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STUDIES ON ELEMICIN SYNTHESES

BY

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A Thesis

Submitted to the Graduate Faculty of
McNeese State University
In Partial Fulfillment of the
Requirements for the Degree

MASTER OF SCIENCE IN CHEMISTRY

December, 1976

Lake Charles, Louisiana

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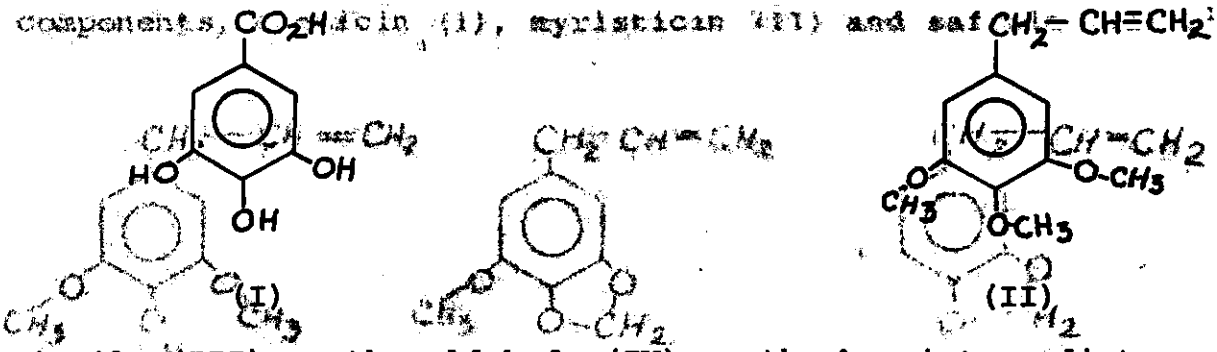
LIST OF SCHEMES

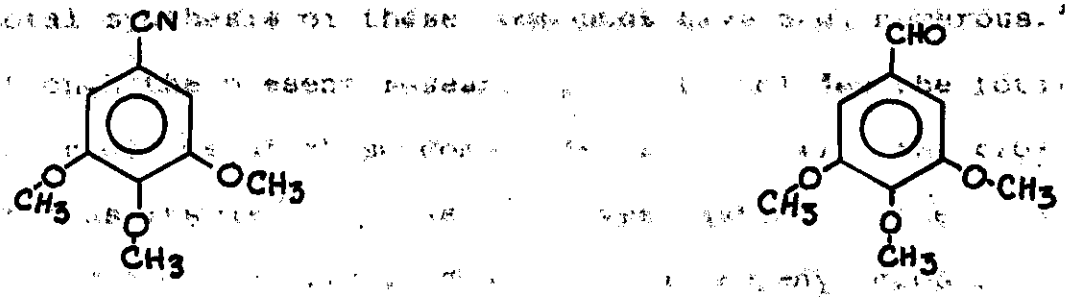
ABSTRACT

The emphasis of this research was the investigation of several pathways for the conversion of gallic acid (I) into elemicin (II). Pathways considered had either the



(I) (II)

nitrile (III) or the aldehyde (IV) as the key intermediate. The conversion of the aldehyde (IV) into isoelemicin via a Wittig reaciton followed by Brown's procedure resulted in the formation of elemicin (II). Other approaches involved

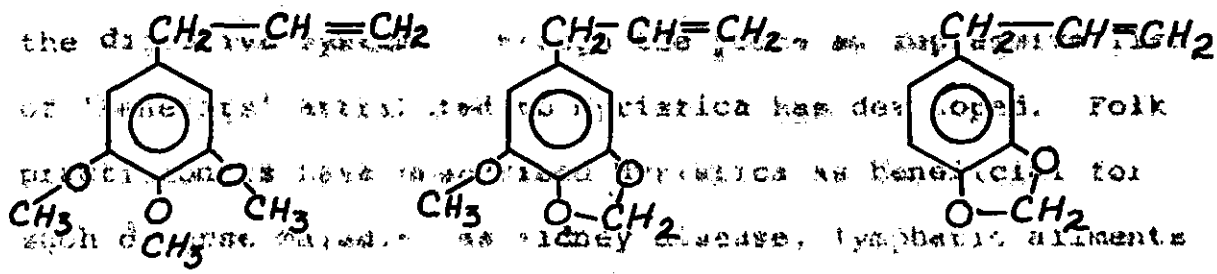


(III) (IV)

the addition of various Grignard reagents to the nitrile (III) and the aldehyde (IV); but these, however, were not successful pathways to elemicin (II).

INTRODUCTION

The aromatic fraction of the volatile oils obtained by steam distillation of the crushed seed from the nutmeg tree, Myristica fragrans, is composed primarily of three major components, elemicin (I), myristicin (II) and safrole (III).[1]



(I) (II) (III)

[illegible] catalogued by [illegible] physicians as a remedy for disorders of the digestive system, [illegible] or "nervous" ailments. Folk practitioners have [illegible] myristica as beneficial for such diverse [illegible] as kidney disease, lymphatic ailments and cancer. [illegible] (II) also include [illegible] (III) as an [illegible] These compounds are suspected of contributing to the psychoactive effect produced when large doses of nutmeg (orimace) are ingested.[2] Laboratory efforts directed toward the total synthesis of these compounds have been numerous.[3,4,5] Even though the present research project includes the total synthesis of one of these compounds, elemicin (I), the project has as its main purpose the investigation of the conversion of a carboxylic acid group to a propenyl group. Understanding this conversion is important because of the frequently encountered propenyl side chain in naturally occurring compounds and because this conversion is envisioned as a key operation in another synthetic problem currently under study in this laboratory.

HISTORY

The spices, nutmeg and mace, obtained from the nutmeg tree, Myristica fragrans (family Myristicacease), have long held an important place in folk medicine. Early in the 7th century A. D., use of Myristica (nutmeg and mace) was first catalogued by Arab physicians as a remedy for disorders of the digestive system. Through the years an impressive list of 'benefits' attributed to Myristica has developed. Folk practitioners have prescribed Myristica as beneficial for such diverse maladies as kidney disease, lymphatic ailments and cardiac diseases. Claims also include its power as an aphrodisiac, a carminative and soporific.[2,6]

The end of the 19th century saw a resurgence of Myristica's importance as a medicine when it was suggested that it could bring on overdue menstruation and even induce abortion. During this resurgence the toxic effect of Myristica was well documented; however, only one fatality has ever been ascribed to nutmeg ingestion.[7]

The observation that large doses of Myristica exert an intoxicating effect dates back to the Middle Ages. In 1963 a published report appeared for the first time detailing the narcotic effects of Myristica when deliberately ingested.[8] Most of the information on nutmeg as a psychoactive drug, however, comes from undocumented anecdotes.

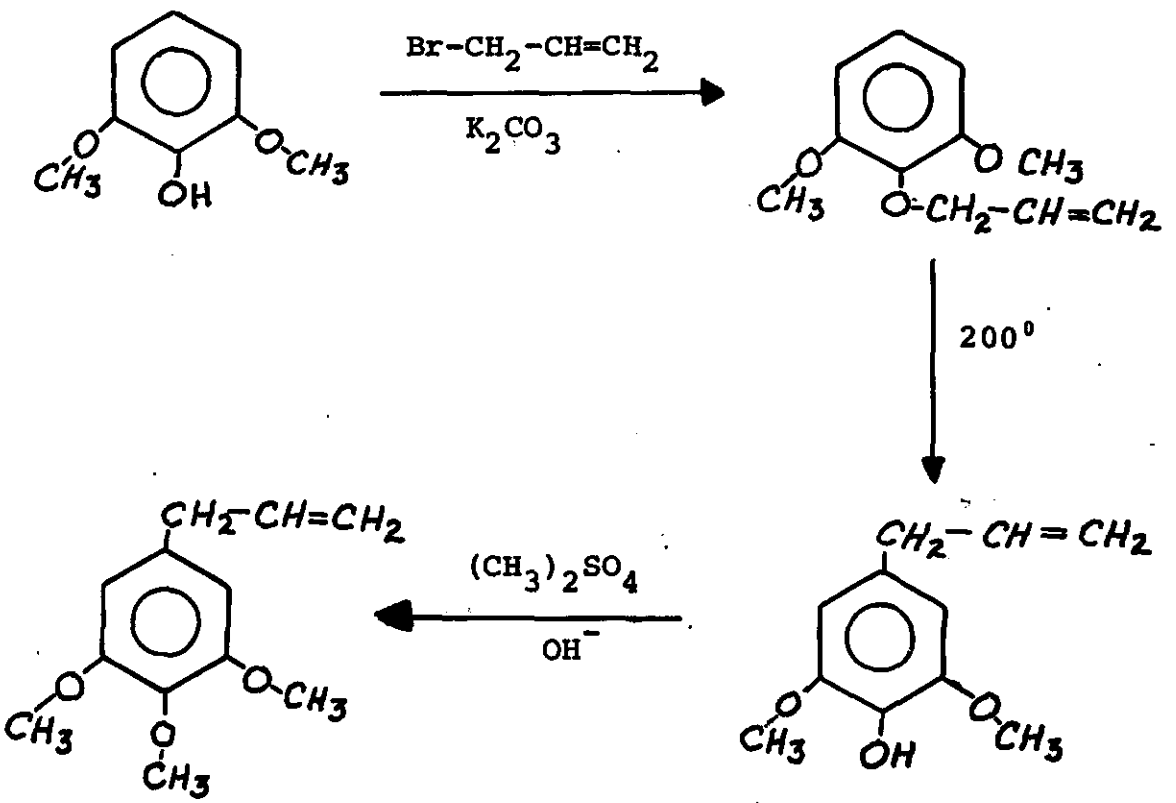
Many naturally occurring as well as synthetic compounds

containing the trimethoxybenzene system have been found to exert pharmacological actions.[9,10,11] The difference in the activity of these different trimethoxybenzene derivatives might be attributed to the various attachments to the trimethoxybenzene structure.

An investigation of the chemical components of the fruit from the nutmeg tree was reported as early as 1676.[12] There are two classical ways of extracting the potentially interesting material from the whole fruit. Subjection of the total crushed seed to steam distillation removes the volatile oil fraction, some 10 to 15% of the weight. Extraction with an organic solvent, however, removes the fixed oils which include the volatile oils; the fixed oils make up about a third of the total original weight.[4] The physiological effect of Myristica is generally agreed to be attributed to the volatile oils.[2] The volatile fraction is composed primarily of terpenes (80%) and aromatics (20%). Three major components, elemicin (I), myristicin (II) and safrole (III), constitute nearly 90% of the second group.[1]

Interest in the development of a laboratory synthesis of elemicin began early in this century, the first being reported in 1918.[3] This synthesis, diagrammed in Scheme I, was carried out by F. Mauthner and sets the general approach followed by other investigators.[13] Later syntheses involve the conversions of other related volatile oils to

elemicin.[illegible] The most[illegible]SCHEME[illegible]synthesis, reported in 1974, was undertaken to prepare ^{14}C-elemicin to facilitate further biological study on its pharmacological activity.[16]



elemicin.[4,14,15] The most recent synthesis, reported in 1974, was undertaken to prepare ^{14}C-elemicin to facilitate further biological study on its pharmacological activity.[16]

Fifty grams (0.29 mole) of gallic acid (IV), 3,4,5-trihydroxybenzoic acid, in a one liter round-bottom flask was treated with a cold sodium hydroxide solution prepared from [illegible] g of NaOH in 500 ml of water. The flask was immediately stoppered and shaken until the acid was dissolved. Dimethyl sulfate (67 ml, [illegible] mole) was added and shaken for twenty minutes with periodic cooling. Another portion of 67 ml of dimethyl sulfate was added. After being shaken for ten minutes, the reaction was refluxed for two hours. Twenty grams of sodium hydroxide in [illegible] ml of water was added to the mixture which was refluxed for an additional two hours. The reaction mixture was cooled and acidified with dilute HCl. The solid was filtered, washed with water, and allowed to dry. The yield of crude 3,4,5-trimethoxybenzoic acid [illegible]

EXPERIMENTAL

Preparation of 3,4,5-Trimethoxybenzoic Acid (V).[17] Fifty grams (0.29 mole) of gallic acid (IV), 3,4,5-trihydroxybenzoic acid, in a one liter round-bottom flask was treated with a cold sodium hydroxide solution prepared from 80 g of NaOH in 500 ml of water. The flask was immediately stoppered and shaken until the acid was dissolved. Dimethyl sulfate (67 ml, 0.8 mole) was added and shaken for twenty minutes with periodic cooling. Another portion of 67 ml of dimethyl sulfate was added. After being shaken for ten minutes, the reaction was refluxed for two hours. Twenty grams of sodium hydroxide in 30 ml of water was added to the mixture which was refluxed for an additional two hours. The reaction mixture was cooled and acidified with dilute HCl. The product was filtered, washed with water, and allowed to dry. The yield of crude 3,4,5-trimethoxybenzoic acid (V) was 55.8 g (90%) which, after recrystallization from methyl alcohol, gave 39.6 g (64%) of the acid (V) as colorless needles with mp 166-167° (lit.[17] 167°). The carbonyl infrared absorption band was observed at 1680 cm^{-1}.

Preparation of 3,4,5-Trimethoxybenzamide (VII). Ten grams (0.047 mole) of the acid (V) was treated with 10 ml of freshly distilled thionyl chloride and heated under reflux for two hours. At the end of this time the excess thionyl chloride was removed under reduced pressure and the residual

crude 3,4,5-trimethoxybenzoyl chloride (VI) was dissolved in sodium dried benzene. Ammonia gas was allowed to bubble through the reaction mixture for about six hours. Concentrated ammonium hydroxide was then added to ensure that the reaction mixture remained basic. The white residue was collected by filtration and was recrystallized from ethyl alcohol. The 3,4,5-trimethoxybenzamide (VII) crystallized in long needles yielding 8.1 g (81%), mp 177-178° (lit.[18] 176-178°). The major infrared absorption bands were observed at 3267 and 1660 cm^{-1}.

Preparation of 3,4,5-Trimethoxybenzonitrile (VIII).[19] A solution of 8 g (0.038 mole) of the amide (VII) in 20 ml of hot 1,1,2,2-tetrachloroethylene was treated with 4.0 g of diphosphorus pentoxide (P_4O_{10}). The reaction mixture was stirred under reflux for one hour; then another 4.0 g of P_4O_{10} was added. After allowing the reaction mixture to reflux for an additional thirty minutes, the hot solvent was decanted from the residue. The residue was extracted five times with 10 ml portions of tetrachloroethylene. Each 10 ml addition was followed by a thirty minute reflux period. The solvent was removed from the combined extracts by distillation under reduced pressure. The crystalline material remaining upon recrystallization from ethyl alcohol yielded 4.4 g (60%) of long needles, mp 92-94° (lit.[20] 92-94°).

Preparation of 3,4,5-Trimethoxybenzaldehyde (IX).

(a) Diisobutylaluminum hydride method.[21] A solution of

4.0 g (0.02 mole) of the nitrile (VIII) in 20 ml of sodium dried benzene was placed into a 50 ml three-necked flask equipped with a magnetic stirrer and a dropping funnel. A nitrogen atmosphere was established within the apparatus. Twenty-three milliliters of a solution of 24.8% diisobutylaluminum hydride was introduced into the dropping funnel. This solution was then added dropwise to the stirred solution of the nitrile (VIII) over a two hour period. After the addition was complete, the solution was carefully poured into 250 ml of 5% H_2SO_4 solution, and this mixture was stirred for one hour. The reaction mixture was then extracted several times with ether. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from petroleum ether yielding 2 g of the aldehyde (IX) (50%), mp 74° (lit.[22] 77-78°). The carbonyl absorption band in the infrared was observed at 1690 cm^{-1}.

(b) Raney nickel method.[23] Five grams (0.025 mole) of the nitrile (VIII) was treated with 81 ml of 90% formic acid and 0.3 g of activated Raney nickel. The mixture was stirred at 40-50° for two hours or longer. After dilution with 70 ml of 75% ethanol, the reaction mixture was decanted from the nickel. The nickel was washed with warmed alcohol and then extracted several times with ether. The combined ether and alcohol layers were washed with a dilute sodium bicarbonate solution and water. After drying over anhydrous

magnesium sulfate, the solvent was removed under reduced pressure. The residue was recrystallized from ligroin to yield 4.0 g (80%) of the aldehyde (IX), mp 74°. The infrared spectrum was identical to material prepared by method (a).

Preparation of 3,4,5-Trimethoxybenzyl Alcohol (X).[24] A solution of 1 g of the acid (V) in 20 ml of dry tetrahydrofuran (THF) was added dropwise to a stirred solution of 0.25 g of lithium aluminum hydride dissolved in 10 ml of dry THF. After refluxing for one hour under a nitrogen atmosphere, the reaction mixture was carefully diluted with water, acidified with concentrated hydrochloric acid, and extracted several times with diethyl ether. The combined ether layers were washed with cold 10% NaOH solution and a saturated salt solution. After drying over anhydrous magnesium sulfate, the ether layer was filtered and evaporated, yielding 0.704 g (75%) of a clear oil. No carbonyl infrared absorption band was evident.

Preparation of 3,4,5-Trimethoxybenzaldehyde (IX) from Alcohol (X).[25] A solution of 500 mg of the alcohol (X) in 25 ml of petroleum ether was stirred with 500 mg of freshly prepared manganese dioxide for one hour. The manganese dioxide was removed by filtration and the filtrate provided 222 mg (45%) of the aldehyde (IX) after recrystallization from ligroin. The product was identical to the aldehyde (IX) prepared by previous methods.

Preparation of Isoelemicin (XI).[26] A solution of n-butyllithium in n-hexane (3.3 ml, 27.5%) was added dropwise to a stirred mixture of ethyltriphenylphosphonium bromide (1.2 g) in dry diethyl ether. After the mixture was stirred under a nitrogen atmosphere for three hours, 0.75 g of the aldehyde (IX) was added. The reaciton was refluxed for twenty-four hours. The organic layer was washed with water, a sodium bicarbonate solution and a saturated salt solution and dried over anhydrous sodium sulfate. After the removal of the solvent by evaporation, 0.3 g of crude product was obtained. The infrared absorption bands showed no evidence of a carbonyl group.

Preparation of Elemicin (I) via Brown's Procedure.[27,28] A 100 ml three-necked flask was equipped with a magnetic stirrer, a dropping funnel, a reflux condenser topped with a mercury trap, and an inlet tube connected to a B_2H_6 generator. After flushing the entire system with nitrogen, 1.4 g (0.0067 mole) of crude isoelemicin (XI) in 10 ml of diglyme was added into the flask. The B_2H_6 was generated from 1.0 g of $NaBH_4$ in 10 ml of diglyme and 5 g of BF_3-etherate also in 10 ml of diglyme. The B_2H_6, as generated, was bubbled into the olefin solution over a two hour period; then the reaction mixture was refluxed for six hours.

A solution of 0.77 g of cyclooctene in 10 ml of diglyme was added to the reaction mixture, and the resulting solution was refluxed for an additional sixteen hours. The

reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue weighed 0.650 g.

Preparative thin-layer chromatography (TLC) on silica gel plates was performed on 200 mg of the residue. Development with the solvent system, benzene, ethyl acetate, and methanol (85:10:5) provided material that had an R_f value of 0.557. That portion of the silica gel containing the purified sample was removed and extracted with diethyl ether. Subsequent evaporation of the ether yielded 88 mg of purified elemicin (I). The ir and nmr spectra and the R_f value were identical with those obtained from a known sample of elemicin (I).

Preparation of 3-(3,4,5-Trimethoxyphenyl)-3-hydroxypropene (XII).[29] Two hundred fifty milligrams (1.28 mmole) of the aldehyde (IX) was dissolved in 15 ml of dry THF in a 50 ml three-necked flask equipped with a nitrogen flushing system, a rubber septum, and a magnetic stirrer. One and one-half milliliters of a 1.4M solution of vinylmagnesium bromide in THF was added slowly via a syringe through the rubber septum. The mixture was allowed to stir for two hours. Following careful acidification with dilute sulfuric acid, the mixture was extracted several times with diethyl ether. The combined ether layers were washed with water and a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed yielding 252 mg

of clear oil. Although the infrared spectrum showed a broad hydroxyl band centered at 3470 cm^{-1} and no carbonyl absorption, the occurrence of several spots on TLC plates indicated the heterogeneous nature of the oil.

Preparation of 1-(3,4,5-Trimethoxyphenyl)-1-propanol (XIV).[29] Magnesium turnings (0.283 g; 0.01 mole) and anhydrous diethyl ether (10 ml) were placed into a flask equipped with a nitrogen flushing system, a magnetic stirrer and a dropping funnel which contained a solution of 0.8 ml (1.56 g; 0.01 mole) of ethyl iodide in 5 ml of anhydrous diethyl ether. A few drops of this solution were added to the magnesium turnings which were being gently stirred. After the reaction started, the ethyl iodide solution was added dropwise in order to maintain a mild reflux. When the addition was complete, the reaction mixture was refluxed for an additional thirty minutes. After a solution of 1.96 g (0.01 mole) of the aldehyde (IX) in 50 ml of anhydrous diethyl ether was added slowly via the dropping funnel, the reaction mixture was allowed to stir at room temperature for two hours. Acidification of the reaction mixture with a cold solution of dilute hydrochloric acid was followed by separation of the organic layer and extraction of the aqueous layer with 50 ml of diethyl ether. The combined ether layers were washed with a saturated salt solution and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to yield 1.87 g of a clear oil.

This crude material was chromatographed on a column of silica gel. Development with benzene-petroleum ether provided two major fractions (270 mg and 250 mg); however, TLC showed both to be heterogeneous.

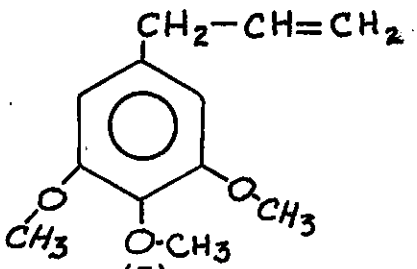
Preparation of 3,4,5-Trimethoxypropiophenone (XV).[30] Magnesium turnings (0.346 g; 0.014 mole) and anhydrous diethyl ether (35 ml) were placed into a flask equipped with a dropping funnel, reflux condenser and magnetic stirrer. The flask was then flushed with nitrogen. A solution of 1.38 ml of ethyl iodide (0.017 mole) in 35 ml of anhydrous diethyl ether was added into the dropping funnel. A few drops of the solution were added to the magnesium turnings which were being stirred gently. After the reaction started, the ethyl iodide solution was added dropwise to maintain a mild reflux. When the addition was complete, the reaction mixture was refluxed for an additional thirty minutes. A solution of 2.0 g (0.01 mole) of the nitrile (VIII) in 50 ml of anhydrous diethyl ether was added slowly via the dropping funnel. After the reaction mixture was allowed to stand overnight at room temperature, it was acidified with an ice and concentrated hydrochloric acid mixture (5:3 v/v, 80 ml). The organic layer was separated, and the aqueous layer was refluxed for one hour and then extracted several times with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the crude material was recrystallized from ligroin

yielding 1.94 g (84%) of the propiophenone (XV), mp 51-52° (lit.[31] 52°). The carbonyl absorption band in the infrared spectrum was observed at 1689 cm^{-1}. The nmr spectrum showed peaks at δ1.2 (triplet), δ2.9 (quartet), δ3.8 (singlet) and δ7.1 (singlet).

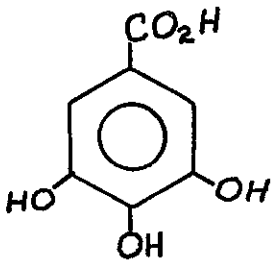
Preparation of 3,4,5-Trimethoxyacetophenone (XVI).[30] The procedure used was the same as that used for the preparation of the propiophenone (XV). Preparation of the Grignard reagent was accomplished using 3.456 g (0.14 mole) of magnesium in 20 ml of anhydrous diethyl ether and 9 ml (0.144 mole) of methyl iodide in 20 ml of anhydrous diethyl ether. The reagent was allowed to react with 10.2 g (0.05 mole) of the nitrile (VIII) in 50 ml of anhydrous diethyl ether. After the reaction was complete, it was acidified with a cold dilute hydrochloric acid solution and extracted with diethyl ether. Evaporation of the solvent yieded crystalline material which was recrystallized from ligroin to give 5.5 g (50%) of the acetophenone (XVI), mp 78° (lit.[31] 78°). The carbonyl absorption band in the infrared spectrum was observed at 1689 cm^{-1}. The nmr spectrum showed peaks at δ2.5 (singlet), δ3.85 (triplet), and δ6.75 (singlet).

DISCUSSION

The initial step in the synthesis of elemicin (I) was the conversion of gallic acid (IV) into 3,4,5-trimethoxybenzoic acid (V), the starting material in Scheme 2. This O-alkylation which rendered the hydroxyl groups relatively inactive was achieved with dimethyl sulfate in the presence of base. This well-established procedure gave a very high yield (90%) of the trimethoxy acid (V).[17]



(I)

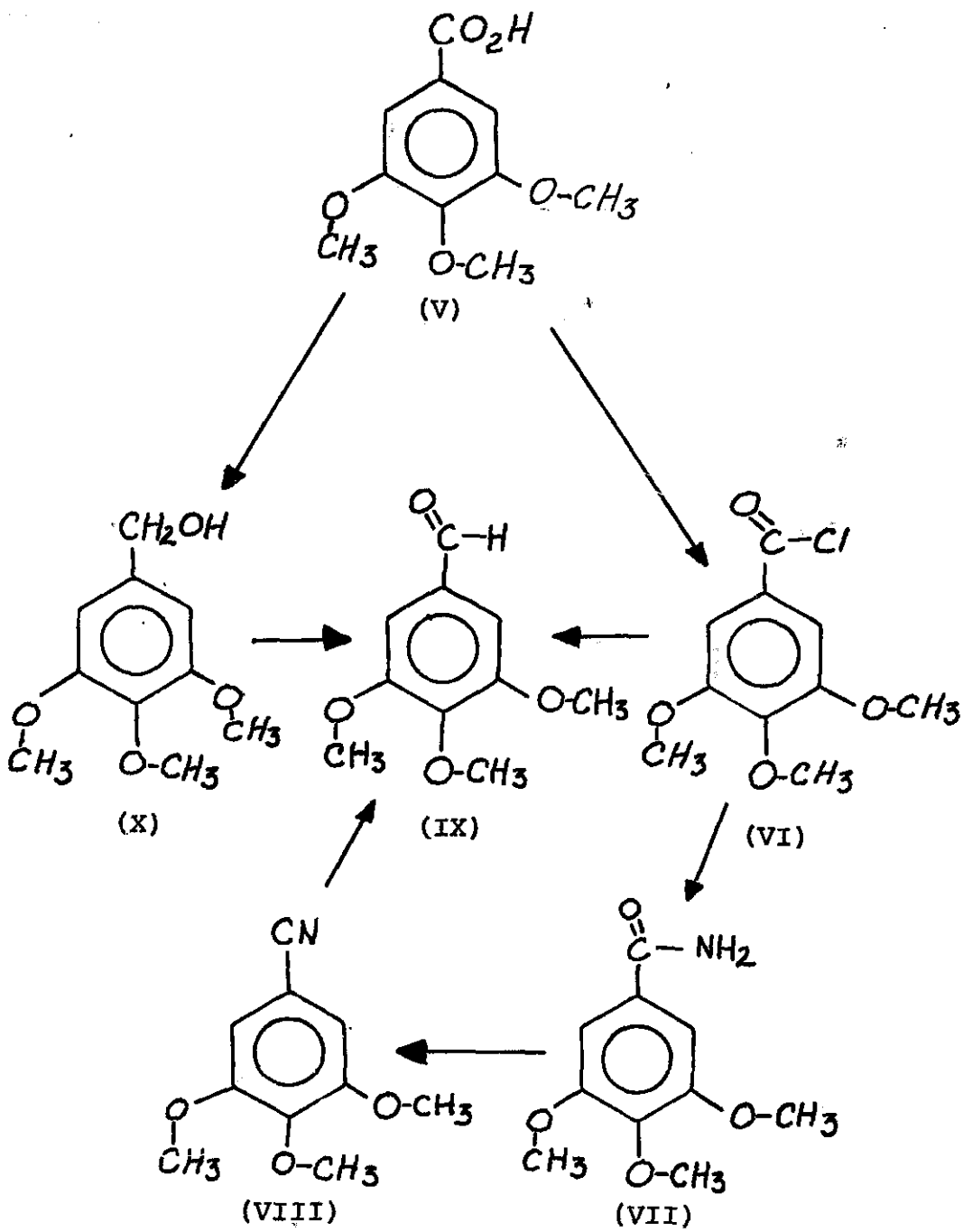


(IV)

The various transformations of the acid (V) to 3,4,5-trimethoxybenzonitrile (VIII) and 3,4,5-trimethoxybenzaldehyde (IX), key compounds in Schemes 3, 4 and 5, are diagrammed in Scheme 2.

Refluxing of the acid (V) with freshly distilled thionyl chloride for two hours resulted in the formation of the acid chloride (VI). After excess thionyl chloride was removed under reduced pressure, the residual crude acid chloride was dissolved in benzene, and treatment with ammonia gas for approximately six hours effected the precipitation of

SCHEME 2



3,4,5-trimethoxybenzamide (VII). The melting point of the long, needle-like crystals obtained by recrystallization from ethyl alcohol was 177-178°, and the yeild was 81%. The dehydration of the amide (VII) to form 3,4,5-trimethoxybenzonitrile (VIII) was accomplished by refluxing diphosphorous pentoxide with the amide (VII) dissolved in tetrachloroethylene.[19] The needle-like crystals of the nitrile (VIII) remaining after recrystallization from ethyl alcohol had a melting point of 92-94°, and the yield was 60%. The reduction of the nitrile (VIII) with diisobutylaluminum hydride (Dibal) or Raney nickel yielded 3,4,5-trimethoxybenzaldehyde (IX).

The Dibal reduction was carried out in a benzene solution under an atmosphere of nitrogen.[21] A solution of Dibal was added dropwise to the stirred solution of the nitrile (VIII) over a two-hour period. Careful acidification of the reaction mixture and subsequent stirring for an additional hour resulted in the formation of the aldehyde (IX). Isolation and recrystallization from petroleum ether provided the aldehyde (IX) (mp 74°) in 54% yield.

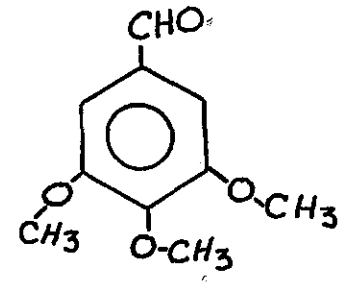
The Raney nickel reduction proved to be a better method than the Dibal reduction for the preparation of the aldehyde (IX). After treatment of the nitrile (VIII) with formic acid and activated Raney nickel, the reaction mixture was stirred for approximately two hours at 40-50°.[23] Dilution with aqueous ethyl alcohol was followed by several extractions

with diethyl ether; subsequent evaporation of the ethereal layer yielded crystalline material. Recrystallization from ligroin provided the aldehyde (IX) (mp 74°) in 80% yield.

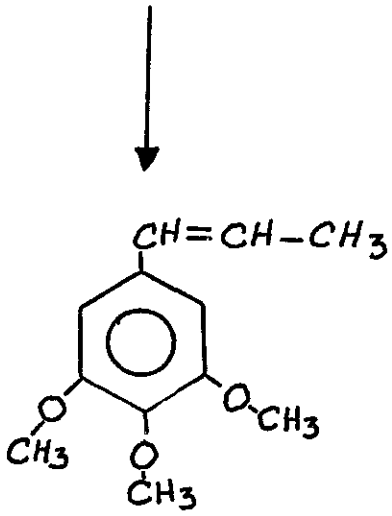
An alternate preparation of the aldehyde (IX) was by the reduction of the acid (V). A solution of the acid (V) in THF was added dropwise to an excess of lithium aluminum hydride dissolved in THF.[24] The reaction mixture was refluxed for one hour, acidified, and the organic layer removed. Evaporation of the solvent yielded 3,4,5-trimethoxybenzyl alcohol (X) as a clear oil which showed no carbonyl absorption in the infrared spectrum. The benzyl alcohol (X) dissolved in petroleum ether was treated with manganese dioxide for one hour.[25] The aldehyde (IX) was isolated in 45% yield.

A synthesis of elemicin (I) was accomplished in a two-step pathway from the starting aldehyde (IX) (Scheme 3). The treatment of ethyltriphenylphosphonium bromide in benzene with n-butyllithium followed by addition of the aldehyde (IX) provided isoelemicin (XI) in 38% yield. Conversion of isoelemicin (XI) into elemicin (I) was accomplished by Brown's procedure.[27,28] This procedure involves the formation of an organoborane which first undergoes an intramolecular migration to the terminal position then an intermolecular migration to another olefin resulting in double bond formation at the terminal position. (See page 20.) This sequence provided elemicin (I) in 20% yield. All data corresponds favorably with elemicin (I) obtained from

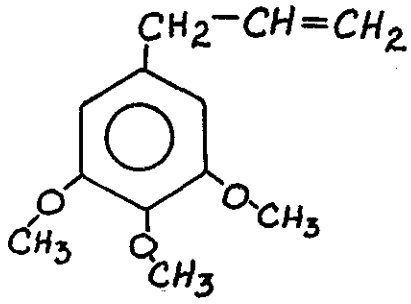
SCHEME 3



(IX)

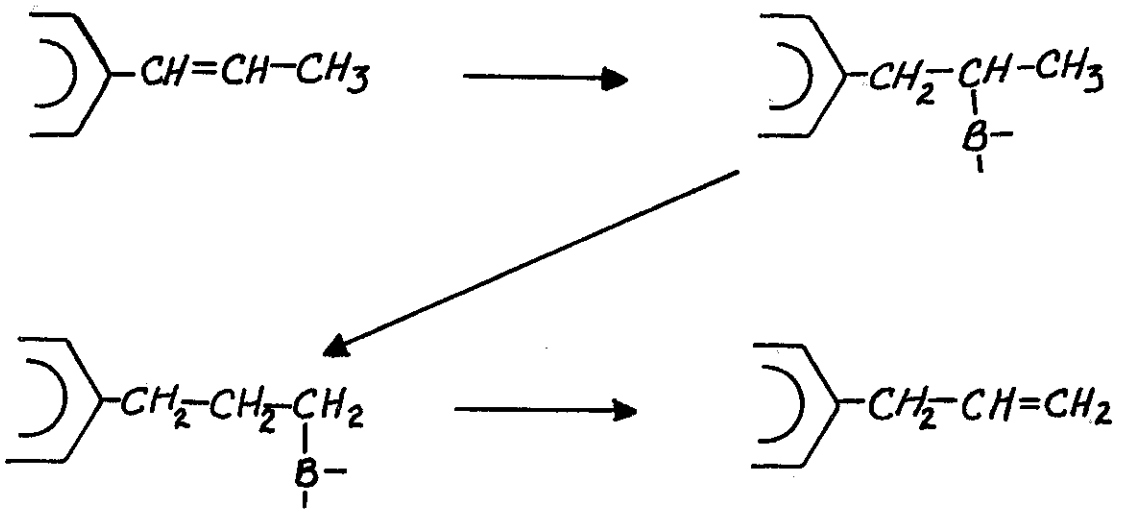


(XI)



(I)

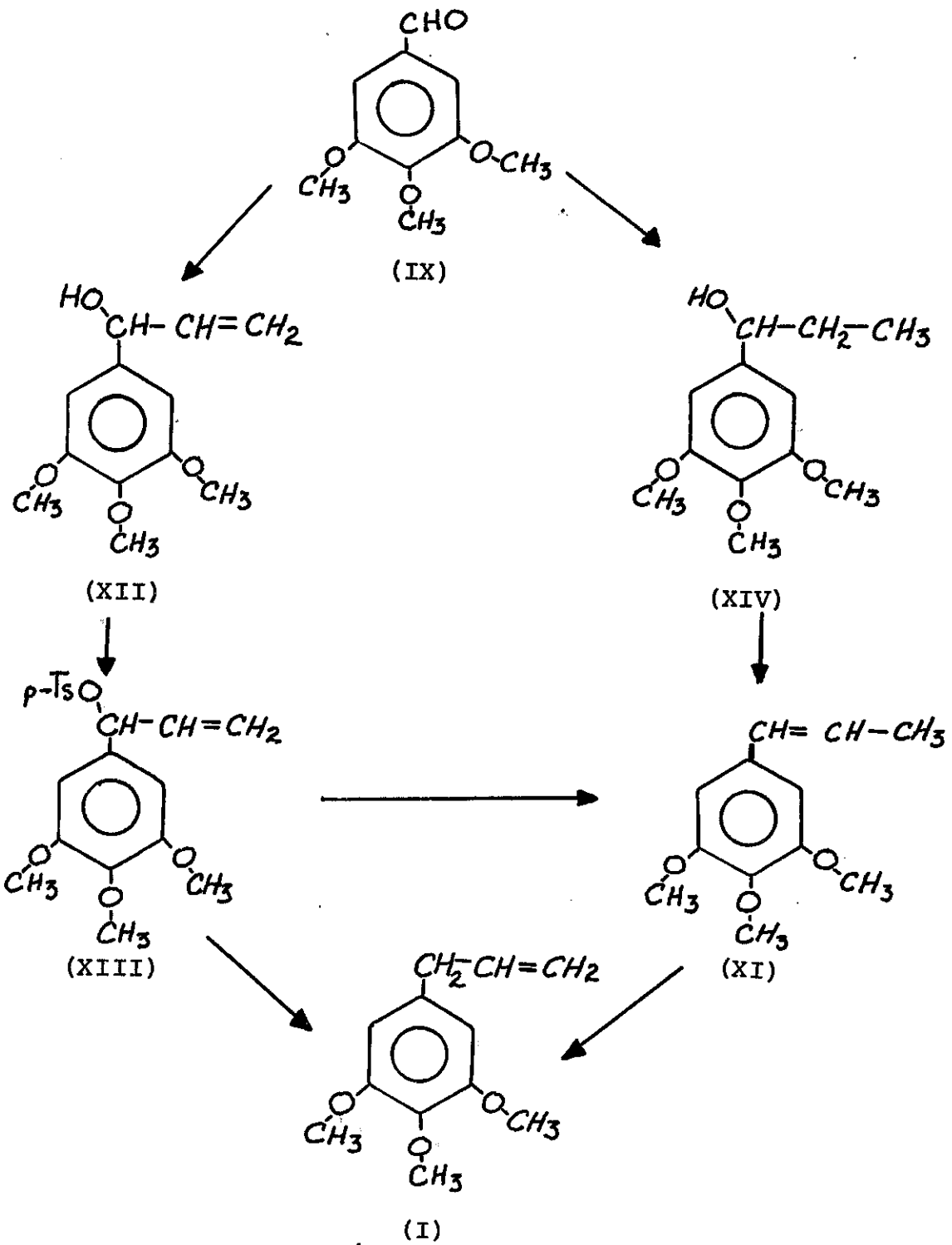
treatment of 4-allyl-2,6-dimethoxyphenol with potassium carbonate and methyl iodide.[32]



Two other pathways may be envisioned for the conversion of the aldehyde (IX) into elemicin (I) (Scheme 4), each having as its first step the treatment of the aldehyde (IX) with Grignard reagents. Both Grignard approaches proceed to elemicin (I) in four steps.

One pathway suggests the treatment of the aldehyde (IX) with vinylmagnesium bromide to yield the allyl alcohol (XII) which may be converted to the corresponding tosylate (XIII).[33] Reduction by lithium aluminum hydride should lead to isoelemicin (XI) and elemicin (I) <u>via</u> S_N2' and S_N2 mechanisms respectively.[34] Isoelemicin (XI) may be isomerized to elemicin (I) using Brown's procedure.

SCHEME 4


CHO
(IX)
HO CH- CH=CH2
(XII)
HO CH-CH2-CH3
(XIV)
p-Ts O CH- CH=CH2
(XIII)
CH= CH-CH3
(XI)
CH2-CH=CH2
(I)

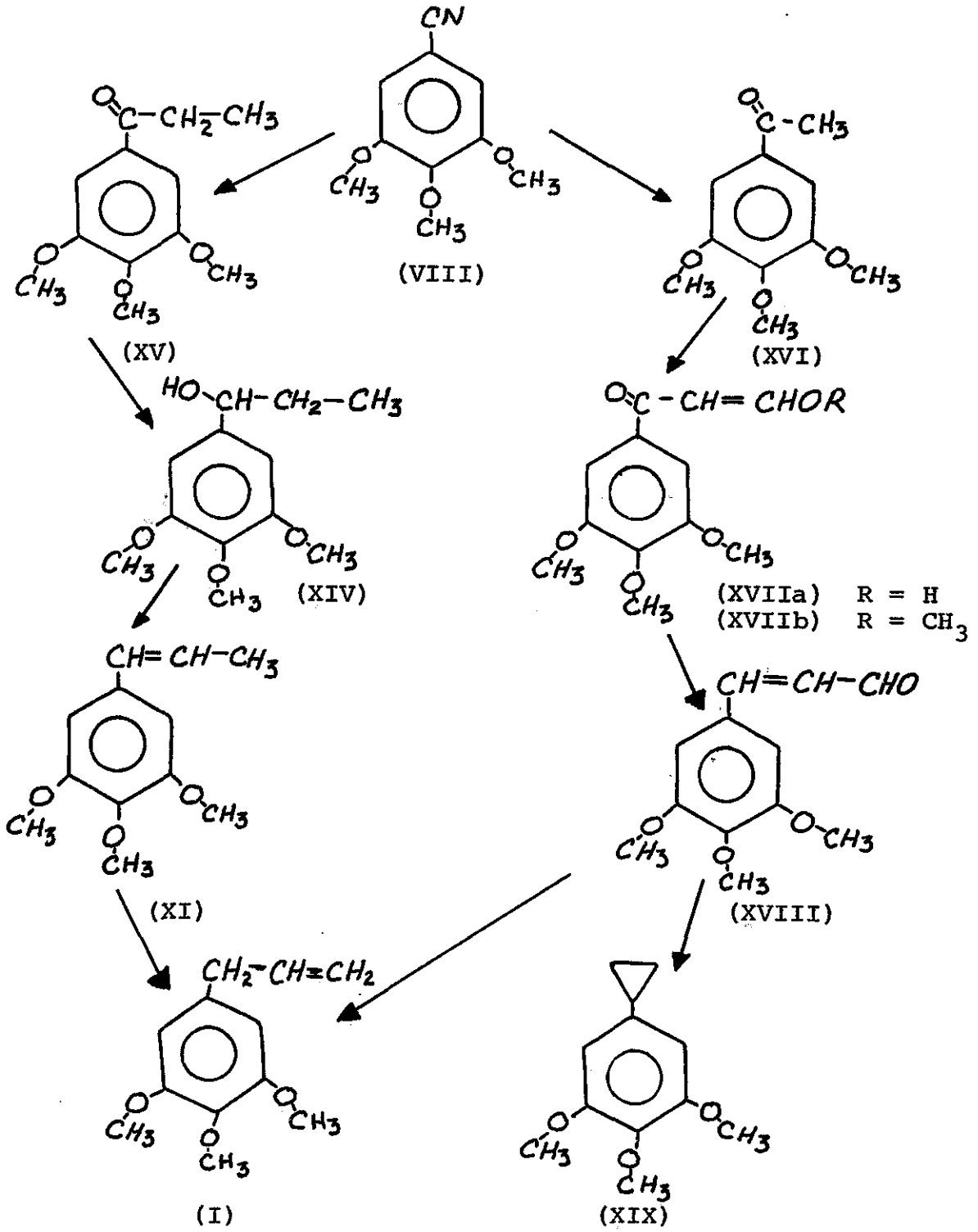
The second method involves the treatment of the aldehyde (IX) with ethylmagnesium iodide to provide the benzylic alcohol (XIV). Dehydration of the alcohol (XIV) with p-toluenesulfonic acid (p-TsOH)[35] in benzene would yield isoelemicin (XI) which may be converted into the desired product via Brown's procedure.

The attempted treatment of the aldehyde (IX) with either Grignard reagent yielded clear oils which showed multiple spots on thin-layer chromatograms. Although ir and nmr spectra of compounds partially purified by column chromatography were taken, identification was not possible due to the complexity of the products.

3,4,5-Trimethoxybenzonitrile (VIII) could be converted to a ketone by treatment with various Grignard reagents (Scheme 5). The nitrile (VIII) should be transformed into the propiophenone (XV) when allowed to react with ethylmagnesium iodide in anhydrous diethyl ether.[30] Reduction of the propiophenone (XV) with $NaBH_4$ should yield the corresponding benzylic alcohol (XIV).[36] This alcohol, previously encountered in Scheme 4, would be converted into elemicin (I) by the same pathway. Alternatively, the nitrile (VIII) should yield the acetophenone (XVI) upon treatment with methylmagnesium iodide.[30] The proposed pathway (Scheme 5) for the conversion of the acetophenone (XVI) into elemicin (I) is as follows:

(a) preparation of the hydroxy-methylene derivative

SCHEME 5



(XVIIa),[37]

(b) conversion into the corresponding enol ether (XVIIb),[37]

(c) reduction with sodium borohydride followed by treatment with acid to yield the substituted cinnamaldehyde (XVIII)[38] and finally,

(d) reduction *via* hydrazine and base (Wolff-Kishner) to yield elemicin (I).[39]

It is significant to note that the cyclopropyl compound (XIX) may be formed as a side product if not the major product.[40]

The reaction of the nitrile (VIII) with ethylmagnesium iodide gave the propiophenone (XV) in an 84% yield. Accordingly, methylmagnesium iodide when allowed to react with the nitrile (VIII) provided a 50% yield of the acetophenone (XVI). The remaining steps of the pathways proposed in Scheme 5 are currently under investigation in this laboratory.

SUMMARY

This research was undertaken because of the frequently encountered propenyl side chain in naturally occurring compounds and because this conversion is envisioned as a key operation in another synthetic problem currently under study in this laboratory. Since gallic acid (IV) is readily available and its conversion would lead to a natural product that has recently generated particular interest, the major goal was to seek synthetic pathways to this compound, elemicin (I).

Several methods of approach were investigated having as the key intermediate 3,4,5-trimethoxybenzaldehyde (IX) or 3,4,5-trimethoxybenzonitrile (VIII). A successful pathway involved:

1) conversion of gallic acid (IV) into 3,4,5-trimethoxybenzoic acid (V);
2) transformation of the acid (V) into either 3,4,5-trimethoxybenzonitrile (VIII) or 3,4,5-trimethoxybenzyl alcohol (X);
3) conversion of either the nitrile (VIII) or the alcohol (X) into 3,4,5-trimethoxybenzaldehyde (IX);
4) transformation of the aldehyde (IX) into isoelemicin (XI); and
5) conversion of isoelemicin (XI) into elemicin (I).

Other methods attempted involved the addition of various

Grignard reagents to the aldehyde (IX) or the nitrile (VIII). These did not yield sucessful synthetic pathways to elemicin (I).

BIBLIOGRAPHY

1. E. A. Benjnerowicz and E. F. Kirch, J. Pharm. Sci., 53, 988 (1963).

2. D. H. Efron (Ed.), Ethnopharmacologic Search for Psychoactive Drugs, 185-229, U. S. Dept. of Health, Education and Welfare (1967).

3. F. Mauthner, Ann., 414, 250 (1918).

4. P. C. Dandiya, P. K. Sharna and M. K. Menon, Indian J. Med. Res., 50, 750 (1962).

5. L. Bert, Compt. Rend., 213, 873 (1941).

6. H. Wallnofer and A. von Rottauscher, Chinese Folk Medicine, 57, Bell Publishing Company, Inc., New York (1965).

7. A. R. Cushny, Proc. Royal Soc. Med., I, 39 (1908).

8. R. B. Payne, New Eng. J. Med., 269, 36 (1963).

9. P. J. Hanzlik, California and Western Medicine, 44, i July-August (1938).

10. G. A. Alles, Neuropharmacology, The Josiah Macy, Jr. Foundation, Madison Printing Company, New York (1959).

11. J. Borsy, Arch. Int. Pharmacodyn, 126, 426 (1960).

12. A. T. Shulgin, S. Bunnell and T. Sargent, Nature, 189, 1011 (1961).

13. A. T. Shulgin, J. Chromatogr., 30(1), 54 (1967).

14. Y. Fujita, S. Fujita and W. H. Huang, Yakugaku Zasshi, 91(1), 132 (1971).

15. V. Rao, T. R. Seshadri and T. R. Thiruvengadam, Proc. Ind. Acad. Sci., 30A, 114 (1949).

16. M. Walker, J. McKinney and E. Oswald, J. Labelled Cmpd., 10, No. 3, 405 (1974).

17. H. Gilman and A. H. Blatt (Ed.), Org. Syn., I, 537 (1942).

18. I. Kh. Fel'dman and E. I. Boksiner, Biol. Aktivn. Soedin., Akad. Nauk. SSSR, 79 (1965).

19. E. C. Horning (Ed.), Org. Syn., III, 584 (1955).

20. M. Descamps and F. Binon, Bull. Soc. Chim. Belges, 71, 579 (1962).

21. T. A. Valdes, "A Synthesis of N-Methyl-3-Methyl-2-Pyrroline," (Thesis, McNeese State University, August 1973).

22. I. Heilbron (Ed.), Dictionary of Organic Compounds, V, 3133, Oxford Univ. Press, New York (1965).

23. O. G. Backeburg and B. Staskun, J. Chem. Soc., 3961 (1962).

24. L. Moreno, Personal Communication (1973).

25. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evens, B. A. Hems, A. B. A. Jansen and T. Walker, J. Chem. Soc., 1094 (1952).

26. R. S. Monson, Advanced Organic Synthesis, 105, Academic Press, New York (1971).

27. H. C. Brown and G. Zweifel, J. Am. Chem. Soc., 89, 561 (1967).

28. H. C. Brown, M. V. Bhatt, T. Munekata and G. Zweifel, J. Am. Chem. Soc., 89, 567 (1967).

29. R. Roberts, J. Gilbert, L. Rodewald and A. Wingrove, An Introduction to Modern Experimental Organic Chemistry, 244, Holt, Rinehart and Winston, Inc., New York (1974).

30. E. D. Amstutz, J. Am. Chem. Soc., 71, 3836 (1949).

31. F. Mauthner, J. Prakt. Chem., 116, 321 (1927).

32. J. D. Tauber, Personal Communication (1976).

33. K. Wiberg and J. Pfeiffer, J. Am. Chem. Soc., 92, 553 (1970).

34. P. B. D. de la Mare, Molecular Rearrangements, Vol. I, Paul de Mayo, Ed., 27-110, John Wiley and Sons, New York (1963).

35. I. Ho and J. G. Smith, Tetrahedron, 26, 4277 (1970).

36. D.L. Fishel and R. C. Fort, Modern Experimental Organic Chemistry, 70, Macmillan Company, New York (1971).

37. W. S. Johnson and H. Posvic, J. Am. Chem. Soc., 69, 1361 (1947).

38. W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi and Y. Hayase, J. Am. Chem. Soc., 89, 1483 (1967).

39. W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisada and S. Kamata, J. Am. Chem. Soc., 92, 3203 (1970).

40. H. E. Baumgarten (Ed.), Org. Syn., V, 929 (1973).

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