelsemine B was also formed directly from gelsemine by refluxing in 20% sulfuric acid for 65 hours.

Hydrogelsemine A was shown to be an alcohol-oxindole by its infrared spectrum (Figure 8), peaks at 2.82μ and 5.88μ, and formed an unpurifiable crystalline acetate believed to be the mono derivative. The ultraviolet spectra of both hydrogelsemine A and its acetate were identical with the spectrum of gelsemine (Figure 4) indicating that the oxindole structure was unchanged. The infrared spectrum of hydrogelsemine A, with a shoulder at 5.95μ, also indicated that it was contaminated with hydrogelsemine B.

Hydrogelsemine B was also an alcohol-oxindole, but shifts of both the hydroxyl (2.94μ) and carbonyl (5.97μ) absorptions in the infrared spectrum (Figure 8) indicated that proton bonding between the hydroxyl and carbonyl groups was appreciable.

The ultraviolet spectrum in ethanol solution, however, was almost identical with that of gelsemine (Figure 4). The diacetyl derivative of hydrogelsemine B, $C_{20}H_{22}O_3N_2$ $(C_2H_3O)_2$, showed three absorption bands in the carbonyl region of its infrared spectrum (Figure 8) and an ultraviolet spectrum (Figure 4) typical of an N-acyl oxindole, features expected for an imide-ester combination. It is worthy of note that gelsemine itself does not form an imide ordinarily but does if the reaction is catalyzed with ferric salts (16). The formation of the imide of hydrogelsemine B and not hydrogelsemine A must be due then to proton bonding in hydrogelsemine B.

Although no analytical proof was obtained, infrared spectra indicated that hydrogelsemine A was a mono-alcohol and therefore an isomer of hydrogelsemine B. Since it is unlikely that a hydroxyl group on a saturated chain would be transfered from one carbon atom to another during sublimation or treatment with aluminum phenoxide, the hydrated products must be epimers. Formation of an imino ether during bromination of gelsemine indicates that the vinyl group is near the oxindole oxygen atom. The epimerization of hydrogelsemine A may be facilitated, therefore, by participation of the oxindole during the reaction.

Although the hydrated products seemed different than

apogelsemine and isoapogelsemine, the hydration products reported by Moore (32), these compounds were synthesized to compare their infrared spectra. Neither apogelsemine nor isoapogelsemine showed the distinct hydroxyl group absorptions of hydrogelsemine A and hydrogelsemine B, but had, instead, the broad absorption bands near 3.0μ of strongly bonded hydroxyl groups. The infrared spectrum of apogelsemine also showed three absorption bands between 7.5μ and 8.0μ, a region often associated with carbon-oxygen single bond stretching, which were also found in the spectrum of hydrogelsemine A (Figure 8). The infrared spectrum of isoapogelsemine showed weak absorption bands at 7.6μ and 7.8μ, similar to the bands found in the spectrum of hydrogelsemine B (Figure 8).

No attempt to clarify the relationship between the four hydration products was made. However, an infrared spectrum of Moore's crude reaction product (32) which he believed to be apogelsemine and isoapogelsemine hydrochlorides, indicated that the mixture consisted largely of the imino-ether, allogelsemine. Since the major product after purification of the crude mixture is apogelsemine, apogelsemine probably is formed by hydrolysis of allogelsemine. Formation of hydrogelsemine A must involve, then, isomerization of the initially introduced hydroxyl group. Both hydrogelsemines A and B differ from desoxooxytetrahydrogelsemine XVIIIa. As will be described later,

this compound is a primary alcohol ; and probably contains the unrearranged skeleton of gelsemine. The probability is high, then, that the isomerization of the hydroxyl group to form hydrogelsemine A was accompanied by rearrangement of the basic skeleton.

Oxidation of hydrogelsemine B with chromic anhydride in pyridine (34) led to formation of a gummy product which could not be obtained in crystalline form. The infrared spectrum of this product was similar to that of gelsemine except that no sharp N-H absorption was apparent and the single carbonyl absorption had shifted to 5.82μ. The ultraviolet spectrum (Figure 4) of the oxidation product was similar to that of apogelsemine but showed additional absorption at 350 mμ(log ε 1.96). However, no carbonyl derivative of the product could be synthesized. A second oxidation, employing a shorter reaction period, lead to formation of a solid product. The infrared spectrum of this product showed no hydroxyl group absorption and a rather broad carbonyl absorption centered at 5.87μ.

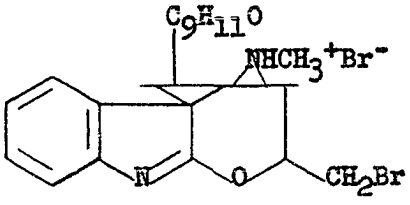
Hydrogelsemine B was also oxidized with iodine and sodium hydroxide. The product was a dark tar and could not be purified.

An indirect method for hydrolysis of the double bond of gelsemine involves formation of bromoallogelsemine hydrobromide,

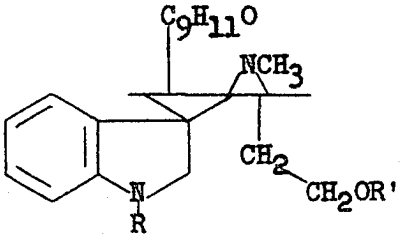
XVII (6, 16), followed by reduction of the imino-ether with lithium aluminum hydride to desoxooxytetrahydrogelsemine, XVIIa (16).

Consideration of a probable mechanism for reduction of bromoallogelsemine, involving an epoxide intermediate, would lead one to expect formation of a secondary alcohol. However, Kuhn-Roth analysis of the amino-alcohol XVIIIa showed that no C-methyl group was present in the compound and indicated that the hydroxyl group must be primary. Eliel and Prosser (11) have shown that analogous epoxides can rearrange, by 1,2-hydride shifts, to aldehydes which are then reduced further. Such a rearrangement must have occurred during the reduction of bromoallogelsemine.

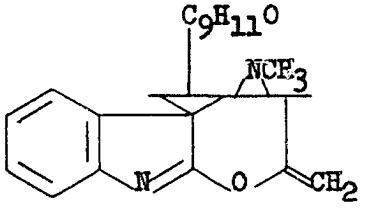
The possibility that formation of the primary alcohol might involve rearrangement in the unknown portion of gelsemine was recognized. Since bromoallogelsemine can be reduced to gelsemine (16), any such rearrangement could occur only during the reduction with lithium aluminum hydride. If the di-tosyl derivative, XVIIIb, of the amino-alcohol were formed, elimination of tosylate would lead to formation of dihydrodesoxotosylgelsemine, XVIa, provided that no rearrangement had occurred. However, the amino-alcohol was converted to an uncrystallizable gum by treatment with tosyl chloride in pyridine. The product could not be purified by chromatography.



Bromoallogelsemine
hydrobromide, XVII



XVIII a) R = R' = H
b) R = R' = Ts
c) R = R' = $COCH_3$
d) R = $COCH_3$, R' = H



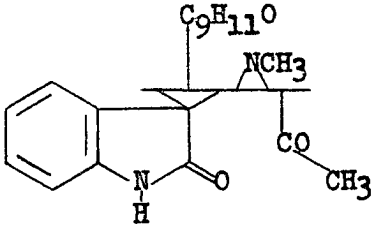


Plate 5. Diagram

Infrared spectra of this gum showed that some sulfonamide had been formed, but that both alcohol and amino groups still were present. Attempted tosylation of the amino-alcohol under more forcing conditions caused formation of intractable tars.

Oxidation of desoxooxytetrahydrogelsemine, XVIIIa, with chromic anhydride-pyridine reagent (34) caused formation of an amorphous product which could not be purified. It was felt that a more specific oxidation could be carried out and the probability of obtaining a single, clean product increased, if the secondary amine were blocked before oxidation.

The amino-alcohol was converted to the amide-acetate, XVIIIc, with acetic anhydride in pyridine. The product was a non-crystalline solid with an infrared spectrum (Figure 9) showing the expected absorption at 5.82μ and 6.08μ, and no absorption in the 3.0μ region. The amide-acetate was hydrolyzed at room temperature to form the amide-alcohol, XVIIId, also a non-crystalline solid. The infrared spectrum of this product (Figure 9) showed absorption at 2.95μ and 6.10μ, and no absorption in the 5.8μ region.

Oxidations of the amide-alcohol with chromic anhydride in acetic acid formed amorphous products and tars. Infrared spectra of the amorphous products showed broad absorption bands around 5.92μ and the characteristic amide absorption at

6.09μ, indicating that the former oxindole ring had not been oxidized. In one case, the infrared spectrum of a crude product showed slight absorption at 5.75μ, possibly indicative of an aldehyde. Chromatography of the crude product failed to provide an enriched sample of this material, however. No pure 2,4-dinitrophenyl-hydrazone derivatives of the amorphous products could be isolated. Oxidations of the amide-alcohol with chromic anhydride-pyridine reagent also formed amorphous products, the infrared spectra of which were very similar to those of the acid oxidation products.

A final attempt to selectively oxidize the double bond also involved utilization of bromoallogelsemine hydrobromide XVII. If hydrogen bromide could be eliminated from the bromo-imino ether, hydrolysis of the resulting unsaturated compound would form a new carbonyl group. This approach also would confirm the proposed structure of the bromo-imino ether.

Treatment of bromoallogelsemine hydrobromide with silver nitrate in anhydrous pyridine produced a mixture which could not be purified by chromatography. Infrared spectra indicated that most of the mixture was bromoallogelsemine, formed by the action of pyridine, and that only a small amount of unsaturation was present.

The mixture was hydrolyzed and two noncrystalline products obtained. The infrared spectrum of the minor product showed a

split carbonyl peak at 5.83μ and 5.9μ and absorption at 2.95μ, possibly indicating that no hydroxyl group had been freed by hydrolysis. The spectrum of the major product showed a double absorption peak at 2.95μ and 3.1μ, implying that this product was the oxindole-alcohol formed by hydrolysis of bromoallogelsemine.

Amine

As was discussed in the Historical Section, standard degradations of the tertiary amine function of gelsemine have produced anomalous results or led to dead ends as far as structure elucidation was concerned. The most promising treatment seemed to be a mild oxidation with ethyl azodicarboxylate, attacking the methylene group adjacent to the amine and causing formation of a carbinol amine, XIX (19). Oxidation of this carbinol amine produced a lactam which could not be hydrolyzed. A method for possible utilization of this mild oxidation had to avoid the formation of the lactam. If the barbinol amine could be cleaved and the carbonyl function changed so that it could not recombine with the amine, a new point of attack would be opened in the gelsemine molecule.

Gelsemine was treated with ethyl azodicarboxylate by the method of Habgood and Marion (19) and the unisolated adduct reduced by a Wolff-Kishner procedure. The crude reduction product was acetylated. Chromatography of the acetylated product,

XX, produced no clear separation but a major fraction was obtained. Infrared spectra (Figure 10) of this fraction showed strong absorption at 6.12μ and weak absorption at 7.2, 7.3 and 7.5μ, indicating that the tertiary amine had been cleaved by the procedure.

The resultant amide proved to be resistant to hydrolysis by mild treatments and decomposed when hydrolyzed under forcing conditions.

In an attempt to obtain a crystalline product and get unequivocable proof of the ring cleavage, the oxidation-reduction procedure was repeated and the crude reduction product treated with toluenesulfonyl chloride. The resulting sulfonamide was gummy and could not be purified by chromatography. Infrared spectra indicated, however, that ring cleavage had occurred and that the sulfonamide had been formed.

Although no crystalline products had been obtained, infrared spectra indicated that the series of reactions was promising enough to warrant further investigation along this line of attack. Dihydrogelsemine was oxidized with ethyl azodicarboxylate and reduced by the same manner as in the earlier experiment with gelsemine. To avoid formation of the unhydrolyzable amide, the reduction product was methylated by the Eschweiler reaction (33, p. 307). The crude methylation

product was acetylated to allow separation of any residual secondary amines. An extraction procedure divided the acetyl product into a major basic fraction and a minor neutral fraction, the infrared spectrum of which indicated that some amide had been formed. The infrared spectrum (Figure 10) of the major basic fraction, XXI, was similar to that of dihydrogelsemine, but differed sufficiently in the 7μ to 9μ region to indicate that reaction had indeed occurred.

To complete removal of the amino group released by ring cleavage, the tertiary amine formed by the Eschweiler reaction was oxidized with mercuric acetate, a procedure developed in the field of indole alkaloids by Weisenborn and Diassi (47) and Wenkert and Roychaudhuri (48). Most of the starting material was recovered, but a small amount of a neutral product, XXII, was isolated. The infrared spectrum of this product exhibited a double peak at 5.83μ and 5.90μ, possibly indicative of a keto group. However, no 2,4-dinitrophenylhydrazone derivative of this product could be formed.

To insure that the ketone formed was not a result of mercuric acetate oxidation of some part of the alkaloid other than in the area of the amine, a sample of gelsemine was treated with mercuric acetate under the same conditions as used for the Eschweiler product. No trace of ketone-containing material could be found.

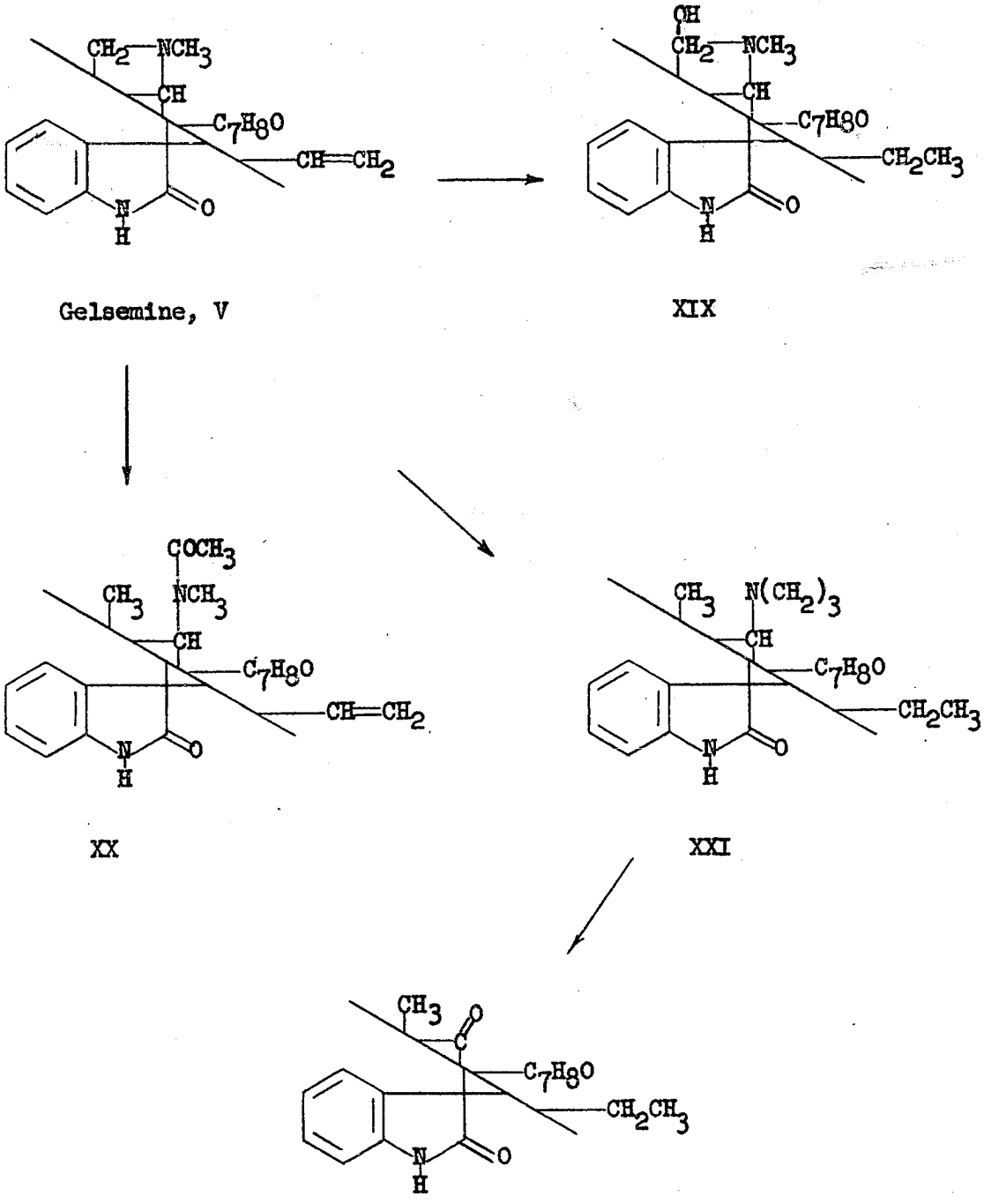

CH2—NCH3
CH
C7H8O
CH=CH2
N
H
O
Gelsemine, V
OH
CH2—NCH3
CH
C7H8O
CH2CH3
N
H
O
XIX
COCH3
CH3
NCH3
CH
C7H8O
CH=CH2
N
H
O
XX
CH3
N(CH2)3
CH
C7H8O
CH2CH3
N
H
O
XXI
CH3
O
C
C7H8O
CH2CH3
N
H
O
XXII

Plate 6.

Part of the tertiary amine formed by the Eschweiler reaction was treated with methyl iodide to form a gummy, non-crystallizable product. This product was degraded under Hofmann conditions to a tarry product, infrared spectra of which were almost identical with those of the tertiary amine.

Examination of the proposed structure IV indicates that elimination of the ammonium group under Hofmann conditions is not favored, and that demethylation was forced. Although the inavailability of a crystalline, analyzable methiodide prevented proof of the quaternization and demethylation, the results of Hofmann reactions on several gelsemine derivatives (20, 23, 37, 51) indicate that this sequence of reactions, from dihydrogelsemine to the Eschweiler product, had not otherwise affected the immediate environment of the amino nitrogen atom.

SPECTRA

Ultraviolet spectra were measured with a Beckman DU Spectrophotometer, using solutions of compounds in 95% ethanol.

Infrared spectra were measured with a Baird Recording Infrared Spectrophotometer. Solvent used is noted on each spectrum.

Figure 1. Ultraviolet spectra

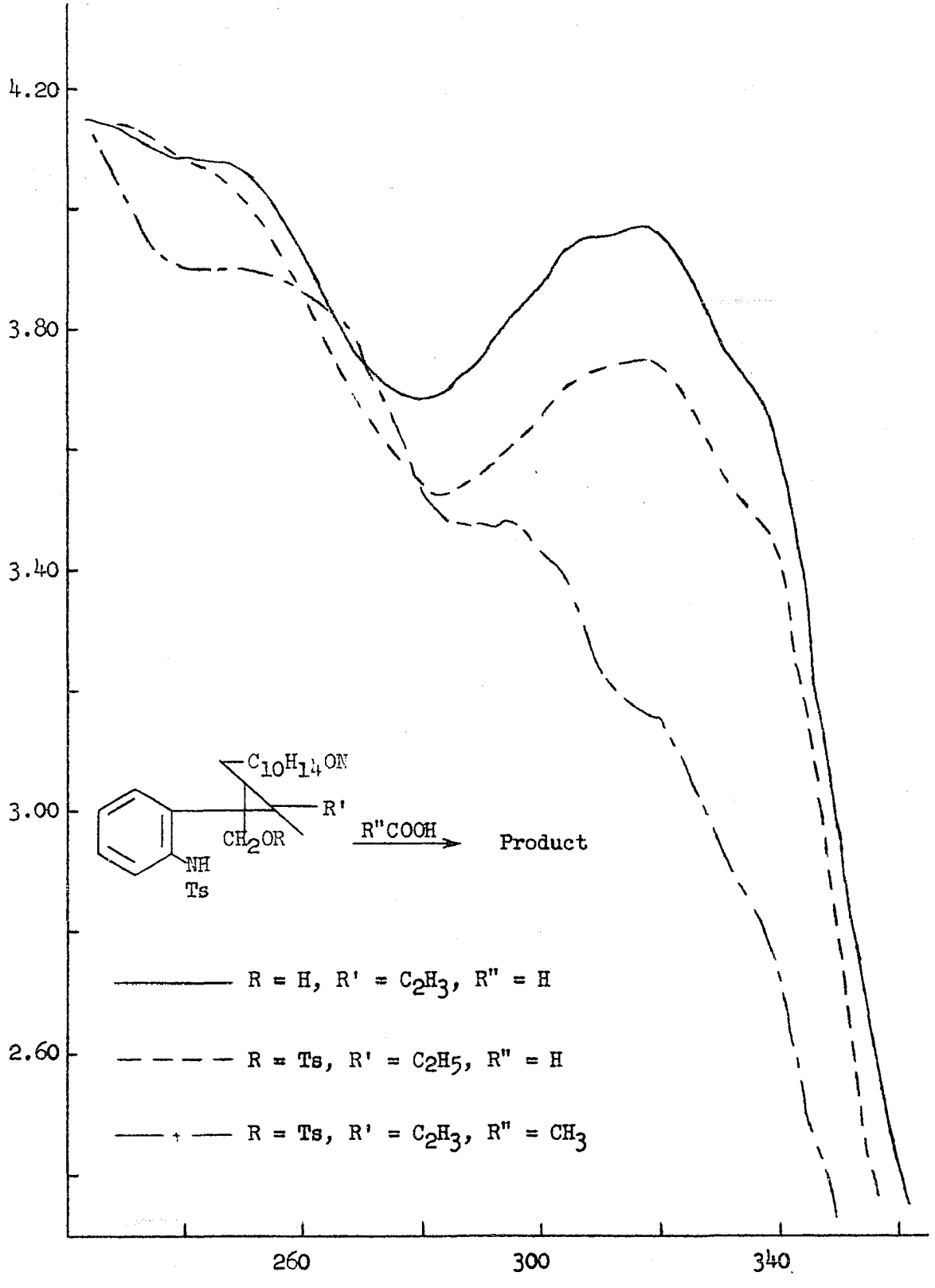

4.20
3.80
3.40
3.00
2.60
260
300
340
$C_{10}H_{14}ON$
R'
CH_2OR
NH
Ts
R"COOH
Product
R = H, R' = C_2H_3, R" = H
R = Ts, R' = C_2H_5, R" = H
R = Ts, R' = C_2H_3, R" = CH_3

Figure 2. Ultraviolet spectra

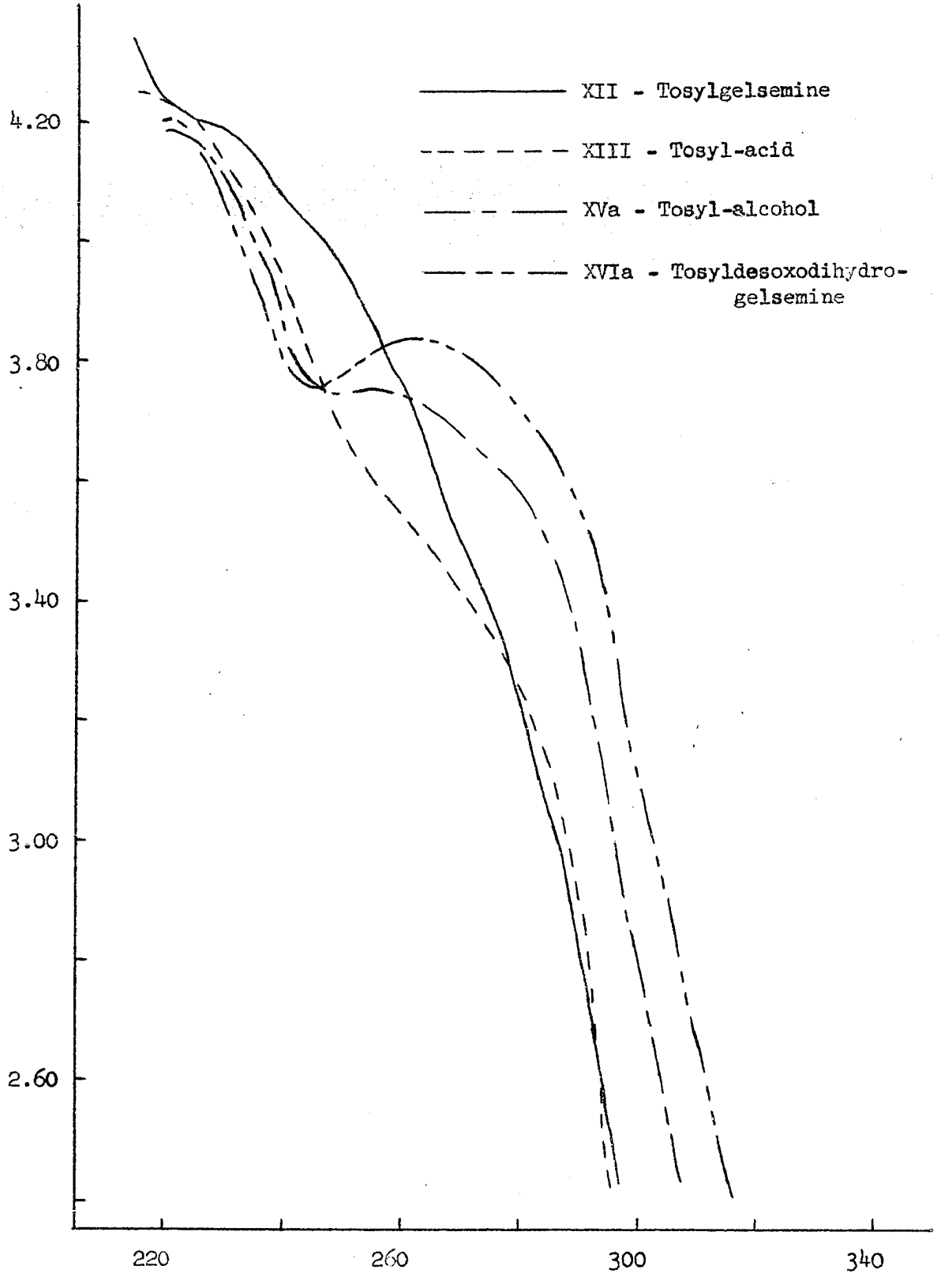

XII - Tosylgelsemine
XIII - Tosyl-acid
XVa - Tosyl-alcohol
XVIa - Tosyldesoxodihydro-gelsemine
4.20
3.80
3.40
3.00
2.60
220
260
300
340

Figure 3. Ultraviolet spectra

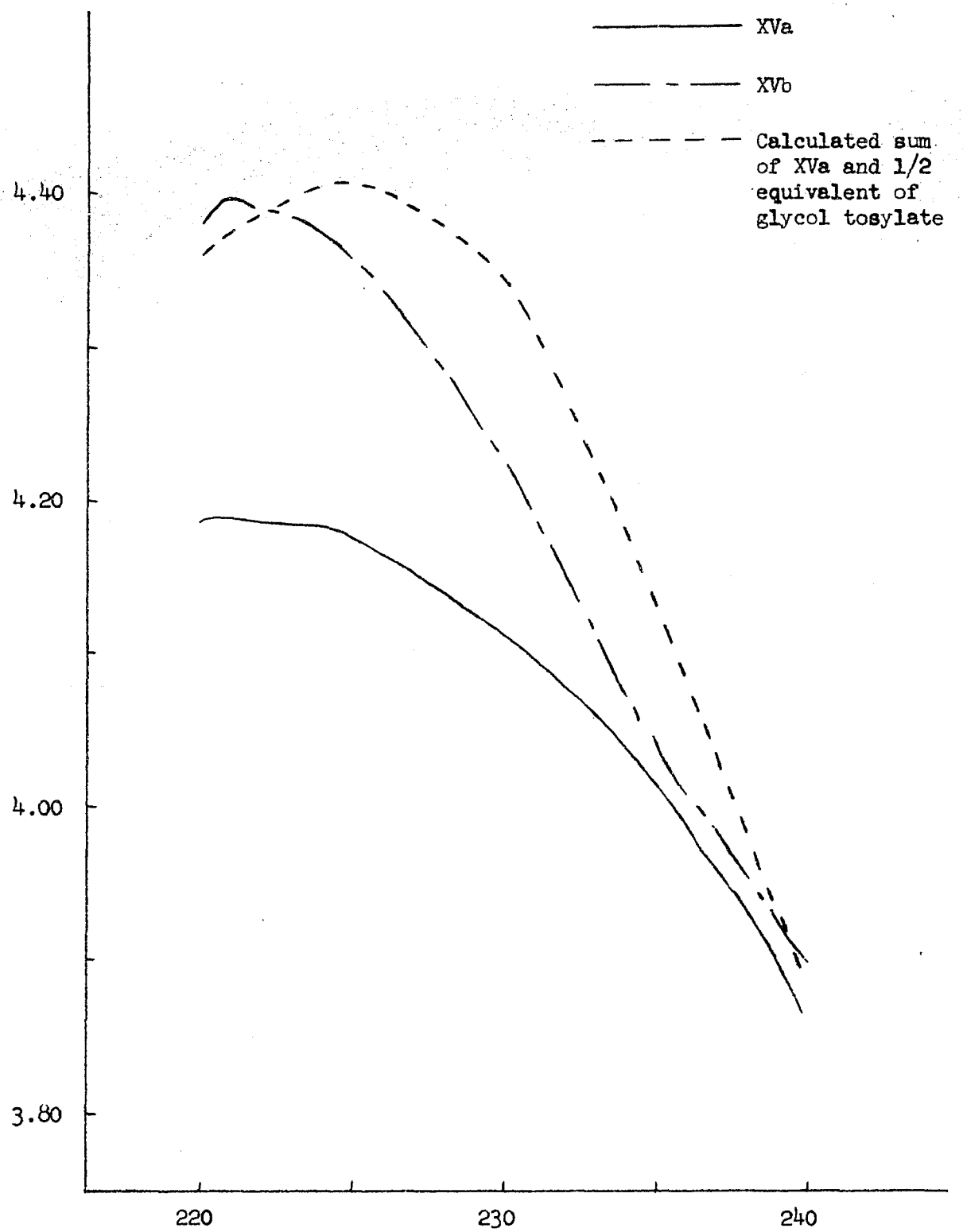

XVa
XVb
Calculated sum of XVa and 1/2 equivalent of glycol tosylate
4.40
4.20
4.00
3.80
220
230
240

Figure 4. Ultraviolet spectra

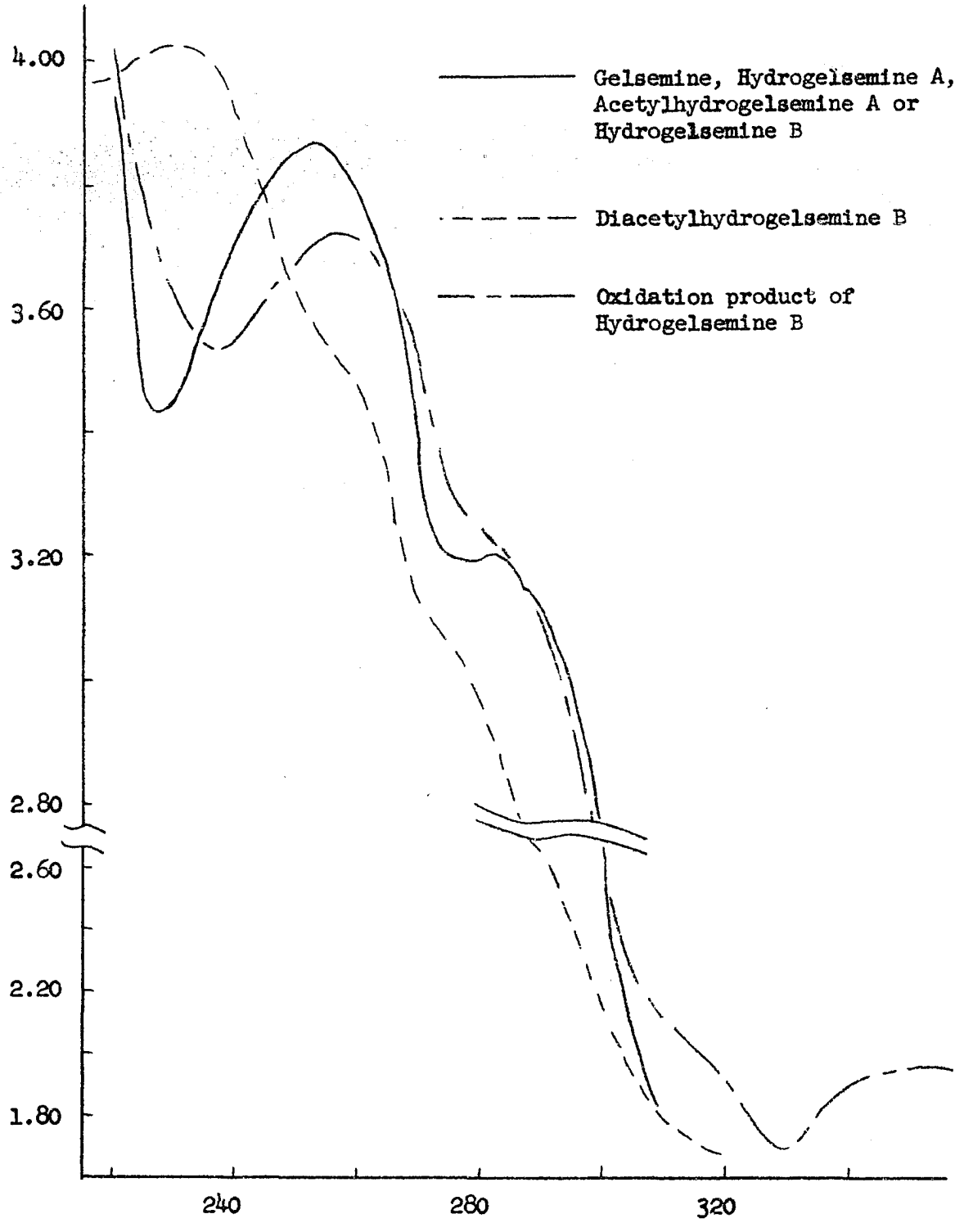
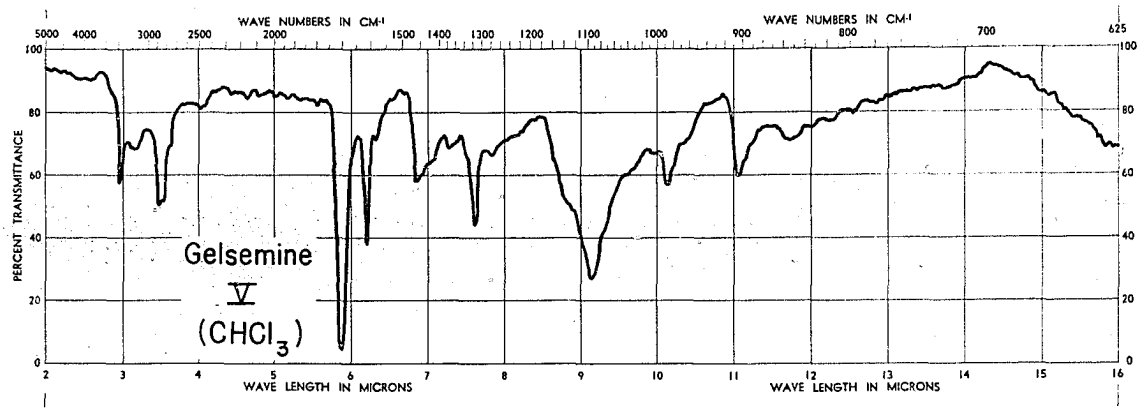
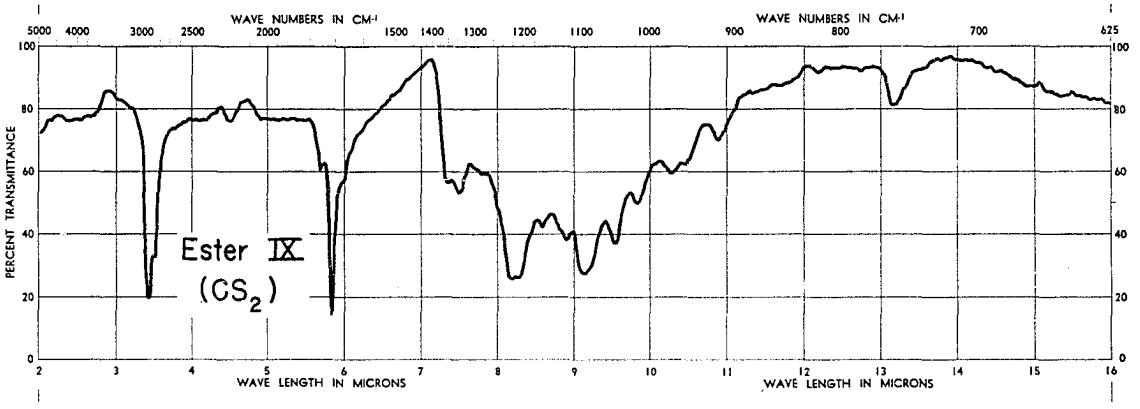

4.00
3.60
3.20
2.80
2.60
2.20
1.80
240
280
320
Gelsemine, Hydrogelsemine A, Acetylhydrogelsemine A or Hydrogelsemine B
Diacetylhydrogelsemine B
Oxidation product of Hydrogelsemine B

Figure 5. Infrared spectra


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
100 80 60 40 20 0
Gelsemine
V
(CHCl3)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
100 80 60 40 20 0
Ester IX
(CS2)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVE LENGTH IN MICRONS

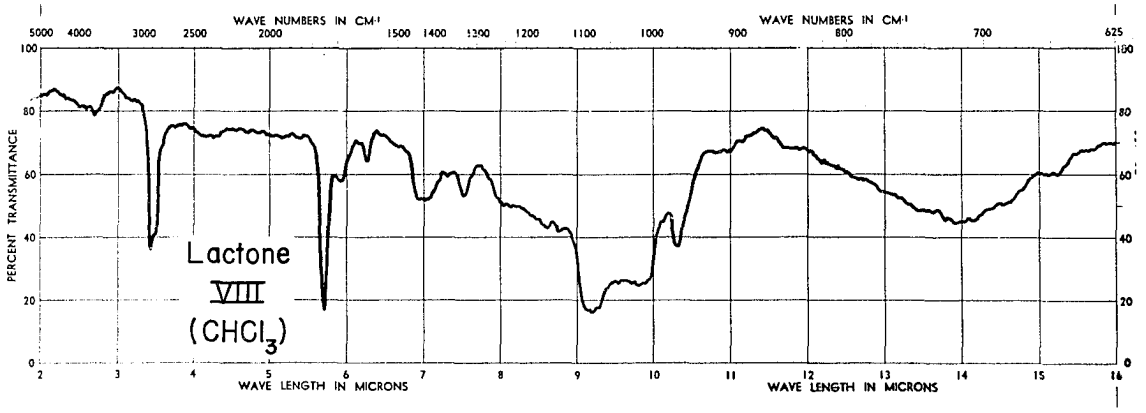
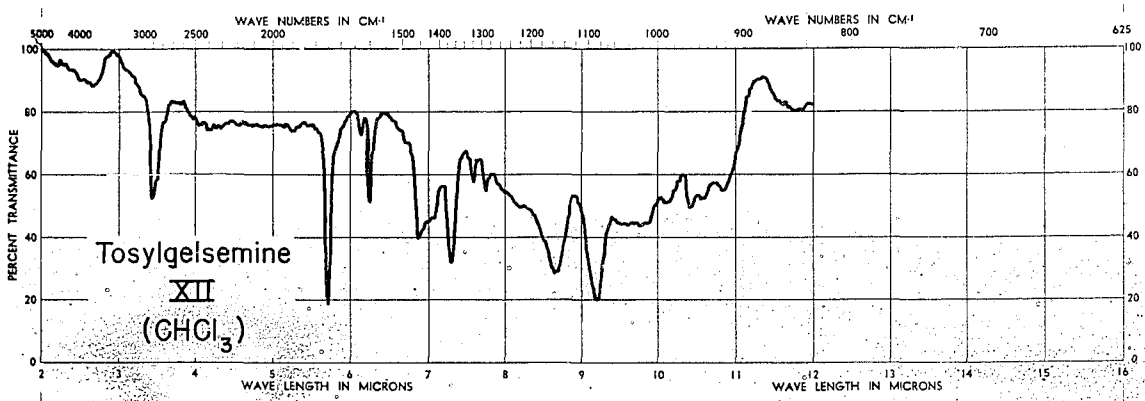
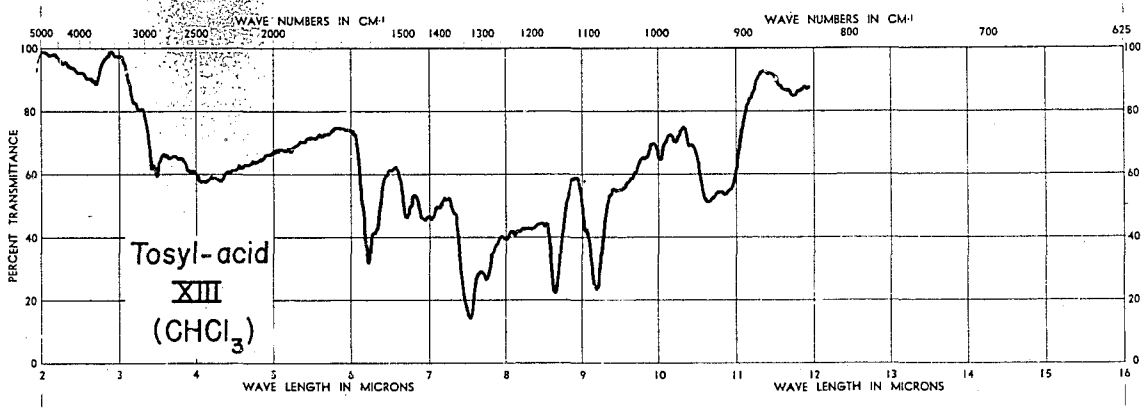

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
100 80 60 40 20 0
Lactone
VIII
(CHCl3)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVE LENGTH IN MICRONS

Figure 6. Infrared spectra


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
100 80 60 40 20 0
Tosylgelsemine
XII
(CHCl3)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
100 80 60 40 20 0
Tosyl-acid
XIII
(CHCl3)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVE LENGTH IN MICRONS

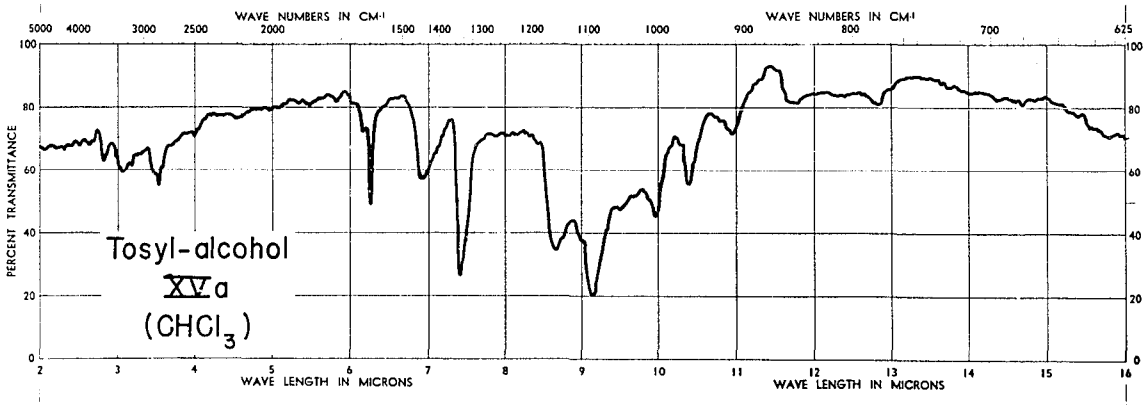
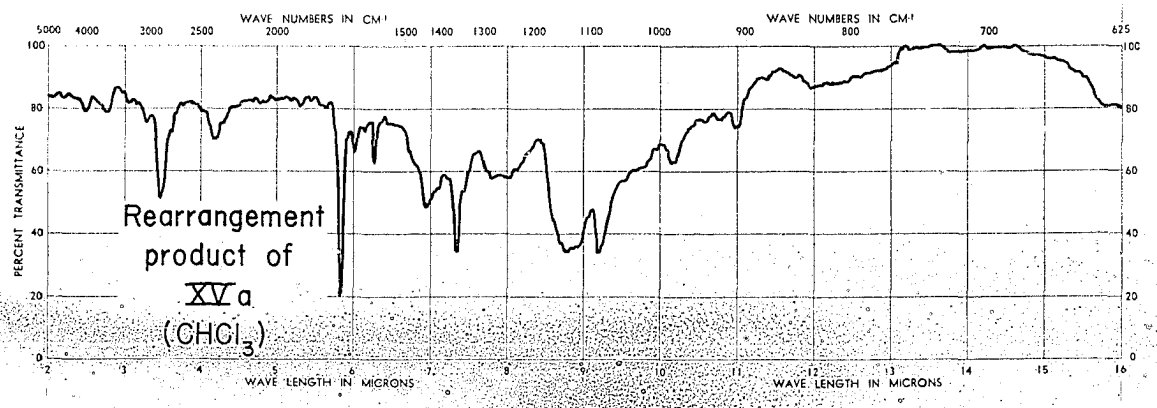
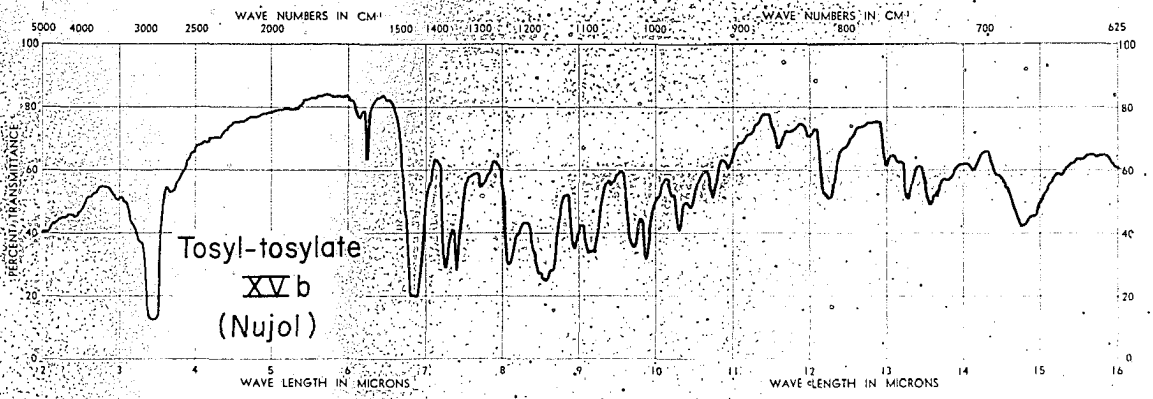
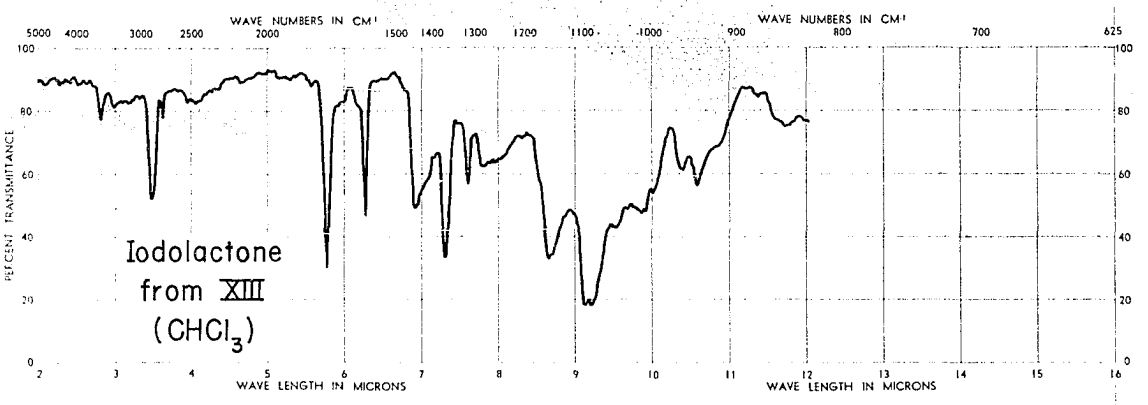

WAVE NUMBERS IN CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
100 80 60 40 20 0
Tosyl-alcohol
XVa
(CHCl3)
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVE LENGTH IN MICRONS

Figure 7. Infrared spectra


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Rearrangement product of XV a (CHCl3)
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Tosyl-tosylate XV b (Nujol)
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Iodolactone from XIII (CHCl3)
WAVE LENGTH IN MICRONS

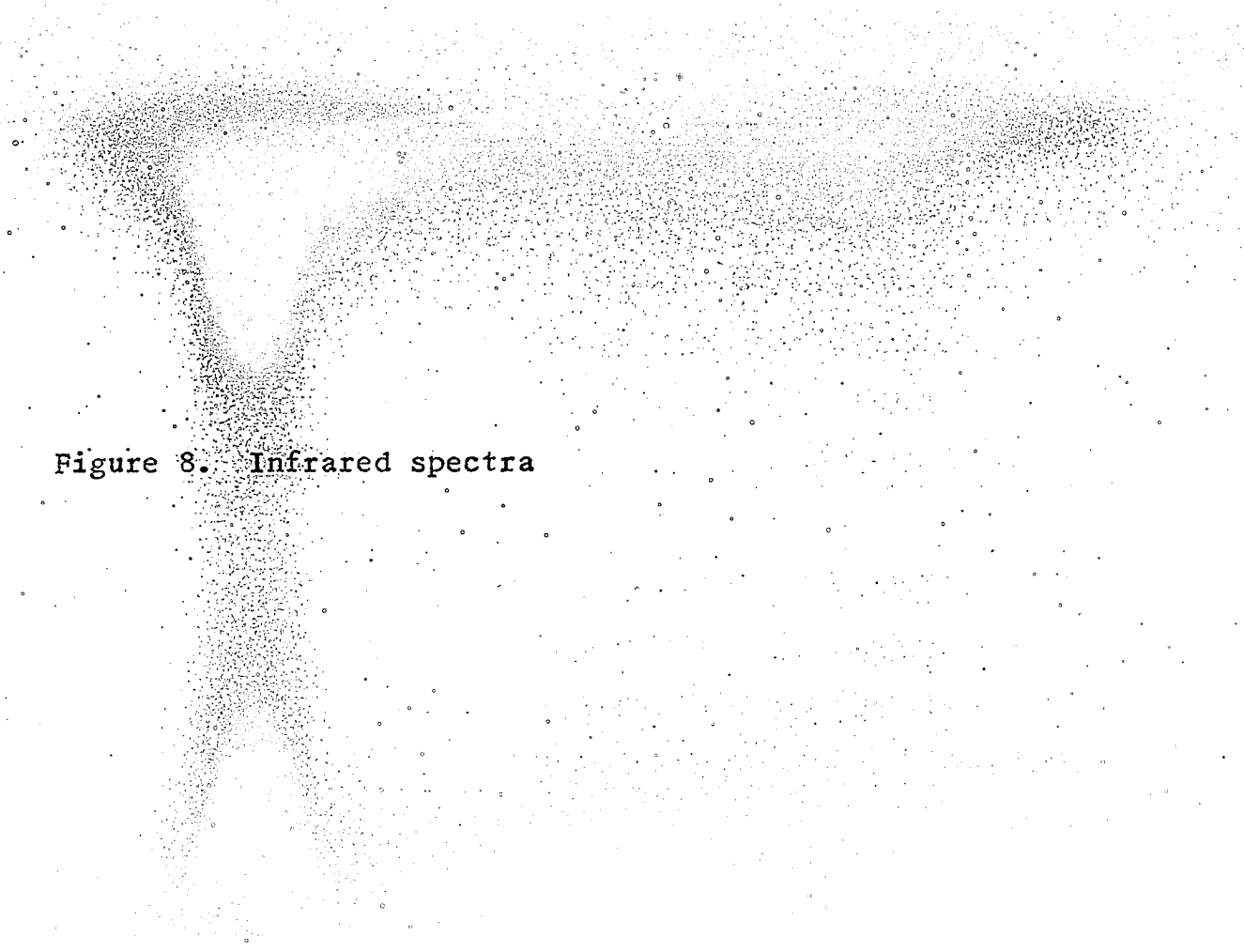
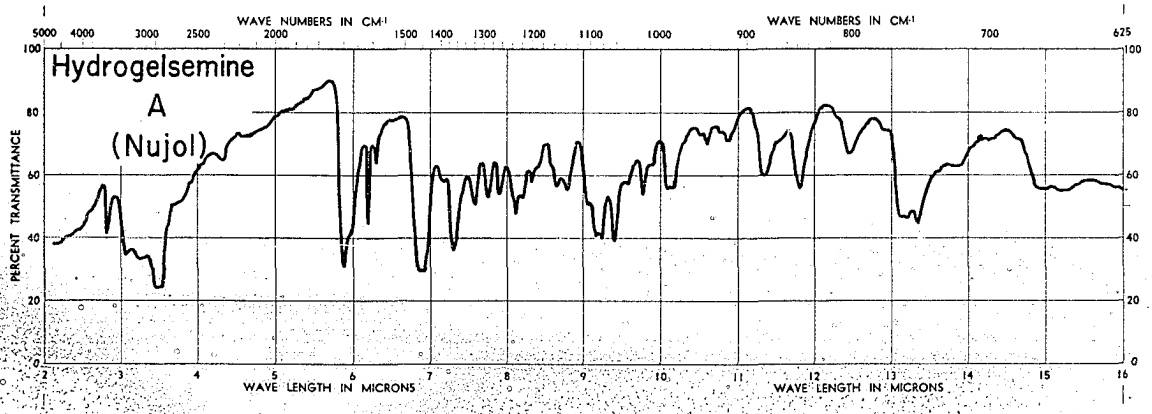
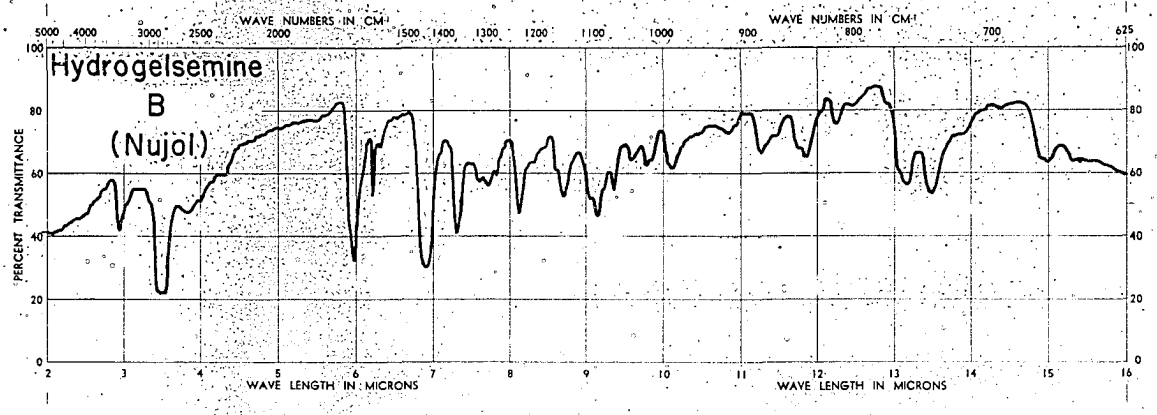
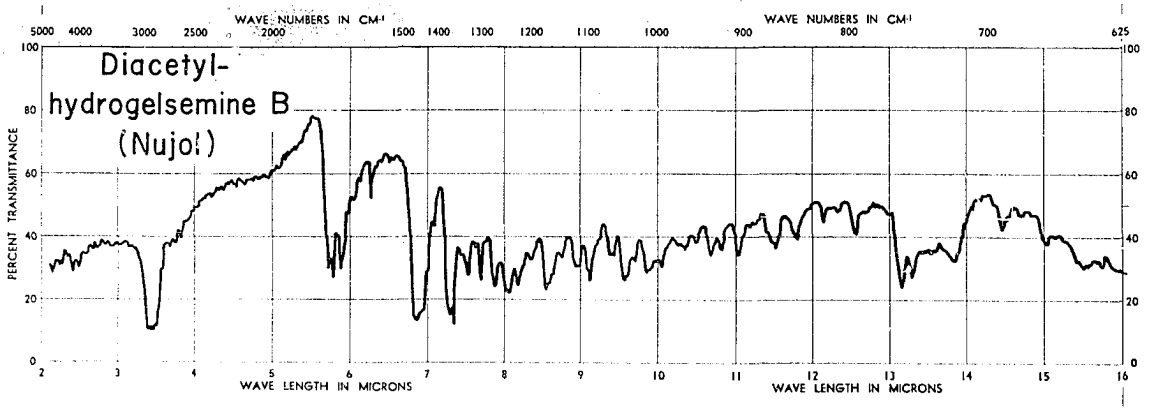


Figure 8. Infrared spectra


Hydrogelsemine
A
(Nujol)
WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS


Hydrogelsemine
B
(Nujol)
WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS


Diacetyl-
hydrogelsemine B
(Nujol)
WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
WAVE LENGTH IN MICRONS

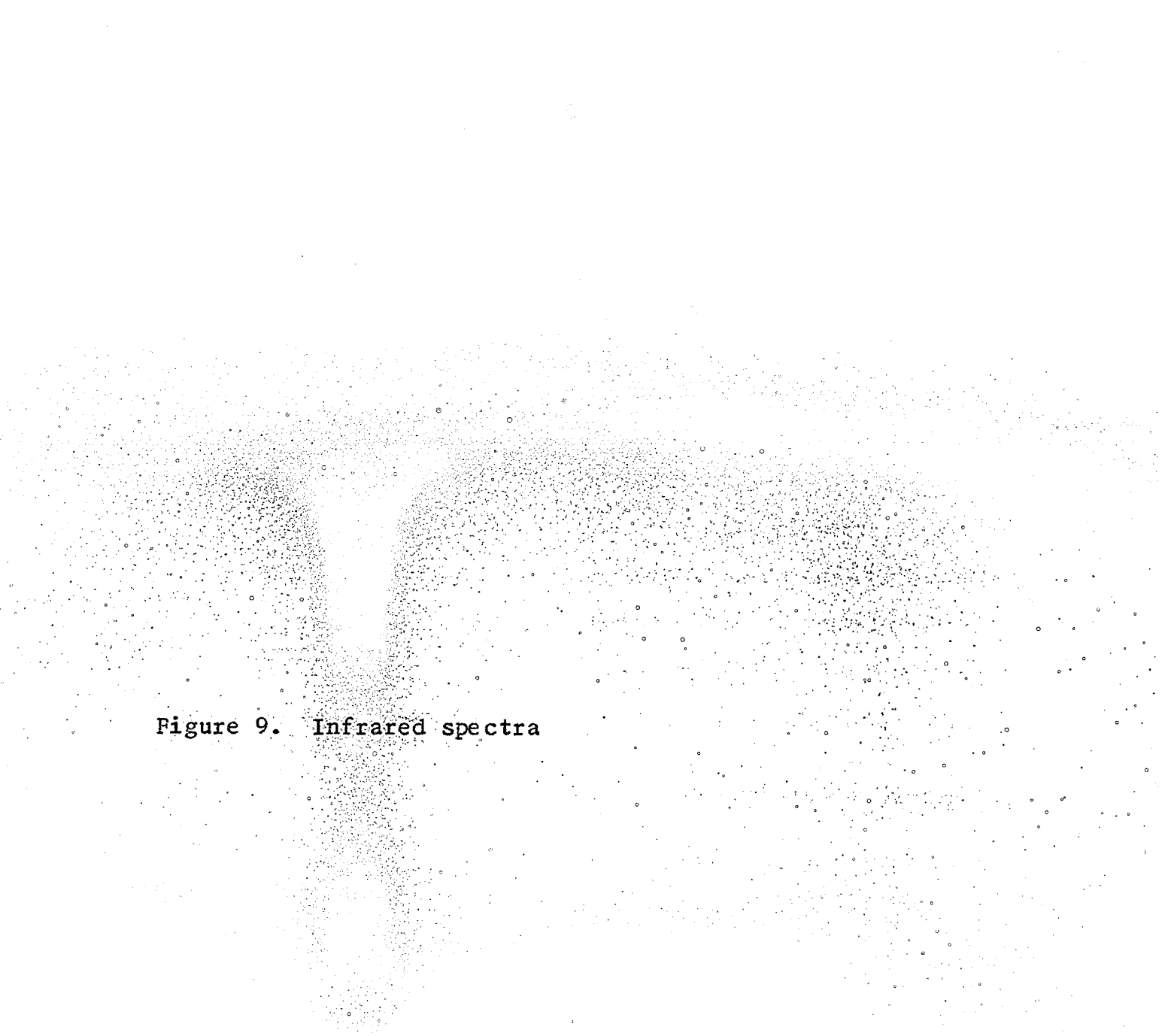
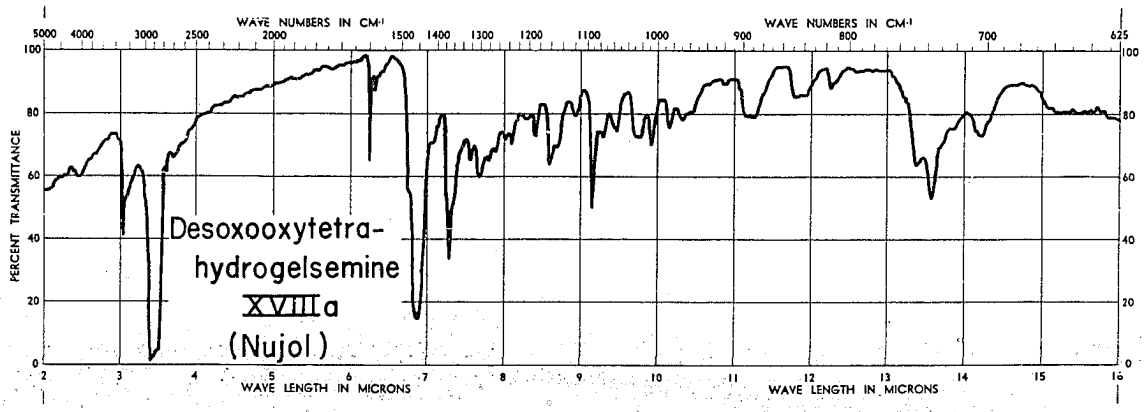
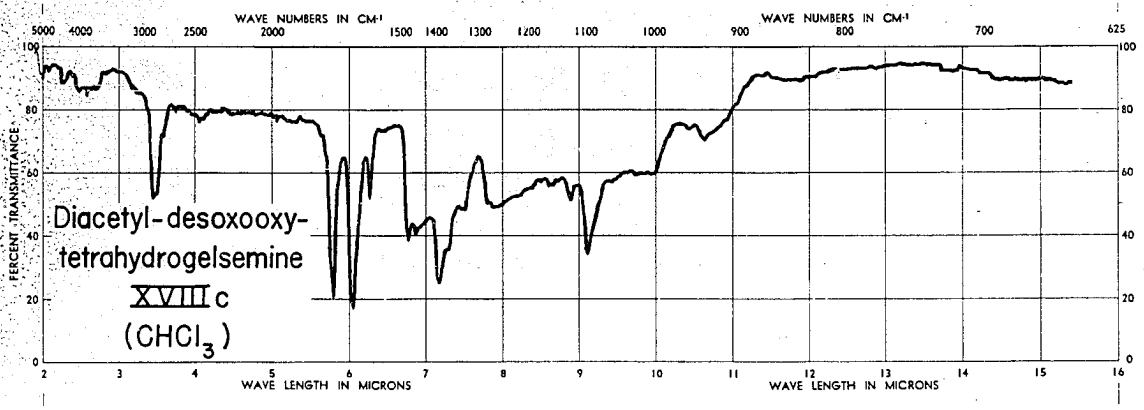


Figure 9. Infrared spectra


WAVE NUMBERS IN CM⁻¹
WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Desoxooxytetra-
hydrogelsemine
XVIII a
(Nujol)
WAVE LENGTH IN MICRONS
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Diacetyl-desoxooxy-
tetrahydrogelsemine
XVIII c
(CHCl3)
WAVE LENGTH IN MICRONS
WAVE LENGTH IN MICRONS

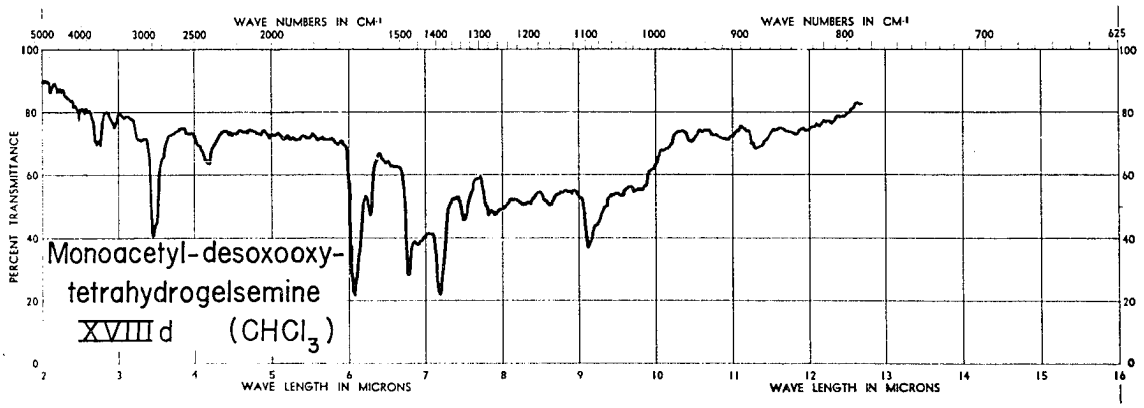
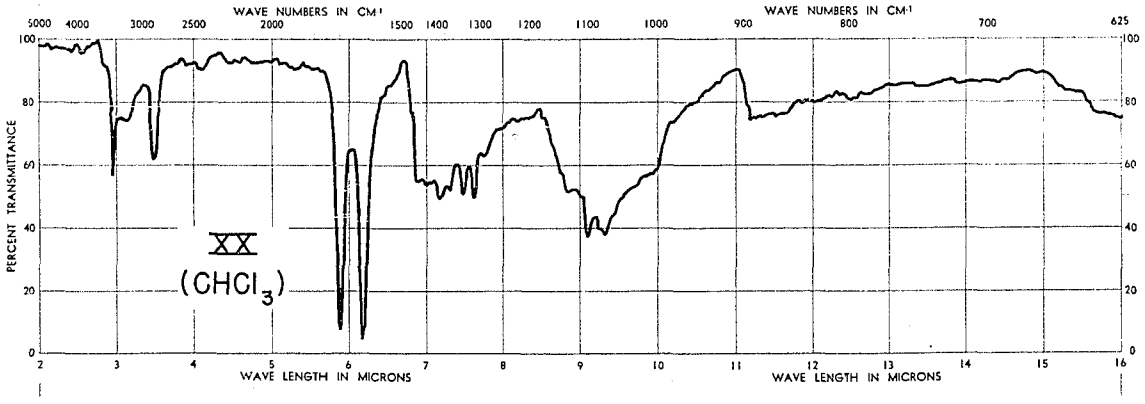
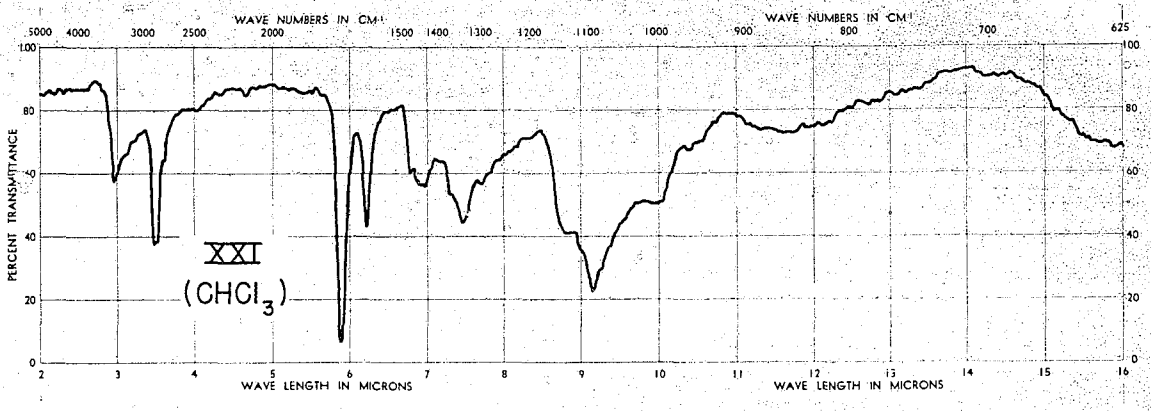

WAVE NUMBERS IN CM⁻¹
WAVE NUMBERS IN CM⁻¹
PERCENT TRANSMITTANCE
Monoacetyl-desoxooxy-
tetrahydrogelsemine
XVIII d (CHCl3)
WAVE LENGTH IN MICRONS
WAVE LENGTH IN MICRONS

Figure 10. Infrared spectra


WAVE NUMBERS IN CM⁻¹
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
XX
(CHCl3)
WAVE LENGTH IN MICRONS
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16


WAVE NUMBERS IN CM⁻¹
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 625
PERCENT TRANSMITTANCE
XXI
(CHCl3)
WAVE LENGTH IN MICRONS
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

EXPERIMENTAL

Microanalyses were made by: 1) Strauss and Weiler Microanalytical Laboratory, Oxford, England; 2) Midwest Microlab, Inc., Indianapolis, Indiana; and 3) L. Dorfman, Ciba, Summit, New Jersey.

Optical rotations were measured with an O. C. Rudolph polarimeter using pyridine solutions of compounds at room temperature.

All melting point measurements are the uncorrected values observed.

Adsorbents for chromatography

Activated alumina, chromatography grade, 80-200 mesh, was used in most operations which would not be affected by the basic character of the adsorbent. For chromatography of sensitive compounds, alumina was neutralized by stirring it with ethyl acetate for 48 hours. The neutral alumina was filtered, then washed by slurrying once with methanol and twice with water. After a final methanol wash and filtration to remove most of the solvent, the adsorbent was reactivated by drying at 120° for 24 hours.

Octahydrogelsemine, VI

Octahydrogelsemine was prepared by hydrogenation of gelsemine, at 3 atmospheres and 50°, in acetic acid with Adams

catalyst. White crystals, m.p. 158-166°, reported 165-167° (16), were obtained by crystallization from acetone. The infrared spectrum of this compound showed a shift of the carbonyl band to 5.95μ, consistent with the saturation of the aromatic ring.

N-Nitroso-octahydrogelsemine, VII

Sodium acetate, 3 g., was slurried in a solution of 1.01 g. octahydrogelsemine in 100 ml. ice-cold carbon tetrachloride. To the slurry was added 20 ml. of an 0.8 N solution of nitrogen tetroxide in carbon tetrachloride, one ml. at a time over a period of 20 minutes with constant stirring. An additional 5 g. sodium acetate and 20 ml. nitrogen tetroxide solution were added and the mixture stirred at 0° for half an hour. The mixture was then washed with 150 ml. ice-cold sodium carbonate solution and the aqueous layer washed with three 50 ml. portions of chloroform. The combined organic layer was dried immediately over magnesium sulfate, filtered and reduced under vacuum to a solid, bright yellow foam, m.p. 95-115°. Infrared spectra, with absorptions at 4.44μ and 5.72μ, indicated the N-nitroso compound had been formed, but absorption at 5.95μ indicated that the compound was contaminated with an estimated 25% of starting material. The product could not be crystallized from common solvents. Because of the expected sensitivity of the nitroso compound, no further attempt was made

to purify the compound and it was used in the impure state in further experiments.

Ester, IX

The yellow nitroso compound, ca. one gram, was refluxed in a solution of 1.87 g. sodium in 125 ml. anhydrous methanol for 8 hours. The methanol was removed under vacuum and the residue partitioned between chloroform and water. After drying and filtration of the organic layer, the solvent was removed and the residue chromatographed on neutral alumina. A major fraction, eluted with benzene, was a yellow gum, shown by its infrared spectrum (Figure 5) to consist mainly of the ester, IX, and a small amount of the lactone, VIII.

Hydrochloric acid treatment of ester, IX

A solution of 200 mg. crude ester, IX, in 25 ml. dioxane, 10 ml. hydrochloric acid and 40 ml. water was refluxed for 20 hours. The solvent was removed under vacuum and the residue partitioned between chloroform and dilute sodium hydroxide solution. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The dark residue was dissolved in benzene and chromatographed, a major fraction being obtained with 2:1 benzene-ether. An infrared spectrum of this fraction showed weak absorptions at 6.05μ and 6.17μ which were not apparent in the spectrum of the ester.

Lactone, VIII

A solution of 150 mg. ester, IX, in 30 ml. 48% hydrobromic acid was refluxed for 5 hours. Most of the solvent was removed by distillation, the remaining liquid dissolved in water and washed with chloroform. The aqueous layer was made basic with sodium hydroxide and the basic organic material extracted with chloroform. The chloroform layer was dried, filtered and reduced to dryness. The residue was dissolved in benzene and chromatographed, a major fraction being obtained with 4:1 benzene-ether. The infrared spectrum of this fraction (Figure 5) exhibited strong absorption at 5.7μ, indicating that the ester had been converted to a lactone.

Bromine oxidation of octahydrogelsemine

A solution of 0.55 g. bromine in 50 ml. anhydrous methanol was added to a solution of 80 mg. sodium and 1.14 g. octahydrogelsemine in 85 ml. anhydrous methanol and the resulting colorless solution refluxed for 90 minutes. Most of the methanol was distilled off and a solution of 0.5 g. sodium hydroxide in 50 ml. ethanol and 125 ml. water was added to the residue. The orange-colored solution was refluxed for 90 minutes. The basic organic material was extracted with chloroform, isolated and chromatographed. Elution with 7:3 benzene-ether brought down a major fraction which was shown to be unreacted octahydrogelsemine. A minor fraction of brown materi-

al was eluted with chloroform. The infrared spectrum of this material showed reduced absorption at 2.96μ and a new band at 6.07μ.

p-Toluenesulfonimidogelsemine, XII

A solution of 3.08 g. (0.00956 mole) of acetone-free gelsemine in 100 ml. anhydrous benzene was stirred and refluxed under nitrogen with 0.40 g. (0.0102 atom) potassium for 16 hours. About 25 ml. of eighth-inch glass beads were added to grind the solids formed. To the resulting cream-colored suspension was added a solution of 1.84 g. (0.00965 mole) of p-toluenesulfonyl chloride in 40 ml. anhydrous benzene and the refluxing and stirring continued for 8 hours. A solution of 50 ml. water and 35 ml. methanol then was added slowly and the mixture stirred for an hour while cooling to room temperature. The aqueous layer was made more basic (pH 10) with sodium hydroxide and the layers separated. The organic layer was washed with water and the aqueous layers washed with two 50 ml. portions of benzene. The combined organic layer was dried over magnesium sulfate, filtered and chromatographed on neutral alumina. A major fraction was eluted with benzene. A minor fraction, which proved to be unreacted gelsemine, was eluted with chloroform. The major fraction was crystallized from ether. After four recrystallizations, 2.35 g. (52%) of white needles were obtained, m.p. 133-135°, $[\alpha]_D$ - 27.4°,

Anal. Calcd. for $C_{27}H_{28}O_4N_2S$: C, 68.05; H, 5.92; N, 5.88. Found: C, 67.98; H, 5.95; N, 6.05.

Workup of the mother liquors gave an additional 1.40 g. (31%) of tosylgelsemine, m.p. 130-134°.

p-Toluenesulfonimidogelsemine methiodide

p-Toluenesulfonimidogelsemine methiodide was formed by refluxing a solution of tosylgelsemine in chloroform with excess methyl iodide for an hour. The residue remaining after the solvent was removed was crystallized from methanol. After three recrystallizations, white flakes were obtained, m.p. 250-252° dec., $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{28}H_{31}O_4N_2SI$: C, 54.37; H, 5.05; N, 4.53. Found: C, 54.43; H, 5.37; N, 4.47.

A solution of 275 mg. of the methiodide and 90 mg. sodium hydroxide in 30 ml. ethylene glycol and 10 ml. water (b.p. ca. 120°) was refluxed for a day under an atmosphere of nitrogen. No neutral product could be isolated by extraction of the reaction mixture. A similar reaction solution was placed in a sealed tube and heated at 150°C for 18 hours. Again, no neutral product could be extracted from the reaction mixture.

p-Toluenesulfonamido-acid, XIII

To a solution of 0.50 g. (0.00105 mole) tosylgelsemine in 40 ml. ethanol was added a solution of 0.162 g. (0.00405 mole)

sodium hydroxide in 30 ml. water. The resulting solution was refluxed for 22 hours and the ethanol distilled off. The aqueous solution was made acidic with hydrochloric acid, then made basic (pH 8) with sodium bicarbonate. The cloudy solution was extracted with ten 60 ml. portions of chloroform and the combined organic layer dried over sodium sulfate. (During another preparation, a white precipitate, formed when the aqueous solution was made basic, could not be extracted with chloroform. It was filtered out and purified in the same manner as the product extracted with chloroform). The solution was filtered and the solvent removed, leaving 0.45 g. (87%) of white solid which was crystallized from methanol. After four recrystallizations, 0.25 g. (48%) small white crystals were obtained, m.p. 185-187°.

The analytical sample was dried under vacuum at 100° for 3 hours.

Anal. Calcd. for $C_{27}H_{30}O_5N_2S\ CH_3OH$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.93; H, 6.45; N, 5.50.

Gelsemine from toluenesulfonamido-acid

To a solution of 0.50 g. (0.00101 mole) of the toluenesulfonamido-acid in 50 ml. ethylene glycol was added a solution of 0.0095 g. (0.000237 mole) of sodium hydroxide in 2.5 ml. water. The solution was distilled until the vapor temperature

was 193°, then refluxed under nitrogen for 2 hours. The solvent was removed under vacuum and the residue dissolved in 50 ml. dilute (pH 2) hydrochloric acid. The solution was extracted with chloroform, then made basic with sodium bicarbonate and extracted with four 50 ml. portions of chloroform. The combined basic extract was dried over sodium sulfate, filtered and the solvent removed, leaving 0.030 g. (91%) of white solid. The infrared spectrum showed that the solid was gelsemine, so it was recrystallized from acetone, giving white crystals, m.p. 173-177°, mixed m.p. with gelsemine acetonide 174-177°.

Tosylgelsemine from toluensulfonamido-acid

To a suspension of 100 mg. of the toluenesulfonamido-acid in 5 ml. water was added slowly 5 ml. of concentrated sulfuric acid. The mixture was cooled to room temperature and allowed to stand for four hours, then poured over 15 g. ice. A flocculent white precipitate, soluble in chloroform, was formed. The resulting slurry was extracted with 175 ml. chloroform in four portions, the chloroform layers washed with a 5% sodium carbonate solution and the combined organic layer dried with magnesium sulfate. After filtration, the extract was dried under vacuum and the residue dissolved in 1:1 petroleum ether-benzene. The solution was chromatographed on neutral alumina, a major fraction (50 mg.) being eluted with benzene. The in-

frared spectrum of this fraction was identical with that of tosylgelsemine (Figure 6).

Attempted lactonization of the toluenesulfonamido-acid

A solution of 50 mg. toluenesulfonamido-acid, and 26 mg. iodine in 50 ml. chloroform was allowed to stand at room temperature in the dark for a day. No color change had occurred, so 1 gm. sodium bicarbonate was added and the mixture allowed to stand in the dark for sixteen days. The still-colored mixture was filtered and the solvent removed under vacuum. A solution of the residue in 1:1 benzene-chloroform was chromatographed on neutral alumina. Elution with the solvent mixture brought down a brown semisolid and a white, noncrystalline solid, the infrared spectra (Figure 7) of which were identical, and very similar to that of tosylgelsemine. However, a shift of the carbonyl absorption to 5.77μ, minor absorption at 2.8μ, a change in the 7.9μ region and a double peak at 9.1-9.2μ indicated that a reaction probably had occurred.

Schmidt reaction with toluenesulfonamido-acid

A solution of 120 mg. toluenesulfonamido-acid in one ml. ice-cold, concentrated sulfuric acid was covered with a layer of 15 ml. chloroform. Sodium azide was activated by precipitation of a water solution of the salt with acetone and 40 mg. of the dried precipitate was added to the two-phase reaction

mixture. As the reaction mixture was warmed to 40°C, gas was evolved. An additional 40 mg. of sodium azide was added and the mixture allowed to stand for ten minutes. The reaction mixture was diluted with 30 ml. water and allowed to stand for sixteen hours. After neutralization of the aqueous layer with sodium bicarbonate, the organic product was extracted with chloroform, the combined organic layer dried, filtered and reduced to dryness under vacuum. Infrared spectra of the crude product showed absorption at 2.95μ, 5.75μ(shoulder), 5.87μ, 7.3μ, 7.6μ and 8.7μ, indicating a mixture of tosyl-gelsemine and a product, presumably the urea, XIV. No appreciable purification was effected by chromatography on neutral alumina.

p-Toluenesulfonamido-alcohol, XVa

A mixture of 605 mg. (0.00127 mole) tosyl gelsemine and 45 mg. (0.00119 mole) lithium aluminum hydride in 50 ml. anhydrous dioxane was refluxed for 16 hours under an atmosphere of nitrogen. After hydrolysis with 10 ml. of a 9:1 methanol-water solution, the reduction mixture was dried under vacuum. The residue was dissolved in 40 ml. 5% hydrochloric acid and the aqueous layer stirred with 40 ml. chloroform as the mixture was slowly made basic with sodium carbonate. The resulting slurry was filtered and the solid was washed twice with 40 ml. portions of boiling chloroform. The two-phase filtrate was

separated and the aqueous layer washed with each of the chloroform layers. The combined organic layer was dried with sodium sulfate, filtered and dried under vacuum. The residue was crystallized four times from benzene. (In an earlier preparation with stoichiometric amounts of reagents, the crude product was chromatographed on neutral alumina. Starting material (35%) was eluted with benzene and fairly pure product (53%) was eluted with 4:1 benzene-chloroform.)

An analytical sample was recrystallized twice more from benzene and dried under high-vacuum for 4 hours at 100°, m.p. 265-266° dec., browning from 240°, $[\alpha]_D$-88.3°.

Anal. calcd. for $C_{27}H_{32}O_4N_2S$: C, 67.48; H, 6.71; N, 5.83. Found: C, 68.01; H, 6.38; N, 5.83.

Rearrangement of toluensulfonamido-alcohol

A solution of 200 mg. tosyl-alcohol in 20 ml. formic acid was refluxed under a nitrogen atmosphere for 70 hours. The reaction solution was reduced to a thick syrup under vacuum and the residue dissolved in 30 ml. 1% hydrochloric acid. The acid solution was made basic (pH 8) with sodium carbonate and extracted with three 30 ml. portions of chloroform. The combined chloroform layer was dried, filtered and dried under vacuum. The tar-like residue was dissolved in 1:1 benzene-

chloroform and chromatographed on neutral alumina. Elution with the solvent mixture brought down a major fraction which was identified as starting material by infrared spectra. A minor fraction (about 30 mg.) of gummy brown material was eluted with chloroform. This fraction could not be obtained in crystalline form from ordinary solvents. Although an infrared spectrum (Figure 7) indicated that a carbonyl group was present in this product, no 2,4-dinitrophenylhydrazone could be formed.

p-Toluenesulfonamido-tosylate, XVb

A suspension of 650 mg. (0.00136 mole) tosylgelsemine and 27 mg. (0.000712 mole) lithium aluminum hydride in 75 ml. anhydrous dioxane was refluxed under nitrogen for 22 hours. A solution of 300 mg. (0.00157 mole) tosyl chloride in 30 ml. anhydrous dioxane was added dropwise and reflux continued for 2 hours. After the reaction solution was cooled, a solution of 150 mg. sodium hydroxide in 2.5 ml. water and 2.5 ml. methanol was added and the mixture stirred for 10 minutes. The mixture was filtered and the solid washed in successive portions of boiling ether, benzene and chloroform. The combined organic layer was reduced to about 4 ml. under vacuum and partitioned between dilute hydrochloric acid and chloroform. After washing with dilute sodium carbonate solution, the chloroform layer was dried, filtered and stripped under

vacuum. The residue was crystallized from dioxane, benzene-chloroform and chloroform, but only amorphous solids were obtained, m.p. 212-213° dec., sinter 210°, $[\alpha]_D$ -76°.

The infrared spectrum of this product (Figure 7) was similar to that of the tosyl-alcohol, except that little absorption in the 3.0μ region was apparent and the absorption at 8.6μ was increased.

Rearrangement of the toluenesulfonamido-tosylate

A solution of 100 mg. of the tosylate in 75 ml. glacial acetic acid was heated at 100° for 46 hours. The product was isolated in the same manner as the rearrangement product of the tosyl-alcohol XVa. Chromatography of the product on neutral alumina separated a major fraction, with 4:1 chloroform-methanol, which could not be crystallized. The product was chromatographed again and the fraction eluted with 17:3 chloroform-methanol was dried under vacuum to a brown foam. An infrared spectrum of this foam showed a medium absorption at 5.79μ, but was otherwise similar to the spectrum of the tosyl-tosylate.

Dihydrotoluenesulfonimidogelsemine

Dihydrotosylgelsemine was prepared from dihydrogelsemine by the method used to prepare tosylgelsemine. After chromatography, the fraction eluted with benzene was crystallized

twice from petroleum ether to give crystals, m.p. 156-157°. A flocculent material which could not be removed from the crystallization solution was observed, however, so the product was considered to be impure. The infrared spectrum of the product was very similar to that of tosylgelsemine, except for a strong absorption at 7.23μ (intensity equivalent to the carbonyl absorption) and lack of absorption in the 9.0μ region.

Formation of dihydrotosylgelsemine by hydrogenation of tosylgelsemine in ethanol with Adams catalyst proved unsuccessful. Uptake of hydrogen was extremely slow, and infrared spectra of the hydrogenation product showed it to consist almost entirely of starting material.

Crystalline dihydrotosylgelsemine was reduced with lithium aluminum hydride and treated with tosyl chloride by the method used with tosylgelsemine. Chromatography and infrared spectra of the fractions eluted indicated that an appreciable part of starting material had not reacted, and of the reduced product, little had reacted with the tosyl chloride. A solution of the reduced product in formic acid was refluxed for 20 hours. The almost-black solution was reduced to dryness under vacuum, the residue dissolved in water and made basic with sodium bicarbonate, and the organic product extracted with chloroform. The product was chromatographed on neutral alumina, the major fraction being eluted with chloroform. The infrared

spectrum of the major fraction showed a medium absorption at 5.7μ with a shoulder at 5.8μ.

Dihydrodesoxotosylgelsemine, XVIa

Dihydrodesoxogelsemine, XVIb, was prepared by the method of Kates-Marion (25). Plates, m.p. 138-139° (reported 137.0-137.5°), were obtained by crystallization from ether. A solution of 170 mg. of the crystals and 140 mg. tosyl chloride in 10 ml. pyridine was warmed on a steam bath for half an hour, at which time the solution was a red-orange color. The solution was allowed to stand at room temperature overnight, 10 ml. water was added and the solution reduced to a thick, pink syrup under vacuum. The syrup was partitioned between chloroform and dilute sodium hydroxide solution, the organic layer dried over magnesium sulfate, filtered and reduced to dryness under vacuum. The residue was chromatographed on neutral alumina, the major fraction being eluted with 4:1 benzene-chloroform. After three recrystallizations from ether, white needles were obtained, m.p. 153-155°, $[\alpha]_D$ -44°. A sample for analysis was dried at 100° under high vacuum for an hour.

Anal. Calcd. for $C_{27}H_{30}O_3N_2S$: C, 70.10; H, 6.54; N, 6.06. Found: C, 70.39; H, 6.52; N, 6.10.

Tetrahydrodesoxotosylgelsemine

A suspension of 0.40 g. dihydrogelsemine and 0.20 g. lithium aluminum hydride in 50 ml. anhydrous dioxone was

stirred and refluxed under nitrogen for 24 hours. A solution of 9 ml. methanol and one ml. water was added and reflux continued for an hour. The mixture was filtered, the filtrate dried under vacuum and the combined solid fractions extracted with three 40 ml. portions of boiling chloroform. The chloroform extract was dried under vacuum and the light yellow, gummy product used without further purification.

A solution of the crude product and 0.40 g. tosyl chloride in 20 ml. pyridine was heated on a steam bath for 2 hours, 10 ml. water was added and the solution allowed to stand overnight. The solvent was removed under vacuum and the residue partitioned between chloroform and dilute sodium hydroxide solution. The organic layer was dried and filtered, the solvent was removed under vacuum and the residue chromatographed on neutral alumina. Elution with benzene produced a white gum. An ether solution of the gum deposited colorless rosettes of crystals as the solvent evaporated, but a film of light brown gum contaminated the crystals. Trituration with petroleum ether failed to remove the contaminant and attempted crystallization of the product from petroleum ether produced a white gum.

Hydrogelsemine A

A solution of 1.18 g. gelsemine in 40 ml. water and 10 ml. sulfuric acid was refluxed for 19 hours. The solution was

cooled and made basic with sodium hydroxide, then extracted with 1050 ml. chloroform in ten portions. The combined organic layer was dried over magnesium sulfate, filtered and evaporated to dryness, leaving a white residue. Crystallization of the residue from acetone produced 0.52 g. of a white powder, m.p. 250-300° with extensive charring, $[\alpha]_D$ +0.2°, which was a mixture of amorphous particles, hexagonal needles and hexagonal plates.

The acetate of hydrogelsemine A was formed by heating a solution of 150 mg. hydrogelsemine A and 20 drops of pyridine in one ml. acetic anhydride for 2.5 hours. After hydration of the remaining anhydride with water, the solution was made basic with dilute sodium carbonate solution and extracted with four 40 ml. portions of chloroform. The combined chloroform layer was dried, filtered and the solvent distilled. The residue was chromatographed on neutral alumina, the major fraction being eluted with 1:1 benzene-chloroform. This fraction could not be crystallized from common solvents, but slow evaporation of an acetone solution caused deposition of crystals, m.p. 230° with decomposition from 140°. The infrared spectrum of these crystals, with absorption at 5.82μ and 5.88μ and with no absorption at 2.8μ, and the ultraviolet spectrum (Figure 4), identical with that of gelsemine, indicated that the monoacetyl derivative had been formed.

Hydrogelsemine B

(a) A solution of 5.62 g. gelsemine in 120 ml. water and 25 ml. sulfuric acid was refluxed for 65 hours. The hydrated product was isolated by the same method used for hydrogelsemine A. The product was crystallized from chloroform to form an amorphous powder.

(b) Hydrogelsemine A was sublimed at 0.001 mm. and 200°. Infrared spectra showed that the sublimate was hydrogelsemine B.

(c) To a solution of 0.72 g. hydrogelsemine A and 7.2 g. cyclohexanone in 50 ml. anhydrous benzene was added 4 g. aluminum phenoxide in 30 ml. anhydrous benzene. After refluxing for 23 hours, the solution was cooled and extracted to isolate the basic organic fraction. The infrared spectrum of the product was identical with that of hydrogelsemine B.

A sample of hydrogelsemine B was sublimed twice at 0.001 mm. and 220° to form an amorphous powder, m.p. 285-287°, dec. with browning from 245°, $[\alpha]_D$ +4.9°.

Anal. Calcd. for $C_{20}H_{24}O_3N$: C, 70.56; H, 7.11; N, 8.23; Found: C, 69.81; H, 7.44; N, 7.82.

A sample of hydrogelsemine B was regenerated from its picrate salt, and crystallized from chloroform to give small

crystals, m.p. 268°, dec. with browning from 248°. Analyses of this product were no better than that of the sublimed product.

The picrate of hydrogelsemine B was formed, crystallized thrice from ethanol and dried under vacuum for 4 hours at 78°. The sample sent for analysis showed m.p. 273°, dec. with evolution of gas, with browning from 200° and sintering at 270°, $[\alpha]_D$ + 34.8°.

Anal. Calcd. for $C_{26}H_{27}O_{10}N_5$ C_2H_5OH: C, 54.63; H, 5.40; N, 11.38. Found: C, 55.01; H, 5.81; N, 11.27.

Diacetylhydrogelsemine B

A solution of 100 mg. hydrogelsemine B in 2 ml. acetic anhydride and 2 ml. pyridine was heated on a steam bath for 2 hours. The reaction mixture was cooled, diluted with 30 ml. water and made basic with sodium carbonate. The solution was washed with two 50 ml. portions of ether, the combined ether layer dried with magnesium sulfate and filtered. After the solvent was removed under vacuum, the residue was crystallized twice from ether-petroleum ether. After recrystallization from ether, the product was obtained as white crystals, m.p. 196-198° with slight dec., $[\alpha]_D$ -7.7°. The analytical sample was dried under vacuum for 4 hours at 100°.

Anal. Calcd. for $C_{24}H_{28}O_5N_2$, 3 C-CH_3: C, 67.90; H, 6.65; N, 6.60; C-CH_3, 10.63. Found: C, 68.01; H, 6.49; N, 6.54; C-CH_3, 7.36.

Oxidation of hydrogelsemine B

To a solution of 500 mg. hydrogelsemine B in 20 ml. cold pyridine was added a mixture of 500 mg. chromic anhydride in 5 ml. pyridine and the mixture allowed to stand at room temperature overnight. The mixture was dissolved in 50 ml. dilute hydrochloric and washed with a chloroform layer which was discarded. The aqueous layer was made basic with sodium hydroxide and washed with four 50 ml. portions of chloroform. The combined organic layer was dried, filtered and evaporated under vacuum. The residue was chromatographed on neutral alumina, a major fraction, which slowly turned dark brown in air, being eluted with 1:1 petroleum ether-benzene. The infrared spectrum of this product showed a sharp peak at 5.82μ and no absorption from 2.8μ to 3.3μ. No 2,4-dinotrophenylhydrazone or crystalline picrate salt of the product could be isolated.

Another oxidation, with one-fifth the above quantities of reagents, was stopped after standing for 5 hours. After isolation, the crude reaction product was chromatographed on alumina. Elution with chloroform brought down a white material which formed a solid foam when the solvent was removed under vacuum, m.p. 260-261°, dec. with browning from 210°. The in-

frared spectrum of this product showed a broad absorption band centered at 5.87μ and no absorption from 2.8μ to 3.1μ.

Bromoallogelsemine hydrobromide, XVII

The formation of this compound and the following compound, desoxooxytetrahydrogelsemine XVIIIa, have been outlined by Goutarel, et al. (16). However, full experimental details will be included here.

A solution of 1.48 g. (0.00459 mole) of acetone-free gelsemine in 50 ml. dry chloroform was cooled to -5° in an ice-salt bath. A solution of 0.74 g. (0.00463 mole) of bromine in 50 ml. dry chloroform was added dropwise over a period of one hour with continuous stirring. The resulting colorless solution was kept at 5° and stirred for two hours. The solution was then reduced to dryness under vacuum and the residue crystallized from methanol. After the solution had been stored in the icebox for three days, 1.69 g. (76%) of white, powdery crystals had formed, m.p. 321-324° dec., reported 324° dec.(16).

Desoxooxytetrahydrogelsemine, XVIIIa

A suspension of 1.69 g. (0.00351 mole) of bromoallogelsemine hydrobromide and 1.33 g. (0.0351 mole) of lithium aluminum hydride in 100 ml. anhydrous dioxane was stirred and refluxed under nitrogen for 16 hours. A solution of 5 ml. water

in 30 ml. methanol was added dropwise and the resulting slurry refluxed and stirred for four hours. The mixture was filtered, the residue washed twice with boiling methanol and the combined organic layer reduced to dryness under vacuum. The residue was extracted twice with boiling acetone and the combined organic layer boiled down to about 5 ml. After standing in the icebox overnight, 0.67 g. (58.5%) of colorless crystals had formed, m.p. 258-261° slight dec., reported 258-261° (16). An additional 0.20 g. (17.5%) of impure product, m.p. 241-257°, was obtained by concentrating the mother liquors.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: 1 C-CH_3, 4.66. Found: C-CH_3, (1) 0.54, (2) negative.

Ditosyl-desoxooxytetrahydrogelsemine, XVIIIb

A mixture of 0.67 g. desoxooxytetrahydrogelsemine, XVIIIa and 0.90 g. tosyl chloride in 20 ml. pyridine was heated on a steam bath. A bright red-orange color appeared immediately but the amino-alcohol did not dissolve completely for about 7 hours. Heating was continued for 17 hours more. The orange solution was reduced to dryness under vacuum and the residue partitioned between chloroform and sodium bicarbonate solution. The organic layer was dried, filtered and evaporated to dryness under vacuum. An attempt to crystallize the residue from ether produced an amorphous yellow powder, so the product was chroma-

tographed on neutral alumina. Elution with a series of chloroform-containing eluants produced an almost continuous flow of gummy product. Infrared spectra of the fractions indicated that no clear separation was effected. The spectra showed broad absorptions near 3.0μ and sharp peaks at 7.4μ and 8.6μ, indicating that tosylation of the amino-alcohol was not complete.

Attempted tosylation by the same method using quinoline as the solvent-base, caused formation of black tar which could not be purified.

Diacetyl-desoxooxytetrahydrogelsemine, XVIIIc

A solution of 560 mg. desoxooxytetrahydrogelsemine, XVIIIa, in 10 ml. acetic anhydride and 10 ml. pyridine was heated on a steam bath for 3 hours, then allowed to stand at room temperature overnight. The solvent was removed under vacuum and the residue partitioned between dilute sodium bicarbonate solution and chloroform. The organic layer was dried over magnesium sulfate, filtered and the solvent distilled. The residue was chromatographed on neutral alumina and a major fraction, 0.51 g., was eluted with 3:1 benzene-chloroform. Although this fraction could not be crystallized, vacuum evaporation of a chloroform solution of it produced a white foam, m.p. 100-105° with shrinking at 90°. Infrared spectra (Figure 9) of the product showed absorption bands attributable to an amide-ester.

Monoacetyl-desoxooxytetrahydrogelsemine, XVIIId

A solution of 510 mg. diacetyl-desoxooxytetrahydrogelsemine, XVIIIc, and 53 mg. sodium hydroxide in 25 ml. methanol and 4 ml. water was allowed to stand for 21 hours at room temperature. The solvent was removed under vacuum and the residue dissolved in chloroform and dilute sodium carbonate. The separated chloroform layer was dried and filtered. Evaporation of the solvent left a residue which was chromatographed on alumina. The major fraction, eluted with 1:1 benzene-chloroform, could not be crystallized, but, when dried under vacuum, formed a white foam, m.p. 115-120° with shrinking from 100°, $[\alpha]_D$ -33.6°. Infrared spectra (Figure 9) of the foam exhibited hydroxyl and amide absorptions, but no absorption attributable to an ester.

Oxidation of monoacetyl-desoxooxytetrahydrogelsemine, XVIIId

To a solution of 100 mg. of the monoacetyl compound in 15 ml. acetic acid was added a solution of 150 mg. chromic anhydride in 4 ml. acetic acid and one ml. water. A brown solid, which formed immediately, dissolved in the reaction solution after being stirred for 90 minutes. After stirring for 90 minutes more, the solvent was removed under vacuum and the dark brown residue dissolved in water. Chloroform was used to extract the basic organic product from the aqueous layer. After isolation, the product was chromatographed on alumina.

About 15 mg. of oxidation product was eluted with 4:1 benzene-chloroform and a major fraction, mostly starting material, was eluted with 3:2 benzene-chloroform. Attempted crystallization of the oxidation product failed and only amorphous gums were obtained. The infrared spectrum of the product showed strong absorption bands at 5.92μ and 6.09μ.

Similar oxidations with chromic anhydride in acetic acid, utilizing reaction times up to 19 hours, led to formation of gums with similar infrared spectra. In one case, reaction time ca. 7 hours, the infrared spectrum showed a shoulder at 5.75μ on a broad absorption band centered at 5.9μ. Solid 2,4-dinitrophenylhydrazone derivatives of the oxidation products could not be isolated.

Oxidation of the monoacetyl compound with Sarett reagent (34) also formed amorphous products. The infrared spectra of these compounds were almost identical with the spectra of the acid oxidation products, except that no trace of the absorption at 5.75μ was observed.

Attempted debromination of bromoallogelsemine hydrobromide

To a solution of 100 mg. bromallogelsemine hydrobromide in 25 ml. anhydrous pyridine was added 400 mg. silver nitrate. The solution was stirred for 24 hours at room temperature in the dark. The solvent was removed under vacuum and the resi-

due partitioned between chloroform and ice-cold, dilute sodium bicarbonate solution. The chloroform layer was dried immediately with sodium sulfate, filtered and stripped under vacuum. The residue was chromatographed on neutral alumina but no clear separation was effected. Infrared spectra showed strong absorption at 6.3μ, weak absorption at 5.9μ and no appreciable absorption near 3.0μ, indicating that little hydrolysis had occurred. In addition, a medium absorption at 6.02μ was observed.

A solution of the debromination product and 0.2 g. sodium carbonate in 20 ml. methanol and 5 ml. water was allowed to stand at room temperature for 6 hours. The methanol was distilled away and the cloudy solution diluted with 20 ml. water. The basic product was extracted with chloroform. After isolation, this product was chromatographed on neutral alumina. A small amount (ca. 10 mg.) of colorless gum was eluted with benzene. The infrared spectrum of this fraction exhibited a sharp absorption band at 2.95μ, a double peak at 5.83μ and 5.9μ and a medium peak at 6.03μ. A second fraction (ca. 50 mg.) of colorless gum was eluted with 1:1 benzene-chloroform. The infrared spectrum of this fraction showed a double peak at 2.95 and 3.10μ, a peak at 5.83μ, a shoulder at 5.88μ and weak absorption at 6.03μ.

Oxidation of gelsemine with ethyl azodicarboxylate

To a solution of 200 mg. gelsemine acetonide in 5 ml. of methanol was added dropwise 100 mg. of ethyl azodicarboxylate. The orange color of the azo compound disappeared in 20 minutes and the colorless solution was allowed to stand for sixtten hours at room temperature.

To the methanol solution was added 30 ml. of distilled diethylene glycol, 10 ml. of water, 2 ml. of hydrazine and 400 mg. potassium hydroxide. The resulting solution was refluxed for two hours, then distilled slowly until the temperature of the boiling residue was 217°. Refluxing was continued at this temperature for three hours. The solution was cooled, diluted with 70 ml. of water and extracted with three 50 ml. portions of chloroform. After drying with sodium sulfate, the combined organic layer was filtered and reduced to dryness under vacuum.

The gummy, brown residue was taken up in 10 ml. of acetic anhydride and 10 ml. of pyridine and the solution warmed on a steam bath for an hour. After cooling, the solution was allowed to stand at room temperature overnight. The solvent was then removed under vacuum, 40 ml. of methanol and 30 ml. of 10% sodium bicarbonate solution added and the resulting solution allowed to stand at room temperature for three days.

The methanol was boiled off. The aqueous residue was extracted with chloroform and the organic layer washed with 5% hydrochloric acid. After the organic layer was dried and filtered, the chloroform was boiled off and the residue (190 mg.) dissolved in 9:1 benzene-chloroform. The solution was placed on a column of neutral alumina and eluted with gradually changing solutions of benzene and chloroform. No clear separation was accomplished, but a major fraction was obtained by elution with 6:4 benzene-chloroform. The infrared spectrum (Figure 10) of the light-brown gummy residue, XX, showed absorptions at 6.15μ (amide) and 7.2, 7.3, 7.5, and 7.7μ. No significant absorption below 2.9μ was observed.

The gummy residue was dissolved in an ethanol-water solution, potassium hydroxide added and the solution refluxed for eight hours. No basic products could be isolated from the reaction mixture and infrared spectra showed the neutral product to be unchanged amide. Part of the recovered amide was refluxed for six days in ethanol with sodium hydroxide. Only a small amount of tarry black residue was isolated from the reaction mixture. The remainder of the amide was dissolved in water and diethylene glycol, b.p. ca. 130°, potassium hydroxide was added and the mixture refluxed for two hours. Again, only a small amount of tarry residue could be recovered. Infrared spectra of these tarry residues showed only minor absorptions in the 5.8 to 6.0μ region.

The oxidation with ethyl azodicarboxylate and Wolff-Kishner reduction was repeated, utilizing 260 mg. of gelsemine and proportionate amounts of other reagents. To a solution of the resulting product in 10 ml. pyridine was added 400 mg. of p-toluenesulfonyl chloride and the solution heated on a steam bath for six hours. Water, 10 ml., was added, and after heating had been continued for two hours, the solvent was removed under vacuum. The residue was dissolved in chloroform and the organic solution extracted successively with dilute hydrochloric acid and 5% sodium carbonate solution. After drying and filtration, the chloroform solution was reduced almost to dryness by distillation and the residue taken up in benzene. The benzene solution was placed on a colum of neutral alumina and eluted with 2:1 benzene-chloroform, chloroform and 3:1 chloroform-methanol. Infrared spectra of the three fractions eluted were almost identical, with strong absorptions near 7.4μ and 8.8μ, characteristic of the toluene sulfonamide group.

Oxidation of dihydrogelsemine with ethyl azodicarboxylate

Ethyl azodicarboxylate, 300 mg., was added dropwise to a solution of 356 mg. dihydrogelsemine in 15 ml. of methanol and the solution allowed to stand at room temperature for 16 hours. To the colorless solution was added 40 ml. of diethylene glycol, 10 ml. of water, 4 ml. of hydrazine and 800 mg. potassium hydroxide. The resulting solution was refluxed for 16 hours,

then distilled until the vapor temperature reached 215°C, and reflux continued overnight. The solution was cooled, diluted to 100 ml. with water and extracted with four 100 ml. portions of chloroform. The combined organic was dried, filtered and reduced to dryness under vacuum, leaving a gummy residue.

The residue was dissolved in 20 ml. of formic acid, 10 ml. of 37% formaldehyde solution was added and the mixture refluxed on a steam bath for 16 hours. A solution of 4 ml. of hydrochloric acid in 20 ml. of water was added and the solution reduced to about 5 ml. by distillation. The residue was dissolved in water, made basic and the product extracted with chloroform. After the chloroform solution was dried and filtered, the chloroform was removed under vacuum leaving a light-brown, semi-solid residue. The residue was acetylated with acetic anhydride in pyridine and the product subjected to mild hydrolysis (insuring that no acetylated oxindole remained) in the same manner as was the reduced oxidation product of gelsemine (p. 95).

The crude product was dissolved in dilute hydrochloric acid and extracted with chloroform to isolate a neutral fraction. After neutralization of the acidic aqueous layer with sodium carbonate, extraction with chloroform removed the remaining basic fraction. Both fractions were isolated from their respective chloroform solutions under vacuum after stand-

ard drying and filtration operations. The infrared spectrum (Figure 10) of the basic fraction, XXI, was very similar to that of dihydrogelsemine except that a medium absorption at 7.45μ replaced the 7.6μ absorption of dihydrogelsemine. The infrared spectrum of the minor, neutral fraction was very similar to that of product formed after oxidation, reduction and acetylation of gelsemine (p. 96).

Oxidation of the Eschweiler product with mercuric acetate

About 200 mg. of the Eschweiler product was dissolved in 50 ml. of 5% acetic acid solution and 1.5 g. of mercuric acetate was added. The resulting solution was heated on a steam bath for 16 hours, then cooled and extracted with chloroform to obtain basic and neutral fractions. Infrared spectra showed the basic fraction to be unreacted starting material. The infrared spectrum of the neutral fraction, XXI, (15 mg.) exhibited a split absorption band at 5.83 and 5.90μ .

In another attempt to oxidize the Eschweiler product 150 mg. of the tertiary amine and 722 mg. of mercuric acetate in 10 ml. of 75% acetic acid solution was heated on a steam bath for 24 hours. Some solid salts and metallic mercury formed during the reaction. After filtration, the reaction solution was diluted with water, then extracted as before to obtain about 50 mg. of the neutral product, XXII.

A small amount of the neutral product was heated with an acidic solution of 2,4-dinitrophenylhydrazine. No crystalline derivative formed upon cooling. After extraction, the reaction mixture was chromatographed twice, but no separation could be effected. Infrared spectra indicated that the final product after chromatography was a mixture of unreacted starting materials.

Hofmann reaction with Eschweiler product

To a solution of 150 mg. of the Eschweiler product in 5 ml. of methanol was added 2 ml. of methyl iodide. After standing overnight at room temperature, the solvent was removed under vacuum, leaving a gummy yellow residue. The residue was soluble in methanol, slightly soluble in acetone, insoluble in chloroform, ether and water but could not be induced to crystallize.

The residue was dissolved in 20 ml. of diethylene glycol, 20 ml. of water and 0.5 gm. of potassium hydroxide was added and the solution was distilled until the liquid temperature reached 150°. The solution was refluxed at this temperature for 4 hours, then cooled diluted with water and extracted with chloroform. After drying and filtration, the chloroform extract was evaporated. Infrared spectra indicated that the residue was the Eschweiler product.

Oxidation of gelsemine with mercuric acetate

To a solution of 100 mg. of gelsemine in 10 ml. of 75% acetic acid was added 600 mg. of mercuric acetate. After heating the solution for 24 hours on the steam bath, no metallic mercury could be observed in the solution. The solution was diluted with 50 ml. of water, neutralized with sodium bicarbonate and the resulting slurry was dried under vacuum. The dried salts were refluxed with 150 ml. of chloroform for one hour and, after cooling, the chloroform extract was filtered. Upon vacuum drying, a pale yellow residue (78 mg.) was obtained from the chloroform solution. An infrared spectrum of this residue was identical with that of gelsemine, and no trace of the carbonyl absorption peak at 5.83 μ was observed.

SUMMARY

A series of experiments to elucidate the structure of gelsemine, an oxindole alkaloid, has been reported. Although no final proof of structure was reached, several new derivatives of gelsemine have been characterized.

Two new hydration products of the vinyl group of the alkaloid, isomers of previously reported hydration products, seem to be epimers. The less stable of these products is converted to the other by pyrolytic, strongly basic or acidic conditions. Oxidation of these hydration products did not lead to controlled degradation of gelsemine.

The lactam ring of gelsemine was cleaved by a new method. Tosylation of the lactam nitrogen atom produced a toluenesulfonimide which was readily hydrolyzed to an acid or cleaved reductively to a primary alcohol. Although further, controlled degradation of gelsemine was not achieved via these derivatives the method may be of value with other oxindole compounds.

Extension of a method used earlier with gelsemine allowed reductive cleavage of the tertiary amine ring. Although no well-characterized products were obtained, the method may be of value for degradation of amines in cases where the Emde reduction is not feasible.

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