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STRUCTURE AND SYNTHESIS OF ARCHANGELIN AND STRUCTURE
OF NICANDRENONE, AN INSECTICIDAL PLANT
STEROID DERIVATIVE

by

David James Eckert

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DEPARTMENT OF CHEMISTRY
In Partial Fulfillment of the Requirements
For the Degree of
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In the Graduate College
THE UNIVERSITY OF ARIZONA

1973
I hereby recommend that this dissertation prepared under my direction by David James Eckert entitled STRUCTURE AND SYNTHESIS OF ARCHANGELIN AND STRUCTURE OF NICANDRENONE, AN INSECTICIDAL PLANT STEROID DERIVATIVE be accepted as fulfilling the dissertation requirement of the degree of DOCTOR OF PHILOSOPHY.

Dissertation Director

Date

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SIGNED: [Signature]

David Albert
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ABSTRACT

Initially, the structure of archangelin, a naturally occurring furocoumarin, was reported as Ib. Later, structure Ic was proposed for archangelin. By synthesis and spectral methods the structure of archangelin has now been revised to XVIc. In addition, spectral techniques were developed to distinguish between bergaptyl, isobergaptyl, xanthotoxyl, and sphondyl ethers.

\[ \text{Ib} \quad \text{Ic} \quad \text{XVIc} \]

The insect repellent substance, nicandrenone from *Nicandra physalodes*, was originally thought to be a glycoside with the molecular formula \( C_{27}H_{37}O_7 \). The molecular formula was subsequently changed to \( C_{34}H_{42}O_7 \), but little else was known about the structure except that it contains a hydroxyl group and that it has a conjugated keto function. Evidence is presented here that nicandrenone has structure XXXIII \( (C_{28}H_{34}O_6) \) and is the first reported steroid derivative with ring D.
aromatic. Structure XXXIII was substantiated by other researchers employing X-ray analysis. Their structure XLVIII gives the complete stereochemistry of the molecule.
PART I

STRUCTURE AND SYNTHESIS OF ARCHANGELIN
INTRODUCTION

From the root of the Indian medicinal plant, *Angelica archangelica* L., three furocoumarins, angelicin, C_{11}H_{16}O_{3}, prangolarin, C_{16}H_{14}O_{5}, and archangelin, C_{21}H_{22}O_{4}, were isolated (1).

Archangelin, mp 132°, crystallizes from methanol in thick rods. It does not contain any methoxyl, methylenedioxy, or active hydrogens but does contain at least one methyl group attached to a quaternary carbon. Archangelin is neutral in nature and was shown to be a coumarin by its behavior toward 5% aqueous and alcoholic alkali. The furocoumarin moiety was indicated by the UV [λ_{max}^EtOH = 222 (log ε = 4.38), 251 (log ε = 4.19), and 310 nm (log ε = 4.08)], IR [5.8 μ (conjugated lactone), 8.9 μ (ether), and 9.3 μ benzofuran)], and the NMR [a pair of doublets (J = 2.5 Hz) at τ 2.38 and τ 2.75 for the α and β protons of the furan ring, and a pair of doublets (J = 10 Hz) at τ 1.85 and τ 3.7 for the α,β olefinic protons of the coumarin ring and a singlet at τ 2.99 for the lone aromatic proton].

When archangelin was hydrogenated, pyrolyzed, or acid hydrolyzed, isobergaptol (Ia), C_{11}H_{16}O_{4}, mp 274-278°, was reportedly obtained as well as a C_{10} terpene. Therefore, archangelin was believed to be the isobergaptyl ether of a monoterpene alcohol.
Chatterjee and Dutta (1) interpreted the NMR data (Table 1) and arrived at structure Ib for archangelin.

Table 1. NMR data reported for archangelin.*

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Resonance (τ)</th>
<th>No. of protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumarin</td>
<td>1.85(d), 3.7(d)</td>
<td>2</td>
</tr>
<tr>
<td>Furan</td>
<td>2.38(d), 2.75(d)</td>
<td>2</td>
</tr>
<tr>
<td>Benzene</td>
<td>2.99(s)</td>
<td>1</td>
</tr>
<tr>
<td>Olefinic</td>
<td>4.35(s)</td>
<td>1</td>
</tr>
<tr>
<td>Methylenes</td>
<td>7.58-8.9(m)</td>
<td>7</td>
</tr>
<tr>
<td>Olefinic methyl</td>
<td>8.32(s)</td>
<td>3</td>
</tr>
<tr>
<td>gem-Dimethyl</td>
<td>9.08(s)</td>
<td>6</td>
</tr>
</tbody>
</table>

s = singlet; d = doublet; m = multiplets

* From Chatterjee and Dutta (1).
However, Thalacker (2) re-examined the NMR data and made the assignments depicted on partial structure c. He ruled out structure Ib because there are no vinyl hydrogens present, and the absorption at $\tau$ 5.01 integrates for two protons, not one, and is a singlet, not a triplet as suggested by structure Ib. The absorption at $\tau$ 7.75 (2 protons), though very broad, is suggestive of a triplet with $J = 6$ Hz. The triplet at $\tau$ 8.56 (2 protons; $J = 6$ Hz) suggests that an isolated $\text{CH}_2\text{CH}_2\text{-}$ grouping is present. The somewhat broadened singlet at $\tau$ 8.30 (3 protons) is in the region where vinylic methyl groups absorb. The broadened singlet at $\tau$ 8.16 (2 protons) is due to an isolated methylene while the sharp singlet at $\tau$ 9.08 (6 protons) suggests a gem-dimethyl group. Both structures, Ic and Id, however, are in agreement with the NMR evidence. Structure Ic is favored over Id on biogenetic grounds since cyclolavandulol (IIc) is easily obtained from lavandulol (IV) by acid-catalyzed cyclization (3):

![Chemical structure](image)

The corresponding aldehyde (4) (V) and acid (5) (VI) have been found in nature:
Thalacker (2) believed that the absorption in the region \( \tau 1.8-3.7 \) was in agreement with the isobergaptyl portion of archangelin previously reported (1). Based on the information presented, Thalacker suggested structure Ic for archangelin.

Thalacker attempted to prove his structure for archangelin by synthesizing it. He made the terpene side chain by the following synthetic sequence (Figure 1):

\[
\begin{align*}
\text{VII} & \quad \text{VIII} & \quad \text{IX} + \text{X} \\
\text{IX} + \text{X} & \quad \rightarrow \quad \text{XII} & \quad \rightarrow \quad \text{XI} & \quad \rightarrow \quad \text{VI} & \quad \rightarrow \quad \text{IIc} & \quad \rightarrow \quad \text{IIIc}
\end{align*}
\]

Figure 1. Preparation of \( \beta \)-cyclolavandulyl bromide (IIIc).
Since isobergaptene (Ie) is commercially available, Thalacker tried to demethylate it to obtain isobergaptol (Ia), which he wanted to use as the starting material for his total synthesis. He used the pyridine hydrochloride method for demethylation, a method used in the steroid field (6). However, the product obtained was not the desired isobergaptol. He, therefore, decided to prepare a model compound (XV) and to compare its NMR spectrum with that of archangelin. He made the sodium salt (XIV) of umbelliferone and reacted it with IIIc:

![Chemical structures](image)

The NMR spectrum of XV compared quite well with that of archangelin. The NMR parameters for XV and archangelin have been tabulated in Table 2. Of special interest is the singlet for two protons at \( \tau 5.45 \) (\( \tau 5.01 \) in archangelin) for the isolated, acyclic methylenedioxy. The IR spectrum of XV shows the \( \alpha,\beta \)-unsaturated lactone carbonyl at 5.75 \( \mu \).

Acid-catalyzed degradation of archangelin gave a very small yield of a terpene acetate that compared favorably with the acetate of
IIc, thereby confirming that partial structure (c) is correct for the terpene side chain of archangelin.

Table 2. Comparison of NMR parameters of XV and archangelin.

<table>
<thead>
<tr>
<th>Assignment</th>
<th>XV</th>
<th></th>
<th>Archangelin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resonance (τ)</td>
<td>J (Hz)</td>
<td>Protons #</td>
<td>Resonance (τ)</td>
</tr>
<tr>
<td>Coumarin</td>
<td>3.75(d), 2.35(d)</td>
<td>10</td>
<td>2</td>
<td>3.65(d), 1.97(d)</td>
</tr>
<tr>
<td>Furan</td>
<td>--</td>
<td>-</td>
<td>-</td>
<td>2.94(d), 2.32(d)</td>
</tr>
<tr>
<td>Benzene</td>
<td>3.18(s), 3.13(d), 2.65(d)</td>
<td>10</td>
<td>1</td>
<td>2.80(s)</td>
</tr>
<tr>
<td>Methylene-oxy</td>
<td>5.45(s)</td>
<td>2</td>
<td>2</td>
<td>5.01(s)</td>
</tr>
<tr>
<td>Methylene</td>
<td>7.88(t)</td>
<td>6</td>
<td>2</td>
<td>7.75(t)</td>
</tr>
<tr>
<td>Isolated methyl</td>
<td>8.18(s)</td>
<td>2</td>
<td>2</td>
<td>8.16(s)</td>
</tr>
<tr>
<td>Olefinic methyl</td>
<td>8.25(s)</td>
<td>3</td>
<td>3</td>
<td>8.30(s)</td>
</tr>
<tr>
<td>Methylene</td>
<td>8.60(t)</td>
<td>6</td>
<td>2</td>
<td>8.56(t)</td>
</tr>
<tr>
<td>gem-Dimethyl</td>
<td>9.06(s)</td>
<td>6</td>
<td>6</td>
<td>9.08(s)</td>
</tr>
</tbody>
</table>

s = singlet
d = doublet
t = triplet
DISCUSSION

An NMR comparison of archangelin and Thalacker's (2) model compound XV indicated that the terpene side chain most likely has partial structure (c) but did not verify the structure of the furocoumarin moiety. Therefore, an attempt was made to synthesize compound Ic from the sodium salt of bergaptyl (XVIh) and IIc in order to differentiate between partial structures (c) and (d) and to show that archangelin is the isobergapytyl ether (Ic) rather than the linear, bergaptyl ether (XVIc). The alcohol IIc was prepared by the sequence outlined in Figure 1 (2) with some improvements. Compound 2,6-dimethyl-5-hepten-2-ol (VIII) was prepared from 2-methyl-5-hepten-2-one (methylheptenone, 

\[ \text{XVI} \]

(For a-e, see p. 3) 

VII, NMR spectrum - Figure 10; see Appendix for all spectra, Figures 10 through 50) in nearly quantitative yield by the method of Callen, Dornfeld, and Coleman (7). The product is a tertiary alcohol, so hydrolysis of the corresponding Grignard magnesium salt with strong mineral acid must be avoided since this could result in dehydration to
2,6-dimethyl-2,5-heptadiene (XVII). To simplify the reported procedure a saturated solution of ammonium chloride was added to the reaction mixture until the emulsion broke up (pH = 9). Under these conditions only the desired VIII was obtained, usable for the next step without further purification. The NMR spectrum (Figure 11) of VIII closely matched that reported by Thalacker (2).

Dehydrative cyclization of the alcohol (VIII) was accomplished (2,8) by refluxing an equimolar amount of VIII and oxalic acid with no solvent present. The GLC of the reaction mixture indicated at least four compounds present: 26% IX and 17% X (single peak per GLC; % by NMR), 22% of two unidentified substances (not completely resolved by GLC), and 35% of 2,6-dimethyl-2,5-heptadiene (XVII). Compound XVII was identified by comparison of its retention time on GLC to that of an authentic sample. The NMR spectrum (Figure 12) of XVII gives a broadened triplet centered at $\tau 4.97$ ($J_{ab} = 7$ Hz, 2 protons) with long range coupling ($J \approx 2$ Hz) evident for two olefinic protons. There is another broadened triplet at $\tau 7.39$ ($J_{ab} = 7$ Hz, 2 protons) with long range coupling ($J \approx 1$ Hz) apparent. This absorption is in the appropriate position for a methylene situated between two double bonds, and the coupling constant of 7 Hz is reasonable (9, p. 145) for coupling between $H_a - H_b$ in XVII. There are two olefinic methyl groups at $\tau 8.34$ ($J \approx 2$ Hz, 6
protons), and two more olefinic methyl groups at \( \tau 8.39 \) (\( J \approx 1 \text{ Hz} \), 6 protons). The NMR data are consistent with the structure drawn for XVII. The first time IX and X were prepared, the oxalic acid was carefully removed from the reaction mixture with 5\% aqueous sodium bicarbonate before attempting to separate the mixture of isomers by spinning band distillation. Even after every precaution had been taken, distillation only enriched the desired IX and X, but did not separate them from the other substances present. The GLC indicated that one slightly higher boiling fraction contained 81\% of what is believed to be XIX, 12\% of XVIII, and 7\% of a mixture of IX and X. The NMR spectrum (Figure 13) of this fraction, though contaminated, shows a singlet at \( \tau 5.36 \) for a terminal methylene, a broadened singlet at \( \tau 7.98 \) for an isolated, allylic methylene, a sharp singlet at \( \tau 8.88 \) for gem-dimethyls, and complex absorption between \( \tau 8.2-8.8 \) for 3 methylenes. The NMR evidence suggests the presence of XIX in the reaction mixture. The NMR spectra of other fractions from the spinning band distillation indicated that the other unidentified product may be XVIII. All five isomers may be interconverted by acid catalysis through various carbonium ion intermediates shown in Figure 2. Since the desired products, IX and X, are the most volatile, it seemed reasonable that if the oxalic acid were left in the reaction mixture during the spinning band distillation perhaps the equilibrium shown in Figure 2 might shift toward IX and X as they are distilled from the reaction vessel. This indeed turned out to be the case. The reaction was carried out in the spinning band distillation apparatus with the take off, initially, completely
Figure 2. Intermediates and by-products in the preparation of IX and X.
turned off. After refluxing for 1 hr the reflux ratio was set at 1:1 and a nearly quantitative yield of uncontaminated IX and X was collected. The NMR spectrum (Figure 14) agrees with that reported by Thalacker (2) for IX and X. No attempt was made to separate the isomers since IX reacts preferentially in the succeeding reaction, and unreacted X can more easily be removed later in the reaction sequence.

Friedel-Crafts acylation (2, 10) of the mixture of IX and X with acetyl chloride in the presence of stannic chloride gave a 60-40 mixture of 1-acetyl-2,4,4- and 6-acetyl-1,3,3-trimethylcyclohexenes (XI and XII, respectively). A plausible mechanism is:

![Chemical structure diagram](image)

Figure 3. Intermediates and by-products in the preparation of XI.
Upon refluxing the mixture of XI and XII with N,N-dimethyl aniline, XII was partially isomerized to XI giving an equilibrium mixture (85% XI, 15% XII) of these ketones. This constitutes an 85% yield of XI based on the amount of IX initially present. The NMR spectrum (Figure 15) of the products is in good agreement with Thalacker's (2) spectrum of the mixture of XI and XII.

Oxidation of XI with sodium hypobromite (2,10,11) gave 1-carboxy-2,4,4-trimethylcyclohexene (VI) in 42% yield based on the amount of XI present initially. The NMR spectrum (Figure 16) of the product matched Thalacker's (2) for VI. Crystallization from methanol gave white needles, mp 109-111° [lit (11) 110-111°].

Reduction of the acid (VI) with lithium aluminum hydride gave a poorer yield than did reduction of the corresponding methyl ester (XIII), prepared (2; 12, p. 166) nearly quantitatively from VI with diazomethane. Reduction of the ester (XIII) in ether gives the alcohol (IIC) in essentially quantitative yield (13). The NMR spectrum (Figure 17) of the product compares closely to Thalacker's for IIC.

Alcohol (IIC) was converted to the bromide (IIIc) (2) by the addition of phosphorous tribromide. Due to the possibility that IIIc might decompose upon standing, the next step in the sequence was carried out immediately without characterization of the product (IIIc).

Bergaptol (XVIa) was prepared from both bergamottin (XVII) and bergaptene (XVIe), which were isolated (14) from bergamot oil extra (Fritzsche Brothers). Care must be exercised in this isolation, for limettin (XXI), which is also present in bergamot oil, is difficult to
separate from bergaptene (XVIe) since they have nearly identical $R_f$ values in all of the solvent systems investigated for TLC. Rigorous analysis by NMR was the only method found useful in examining fractions that might contain either or both bergaptene (XVIe) and limettin (XXI). Pure bergaptene (XVIe), mp 188-191° [lit (15) 190-191°], was obtained by crystallization from chloroform. The NMR spectrum (15-20) (Figure 18) of bergaptene contains a doublet at $\tau \, 3.78$ ($J_{ab} = 9.5$ Hz, 1H) for $H_a$; a doublet at $\tau \, 1.88$ ($J_{ab} = 9.5$ Hz, 1H) for $H_b$; a doublet at $\tau \, 2.42$ ($J_{de} = 2.5$ Hz, 1H) for $H_e$; a doublet at $\tau \, 3.00$ ($J_{de} = 2.5$ Hz, 1H) for $H_d$; a singlet at $\tau \, 2.90$ (1H) for $H_c$; and a sharp singlet at $\tau \, 5.77$ (3H) for the methoxyl group. The UV spectrum (Figure 19) of bergaptene ($\lambda_{max}^{EtOH}$ 222 nm, 248 nm, 258 nm, 267 nm, and 311 nm) compares quite well with that reported (21,22). The IR spectrum (23) (Figure 20) of bergaptene shows the typical absorption of a furocoumarin [1728 cm$^{-1}$ (conjugated lactone), 1115 cm$^{-1}$ (ether), and 1070 cm$^{-1}$ (benzofuran)]. Table 3 compares bergaptene to other compounds of interest on TLC.

Bergamottin (XVIf), mp 53-56° [lit (14) 59-61°], isolated from bergamot oil was crystallized from petroleum ether. Its NMR spectrum
Table 3. \( R_f \) values per TLC for various compounds of interest.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R_f )</th>
<th>Color when sprayed with 30% sulfuric acid and heated gently on a hot plate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergamottin</td>
<td>0.70</td>
<td>dark olive green</td>
</tr>
<tr>
<td>Archangelin</td>
<td>0.70</td>
<td>dark olive green</td>
</tr>
<tr>
<td>Limettin</td>
<td>0.58</td>
<td>yellow</td>
</tr>
<tr>
<td>Bergaptene</td>
<td>0.56</td>
<td>green</td>
</tr>
<tr>
<td>Bergaptol</td>
<td>0.42</td>
<td>dark green</td>
</tr>
</tbody>
</table>

(16) (Figure 21) shows the usual furocoumarin pattern with a doublet at \( \tau 3.81 \) (\( J_{ab} = 10 \) Hz, 1H) for \( H_a \); a doublet at \( \tau 1.88 \) (\( J_{ab} = 10 \) Hz, 1H) for \( H_b \); a doublet at \( \tau 2.48 \) (\( J_{de} = 2.5 \) Hz, 1H) for \( H_c \); a doublet at \( \tau 3.09 \) (\( J_{de} = 2.5 \) Hz, 1H) for \( H_d \); and a singlet at \( \tau 2.94 \) (1H) for \( H_e \).

The geranyl side chain has a multiplet at \( \tau 4.50 \) (1H) for \( H_g \); a partially obscured multiplet at \( \tau 4.98 \) (1H) for \( H_h \); a doublet at \( \tau 5.10 \) (\( J_{gh} = 7 \) Hz, 2H) for \( H_g \); a multiplet at \( \tau 7.89 \) (4H) for \( H_j \) and \( H_k \); two methyl singlets at \( \tau 8.35 \) (6H) for \( H_n \) and \( H_i \); and a methyl singlet at \( \tau 8.43 \) (3H) for \( H_m \). The IR spectrum (Figure 22) of bergamottin displays the typical furocoumarin absorption [\( 1725 \) cm\(^{-1}\) (conjugated lactone), \( 1120 \) cm\(^{-1}\) (ether), and \( 1070 \) cm\(^{-1}\) (benzofuran)]. The UV spectrum (Figure 23) of bergamottin [\( \text{EtOH}_{\text{max}} \) 223 nm, 244 nm, 249 nm, 258 nm, 267 nm, and 311 nm] matches that reported (21).
Limettin (XXI) was also isolated from bergamot oil (14) and separated from bergaptene only by careful preparative TLC. Its NMR spectrum (Figure 24) has a doublet at \( \tau 2.14 \) (\( J_{ab} = 10 \text{ Hz}, 1\text{H} \)) for \( H_b \); a doublet at \( \tau 3.96 \) (\( J_{ab} = 10 \text{ Hz}, 1\text{H} \)) for \( H_a \); a doublet at \( \tau 3.68 \) (\( J_{cd} = 2 \text{ Hz}, 1\text{H} \)) for \( H_c \); a doublet at \( \tau 3.81 \) (\( J_{cd} = 2\text{Hz}, 1\text{H} \)) for \( H_d \); and two methoxy groups at \( \tau 6.24 \) (3H) and \( \tau 6.28 \) (3H).

Bergaptene (XVIe) was demethylated by the so-called "dry method" of Schönberg and Aziz (24). This method is much milder than the usual methods which employ stronger acids. Bergaptene and magnesium iodide were heated until all of the solvent evaporated, and the dry residue was further heated at elevated temperatures. Attempts at crystallizing bergaptol failed. The best methods found to purify bergaptol (XVIa) were sublimation (205-220\( ^\circ \), 3 hr, \( 10^{-5} \) torr) and liquid column chromatography. A yellow solid was obtained that melted at 274-278\( ^\circ \) [lit (15) 277-278\( ^\circ \)]. The NMR spectrum (Figure 25) of bergaptol (XVIa) indicates the usual furocoumarin pattern in the region \( \tau 1-4 \) with a doublet at \( \tau 1.61 \) (\( J_{ab} = 9.5 \text{ Hz}, 1\text{H} \)) for \( H_b \); a doublet at \( \tau 3.68 \) (\( J_{ab} = 9.5 \text{ Hz}, 1\text{H} \)) for \( H_a \); a doublet at \( \tau 2.05 \) (\( J_{ed} = 2.5 \text{ Hz}, 1\text{H} \)) for \( H_e \); a doublet at \( \tau 2.65 \) (\( J_{ed} = 2.5 \text{ Hz}, 1\text{H} \)) for \( H_d \); a singlet at \( \tau 2.84 \) for \( H_c \), the lone aromatic proton. The phenolic -OH appears as a very broad peak centered at about \( \tau 5.02 \) (1H).

Apparently one of the fractions from the crystallization of bergaptene contained limettin as well. Upon demethylation with magnesium iodide by the method discussed previously, the limettin was partially demethylated to XXII or XXIII as shown in Figure 4. The NMR
spectrum (Figure 26) of the partially demethylated limettin is very similar to limettin (Figure 24) except for only one methoxyl group at \( \tau 6.82 \). The phenolic -OH appears at \( \tau 5.75 \) as a very broad singlet.

The pair of doublets centered at \( \tau 2.04 \) (\( J_{ab} = 10 \text{ Hz}, 1\text{H} \)) and \( \tau 4.00 \) (\( J_{ab} = 10 \text{ Hz}, 1\text{H} \)) are due to the olefinic protons \( H_b \) and \( H_a \), respectively. The pair of doublets at \( \tau 3.72 \) (\( J_{cd} = 2 \text{ Hz}, 1\text{H} \)) and \( \tau 3.85 \) (\( J_{cd} = 2 \text{ Hz}, 1\text{H} \)) belong to the aromatic protons \( H_c \) and \( H_d \), respectively. Since the \( H_b \) proton in the demethylated product absorbs slightly further downfield (\( \tau 2.04 \)) than in limettin (\( \tau 2.14 \)) it is likely that the demethylated product is XXII rather than XXIII.

Bergamottin (XVII) was cleaved (14) to bergaptol (XVIa) by heating with glacial acetic acid. The acetic acid was evaporated and the bergaptol was purified by sublimation.

The initial intention was to form the di-sodium salt (XXIV) of bergaptol (XVIa) by opening the lactone ring and then react this with IIIc in a modified Williamson ether synthesis:
In this way, upon acidification and relactonization, both of the isomers, Ic and XVIc, would probably be produced. On the basis of steric considerations, it was expected that Ic, which was thought to be archangelin, would predominate in the reaction mixture.

The preparation of the desired di-sodium salt (XXIV) was attempted by mixing a 2:1 mole ratio of sodium methoxide to bergaptol (XVIa) under argon and then heating. At this time all of the bergaptol had dissolved, forming a deep red-brown solution. Heating was continued to assure that the lactone ring had indeed opened. The methanol was evaporated by flushing the system with a strong stream of argon and heating, leaving a bright orange solid. To the reaction vessel, still under argon, was added dimethylformamide, and the solution was cooled to dry ice-acetone bath temperature. Bromide IIIc was added slowly and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was heated gently, and then ether was added slowly followed by acidification with hydrochloric acid with the intention of closing the lactone ring. The ether layer was removed, dried, and the solvent evaporated under vacuum. Thin layer chromatography indicated
that one major and one minor product had been formed and the $R_f$ of the major product was the same as archangelin. The major product crystallized nicely from methanol giving a 51% yield from bergaptol. Both the major product and archangelin had the same characteristic, yellow-green spot on TLC when sprayed with 30% sulfuric acid and heated gently on a hot plate. The NMR spectrum (Figure 27) of the major product compared quite well with that of archangelin (Figures 28 and 29). The major product had a melting point of 131-132° compared to the literature value of 132° (1) for archangelin. The mixed melting point of the major product and archangelin was 131-133° which showed no depression. The X-ray powder pattern of the major product matched that of archangelin (Figure 31). The IR spectrum of the major product (Figure 32) is nearly identical to that of archangelin (Figure 33), even in the fingerprint region. On the basis of all of this information, the major product has been shown to be archangelin.

The minor product from the reaction was obtained in 67% yield from XVIa. Its NMR spectrum (Figure 34) has a doublet at $\tau 1.88$ ($J_{ab} = 10$ Hz, 1H) for $H_b$; a doublet at $\tau 3.78$ ($J_{ab} = 10$ Hz, 1H) for $H_a$; a doublet at $\tau 2.40$ ($J_{ed} = 2$ Hz, 1H) for $H^e$; a doublet at $\tau 3.05$ ($J_{ed} = 2$ Hz, 1H) for $H^d$, a singlet at $\tau 5.16$ (2H) for $H_f$, and a singlet at $\tau 6.21$ (2H) for $H_g$. The absorption between $\tau 8.0-9.2$ and the absence of the aromatic singlet at about $\tau 2.9$ indicate that the minor product probably is either XXV or XXVI:
The mass spectrum (Figure 35) of the minor product indicates a parent peak at m/e 474 corresponding to either XXV or XXVI. Prominent peaks appear at m/e 351, 338, and 216 and they may arise as shown in Figure 6. The molecular ion peaks indicated in the figure could just as easily have arisen from XXV, so the mass spectrum is of little help in differentiating between structures XXV and XXVI. The IR spectrum (Figure 36) of XXVI indicates the typical absorption of a furocoumarin \[1723 \text{ cm}^{-1} \text{ (conjugated lactone), 1132 cm}^{-1} \text{ (ether), and 1107 cm}^{-1} \text{ (benzofuran)}\]. At this point the minor product could be XXV or XXVI.

Though archangelin had been synthesized, doubt still remained about the direction of lactonization. The NMR spectrum (Figure 37) of
Figure 6. Mass spectral fragments of XXVI.
isobergaptene (Ie, obtained from K & K Laboratory) was run; the NMR parameters of isobergaptene (Ie) and bergaptene (XVIe) appear in Table 4 for comparison.

**Table 4. Comparison of NMR parameters of bergaptene and isobergaptene.**

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Bergaptene</th>
<th>Isobergaptene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resonance (τ)</td>
<td>J (Hz)</td>
</tr>
<tr>
<td>Coumarin</td>
<td>3.78(d), 1.88(d) 9.5</td>
<td>2</td>
</tr>
<tr>
<td>Furan</td>
<td>3.00(d), 2.42(d) 2.5</td>
<td>2</td>
</tr>
<tr>
<td>Benzene</td>
<td>2.90(s)</td>
<td>1</td>
</tr>
<tr>
<td>Methoxy</td>
<td>5.77(s)</td>
<td>3</td>
</tr>
</tbody>
</table>

s = singlet  
d = doublet

The compounds have nearly identical absorptions except for the proton attached to the benzene ring. Other bergaptyl ethers [bergaptene (16-20), isoimperatorin (18,25), pranferol (26), oxypeucedanin hydrate (27), isooxypeucedanin (27), bergamottin (16), oxypeucedanin (19)] also absorb near τ 2.9, so this particular peak in the NMR can be used with a fair amount of reliability to distinguish between isobergaptyl and bergaptyl ethers. The NMR spectrum of archangelin (Figures 28 and 29) shows a singlet at τ 2.87, so on this basis it would appear that archangelin has structure XVIc. Another observation that suggested that archangelin may be a bergaptyl ether rather than an isobergaptyl ether
came from TLC. Archangelin, like all of the bergaptyl ethers tested (see Table 3), gave a green spot when sprayed with 30% sulfuric acid and heated gently on a hot plate, whereas isobergaptene gave a blue spot.

The IR spectrum can also be used to distinguish between bergaptyl and isobergaptyl ethers. A visual comparison of the IR spectra of bergamottin (XVI, Figure 22), bergaptene (XVIe, Figure 20), archangelin (Figure 33), and isobergaptene (Ie, Figure 20) shows a striking similarity between the two known bergaptyl ethers, and the spectrum of archangelin is much more like these ethers than isobergaptene. In particular Kovalev, Prokopenko, and Titov (23) reported that the IR spectra (KBr pellet) of isobergaptyl ethers show the lactone carbonyl peak at about 1744 cm\(^{-1}\), whereas bergaptyl ethers absorb at about 1725 cm\(^{-1}\). Archangelin absorbs at 1725 cm\(^{-1}\) (Figure 33), so again it is more like a bergaptyl ether. A number of other unassigned peaks are presented in Table 5 to help differentiate between these two types of ethers. Again, archangelin compares more favorably to the bergaptyl ethers.

The UV spectrum is also of some help in differentiating between bergaptene and isobergaptene. Figure 19 shows the UV spectra of isobergaptene and bergaptene. Even though the spectra are very similar, if one compares the ratio of peak heights at 250 and 268 nm, it will be seen that the ratio for bergaptyl ethers (see Table 6) is about 1.07, whereas that for isobergaptene is 1.47. The ratio for archangelin is 1.14 which is much closer to the average value for the bergaptyl ethers.
Table 5. Comparison of unassigned IR parameters for bergaptyl and isobergaptyl ethers.

<table>
<thead>
<tr>
<th></th>
<th>Bergaptyl ethers</th>
<th>Isobergaptyl ethers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td></td>
<td>1525 w*</td>
</tr>
<tr>
<td>1354-1364 m-s*</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>1197-1206 m-s</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1167 w</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1137 s</td>
<td></td>
</tr>
<tr>
<td>1089-1093 m-s</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>855-867 w*</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>628 m</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>522 w</td>
<td></td>
</tr>
<tr>
<td>503 w*</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>480 w*</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>426 w</td>
<td></td>
</tr>
</tbody>
</table>

* w = weak intensity; m = medium intensity; s = strong intensity

*. Most reliable.
Table 6. Comparison of relative peak heights at 250 and 268 nm for bergaptyl and isobergaptyl ethers.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ratio of relative peak heights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergaptene (XVIe)</td>
<td>1.06</td>
</tr>
<tr>
<td>Bergamottin (XVIf)</td>
<td>1.08</td>
</tr>
<tr>
<td>Natural archangelin (XVIc)</td>
<td>1.15</td>
</tr>
<tr>
<td>Synthetic archangelin</td>
<td>1.13</td>
</tr>
<tr>
<td>Isobergaptene (Ie)</td>
<td>1.47</td>
</tr>
</tbody>
</table>

Also, archangelin shows a $\lambda_{\text{max}}$ at 259 nm as do the other bergaptyl ethers, whereas this peak is absent in the spectrum of isobergaptyl.

Partial structure I was originally assigned to archangelin based on degradation to what was reported to be isobergaptol (Ia, mp 274-278°) (1). However, nowhere else in the literature has isobergaptol ever been reported. Structural assignment based on this observation would be hazardous in view of the facile interconversion of isobergaptol (Ia) and bergaptol (XVIa) (28). We obtained a melting point for bergaptol of 274-278° [lit (15) 277-278°]. Therefore, it is possible that Chatterjee and Dutta (1) had obtained bergaptol instead of isobergaptol. It seems much safer to use the spectral data presented above to distinguish between isobergaptyl and bergaptyl ethers. Based on all of the evidence discussed thus far, it seems very likely that archangelin has structure XVIc.
It seemed reasonable to re-examine the spectral evidence to see if it shows that archangelin is indeed a bergaptyl ether and not a sphondyl (XXX) or xanthotoxyl ether (XXXI), which also occur commonly in nature.

Other isomeric permutations of this fused ring system have not been reported in the literature. Comparing the IR carbonyl peak of bergaptyl ethers (1725 cm\(^{-1}\)) to that of sphondin (XXXe, 1721 cm\(^{-1}\)) does not distinguish between these two types. However, the carbonyl in xanthotoxyl ethers absorbs at about 1709 cm\(^{-1}\). On this basis archangelin still is more like a bergaptyl ether. Table 7 presents the pertinent NMR parameters for several xanthotoxyl ethers as well as sphondin. There are a number of significant differences between these two types of ethers and bergaptyl ethers. The aromatic proton can again be used to differentiate between all three types. In xanthotoxyl ethers the aromatic proton absorbs at about \(\tau\) 2.60, but in sphondin it absorbs at \(\tau\) 3.22. Archangelin absorbs at \(\tau\) 2.87 and is like the bergaptyl ethers, which absorb at about \(\tau\) 2.90. Though none of these spectral differences is by itself convincing, taken collectively they
Table 7. Comparison of pertinent NMR parameters for bergaptyl ethers, xanthotoxyl ethers, and sphondin.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$H_a$</th>
<th>$H_b$</th>
<th>$H_c$</th>
<th>$H_d$</th>
<th>$H_e$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXIg</td>
<td>$\tau 3.60$</td>
<td>$\tau 2.09$</td>
<td>$\tau 2.56$</td>
<td>$\tau 3.11$</td>
<td>$\tau 2.21$</td>
<td>17</td>
</tr>
<tr>
<td>Imperatorin</td>
<td>$d; J_{ab}=10$</td>
<td>$d; J_{ab}=10$</td>
<td>$s$</td>
<td>$d; J_{de}=2$</td>
<td>$d; J_{de}=2$</td>
<td>26</td>
</tr>
<tr>
<td>XVIg</td>
<td>$\tau 3.84$</td>
<td>$\tau 1.95$</td>
<td>$\tau 2.93$</td>
<td>$\tau 3.13$</td>
<td>$\tau 2.40$</td>
<td>18,26</td>
</tr>
<tr>
<td>Isoimperatorin</td>
<td>$d; J_{ab}=10$</td>
<td>$d; J_{ab}=10$</td>
<td>$s$</td>
<td>$d; J_{de}=2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXXIe</td>
<td>$\tau 3.65$</td>
<td>$\tau 2.23$</td>
<td>$\tau 2.67$</td>
<td>$\tau 3.19$</td>
<td>$\tau 2.32$</td>
<td>17,20</td>
</tr>
<tr>
<td>Xanthotoxin</td>
<td>$d; J_{ab}=10$</td>
<td>$d; J_{ab}=10$</td>
<td>$s$</td>
<td>$d; J_{de}=3$</td>
<td>$d; J_{de}=3$</td>
<td>26</td>
</tr>
<tr>
<td>XXXe</td>
<td>$\tau 3.62$</td>
<td>$\tau 2.35$</td>
<td>$\tau 3.22$</td>
<td>$\tau 2.88$</td>
<td>$\tau 2.30$</td>
<td></td>
</tr>
<tr>
<td>Sphondin</td>
<td>$d; J_{ab}=10$</td>
<td>$d; J_{ab}=10$</td>
<td>$s$</td>
<td>$d; J_{de}=2$</td>
<td>$d; J_{de}=2$</td>
<td>19</td>
</tr>
</tbody>
</table>

$s =$ singlet $d =$ doublet
should permit safe assignment of the direction of lactonization as well as a method to differentiate between the various possible ethers that have been found in nature.

When archangelin was finally synthesized, there was a minor product mentioned above that was believed to be either XXV or XXVI. Since archangelin has the structure XVIc, it would seem more reasonable that the minor product has structure XXVI. It could possibly be formed by a p-Claisen rearrangement of archangelin followed by O-alkylation. The IR spectrum (Figure 36) of this substance is more like the bergaptyl ethers than the isobergaptyl ethers with a carbonyl peak (KBr pellet) at 1723 cm$^{-1}$.

When it was still believed that archangelin was an isobergaptyl ether with structure Ic, an attempt was made to deliberately produce the bergaptyl ether. The reaction was carried out like the first archangelin preparation except that a 1:1 mole ratio of sodium methoxide to bergaptol (XVIa) was used to prepare the mono-sodium salt of bergaptol. The reaction was run under argon and was initially kept at dry ice-acetone temperature and then permitted to stir at room temperature for 21 hr. This time only one product could be detected by TLC and the $R_f$, mixed mp, and NMR spectrum corresponded to archangelin. Apparently the lactone ring does not open in a methanolic sodium methoxide solution, and in both preparations of archangelin only the mono-sodium salt of bergaptol exists. It is suggested that in an aqueous solution the lactone ring would open giving the isomeric isobergaptyl ether (Ic), but this hypothesis was not tested.
In conclusion, we are able to synthesize archangelin and thereby show that it has structure XVIc:

![Diagram of XVIc]

Spectral methods were developed to distinguish between bergaptyl (XV), isobergaptyl (I), xanthotoxyl (XXXI), and sphondyl (XXX) ethers. A much improved, nearly quantitative method for preparing 1,5,5- and 1,3,3-trimethylcyclohexenes (IX and X, respectively) was also developed. The final step leading to archangelin involves a modified Williamson synthesis. We suggest that the conditions worked out for archangelin may be general for the preparation of aryl ethers starting with phenols and alkyl halides. The literature and experience indicate that a number of these aryl ethers are prepared in low yield or not at all by the usual methods. We will eventually try to synthesize bergamottin (XVIf) by our method, since this compound has never been prepared in greater than 10% yield by bringing together bergaptyl and geranyl bromide.
EXPERIMENTAL

General Methods

The experimental NMR spectra were run on 10% solutions in deuterochloroform, carbon tetrachloride, or in the case of bergaptol (XVIa), DMSO-d₆ with the Varian T-60, HA-100, or Bruker 90 MHz instruments using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in T units.

The IR spectra were obtained with a Perkin-Elmer 337 Grating Infrared spectrophotometer, either neat, in carbon tetrachloride solutions, or with KBr pellets.

Melting points were taken using a Thomas-Kofler micro hot stage instrument, model 6886-A, and are uncorrected.

The GLC analyses were obtained with a Varian Aerograph model 90-P.

Spinning band distillations were carried out with a Nester-Faust, 6 mm x 46 mm, vacuum-jacketed column.

The UV spectra were obtained on the Cary 14 spectrophotometer.

The X-ray powder patterns were obtained with a Phillips X-ray powder camera.

Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer.
Synthesis of Archangelin

Isolation of Bergamottin (XVII), Bergaptene (XVIIc), and Limettin (XXI) from Bergamot Oil

A modified procedure of Späth and Kainrath (14) was used to obtain bergamottin. To a mixture of 250.0 g of bergamot oil (Fritzsche Bros., N.F., Extra) dissolved in 250 ml of ether in a 2-liter Erlenmeyer flask was added 115 ml of 5% methanolic potassium hydroxide solution. The solution was allowed to stand for 20 hr with magnetic stirring, and then 500 ml of water was added. The ether layer was removed and washed with 200 ml of 2% aqueous potassium hydroxide solution. The combined water layers were extracted 5 times with 75-ml portions of ether and the ether extracts were discarded. The aqueous solution was then acidified carefully to a pH of 5 with glacial acetic acid. After standing for 15 hr, needles had formed at the surface. The solution was extracted 5 times with 25-ml portions of ether. The ether insoluble crystals were removed by vacuum filtration (Fraction A). The phenolic materials were removed by washing the ether solution twice with an equal volume of 5% aqueous potassium hydroxide solution. The ether solution was dried over anhydrous magnesium sulfate and the solvent evaporated, leaving a white, crystalline material which was extracted 5 times with 25-ml portions of low boiling petroleum ether with stirring. Part of the crystalline material (Fraction B) was insoluble in petroleum ether. The petroleum ether extract was evaporated to cloudiness and permitted to crystallize at -20°. Two crops of crystals (Fraction C and D) were taken. When the oily residue was further
cooled to a -78° in a dry ice-acetone bath, an additional crop of white crystals (Fraction E) was obtained. The yields and composition (NMR) of Fractions A–E are presented in Table 8:

Table 8. Composition of bergamot oil.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Wt. (g)</th>
<th>Bergamottin (XVII)</th>
<th>Bergapten (XVIc)</th>
<th>Limettin (XXI)</th>
<th>Unidentified</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.182</td>
<td>-</td>
<td>58%</td>
<td>42%</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>0.108</td>
<td>-</td>
<td>91%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>0.088</td>
<td>20%</td>
<td>62%</td>
<td>18%</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>0.060</td>
<td>96%</td>
<td>-</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>0.025</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
</tbody>
</table>

Bergapten can be separated from limettin by recrystallizing from chloroform with the addition of pentane. With extreme difficulty, limettin and bergapten can be separated using preparative TLC employing silica gel PF-254 (phosphor included) and eluting with low boiling petroleum ether: ethyl acetate (3:1). The plates had to be eluted 3 times, drying between elutions, before limettin and bergapten were resolved. Limettin fluoresces a brilliant white under UV whereas bergapten and bergamottin appear as dark bands when the UV phosphor is used in the silica gel.
Bergaptol (271a) from Bergapten (271c).

Following the so-called "dry method" of Schönberg and Fizaz (274a), 0.553 g of bergapten was dissolved in 45 ml of benzene (A.R. Benzene was dried over anhydrous magnesium sulfate and then distilled from sodium metal and stored over 3 K molecular sieves) and 25 ml of anhydrous ether (dried over magnesium sulfate and stored over 3 K molecular sieves). The solution containing bergapten was placed in a 200-ml, 3-necked flask and under nitrogen with magnetic stirring, a solution of magnesium iodide [prepared by mixing 1.39 g of iodine dissolved in 16 ml of a 1:1 (v/v) mixture of dry benzene to dry ether with 0.126 g of magnesium metal] was dropped in slowly over 10 min. The nitrogen was turned off, the temperature was increased to 65°, and heating was continued under vacuum until most of the solvent was removed. Still under vacuum, heating was continued for 15 min at 115-120° to remove the rest of the solvent and perhaps any residual iodine. The vacuum was turned off and under a nitrogen atmosphere, heating continued for 90 min at 100-110°. After cooling to room temperature, 3.0 ml of 5% sulfuric acid was added to the reaction mixture. A green precipitate formed and heat was liberated. Distilled water (2 ml) was added, and the solid was collected by vacuum filtration. The residue was washed once with 1 ml of 5% aqueous sodium bisulfite to remove the iodine. The residue was dissolved in acetone and filtered again. The acetone was removed, leaving 0.495 g (84%) of a yellowish green solid that contained no bergapten by TLC. Bergaptol is quite insoluble in nearly all organic solvents except acetone and methanol. All attempts
to crystallize bergaptol failed. Bergaptol was further purified by powdering the reaction product and subliming it at 205-220° for 3 hr at 10^{-5} torr. Any impurities were removed at a much lower temperature. Bergaptol [0.108 g, mp 274-278°, lit (15) 277-278°] was obtained in this way. It would probably be preferable to purify the bergaptol by preparative TLC since bergaptol is apparently stable to silica gel. The solvent system petroleum ether:chloroform:ethyl acetate (8:5:12) separates bergaptol from bergaptene fairly well (see Table 3).

**Bergaptol (XVIa) from Bergamottin (XVIf)**

The procedure of Spüth and Kainrath (14) was altered slightly to convert bergamottin (XVIf) to bergaptol (XVIa). Bergamottin (0.198 g) was dissolved in 2.0 ml of glacial acetic acid and placed in a 25-ml round-bottomed flask fitted with a calcium chloride drying tube. The mixture was refluxed for 6 hr and during this time a yellow solid precipitated out of the solution. After cooling, the reaction mixture was treated with a small amount of saturated sodium bicarbonate and the crude bergaptol (XVIa, 0.055 g, 46%) was collected by vacuum filtration. A better method to isolate the bergaptol from the reaction mixture would have been to chromatograph the solid residue after washing with a small amount of saturated sodium bicarbonate to remove the glacial acetic acid.

**2,6-Dimethyl-5-hepten-2-ol (VIII)**

The method of Callen, Dornfeld, and Coleman (7) was used to prepare methylmagnesium iodide. Grignard grade magnesium turnings
and 150 ml of anhydrous ether were placed in a 2-liter, 3-necked flask equipped with a nitrogen inlet, water condenser, mechanical stirrer, and a 500-ml dropping funnel. The magnesium was dried in the oven at 105° for one day and the entire system was flame-dried while passing nitrogen through. Methyl iodide (308.8 g) dissolved in 150 ml of anhydrous ether was dripped in slowly over a 5-hr period, controlling the rate of addition so that the reflux was not too vigorous. After 5 hr the reflux ceased, indicating that the reaction was over.

During the addition of the methyl iodide an additional 600 ml of anhydrous ether was added to the reaction vessel. Methylheptenone (VII, 97.98 g of 6-methyl-5-hepten-2-one, Fritsche Brothers) (29) in 160 ml of anhydrous ether was dripped into the methylmagnesium iodide mixture over a 1-hr period and the reaction mixture was stirred under nitrogen for 5 hr. The reaction vessel was heated over a steam bath for one additional hour and then very carefully poured over 1500 ml of crushed ice. An ice cold, saturated solution of ammonium chloride was added until the emulsion broke up sufficiently to permit separation of the two phases. This occurred at pH 8. The aqueous phase was washed with three, 300-ml portions of ether and the combined ether layers were backwashed with three, 300-ml portions of water. The ether solution was dried over magnesium sulfate, vacuum filtered, and the ether removed on the rotary evaporator, leaving 109.63 g (100%) of the desired product (VIII). The GLC (105°, SE 30 column), indicated that the mixture was at least 98% 2,6-dimethyl-5-hepten-2-ol (VIII) and the NMR
spectrum (Figure 11) was consistent for the desired product. No attempt was made to purify VIII before proceeding to the next step.

1,5,5- and 1,3,3-Trimethylcyclohexenes (IX and X, Respectively)

Alcohol, 2,6-dimethyl-5-hepten-2-ol (VIII, 22.268 g) and anhydrous oxalic acid (27.43 g, 0.382 mol, dried in an oven at 115° for 1 hr) (2,8) were placed in a 100-ml, round-bottomed flask and refluxed for 1 hr on a spinning band distillation apparatus with the take off completely closed. The take off was opened and the reflux ratio was adjusted to 1:1 and the distillation was carried out at atmospheric pressure. Nearly all of the distillate was collected between 85-88° along with some water which formed an immiscible layer and was easily separated. During the distillation the oxalic acid sublimed nearly all the way to the top of the spinning band reflux column. The GLC (87°, 20% Carbowax 20-M on Chromasorb W, acid washed column) indicated that the distillate contained only the desired mixture of IX and X which was not resolved on the column used. A 60:40 mixture (by NMR) of IX and X (18.55 g) was obtained (95% yield).

1-Acetyl-2,4,4- and 6-Acetyl-1,3,3-trimethylcyclohexene (XI and XII, Respectively)

The 60:40 mixture of IX and X (18.546 g) and acetyl chloride (9.05 g) (10) were placed in a 50-ml, 3-necked, round-bottomed flask equipped with a water condenser and nitrogen inlet. At 0° and with magnetic stirring, 0.40 ml (0.905 g) of anhydrous stannic chloride was added as rapidly as possible, but with care since the reaction is quite
The reaction mixture turned yellow immediately upon the addition of the stannic chloride. The mixture was stirred under nitrogen at 0° for 45 min and then poured into 45 ml of a 10% hydrochloric acid solution. The mixture was extracted three times with ether and the ether layers washed twice with saturated sodium bicarbonate and once with water. The ether solution was dried over magnesium sulfate and the ether was removed on the rotary evaporator leaving 21.151 g of a 60:40 mixture (GLC, 153°, 10% FFAP on Chromasorb T; NMR spectrum, Figure 10) of XI and XII, respectively. The crude material was distilled at 110-115° (185 mm), giving 19.807 g (86%) of XI and XII.

**Isomerization of 6-Acetyl-2,3,3-trimethylcyclohexene (XII) to 1-Acetyl-2,4,4-trimethylcyclohexene (XI)**

The mixture of XI and XII (19.807 g) (10) and N,N-dimethylaniline (13.2 g) were placed in a 50-ml round-bottomed flask equipped with a water condenser and nitrogen inlet. The mixture was heated at 165-180° for 4 hr. Ether (30 ml) was added and the solution was extracted 3 times with 20-ml portions of a 5% hydrochloric acid solution, 3 times with 20-ml portions of a saturated aqueous sodium bicarbonate solution and once with water. The ether solution was dried over magnesium sulfate and the ether was removed on the rotary evaporator, leaving 13.422 g of a yellow liquid. The GLC (157°, 20% Carbowax 20M on Chromasorb W column) indicated 85% XI and 10% XII and 5% of an unidentified material suspected of being XX.
1-Carboxy-2,4,4-trimethylcyclohexene (VI)

In a 3-necked, round-bottomed flask fitted with a mechanical stirrer, water condenser, dropping funnel, and nitrogen inlet, was placed a solution of sodium hydroxide (32.24 g) in water (155 ml) (2,10). After cooling to 0° in an ice bath, 11.5 ml of bromine was dripped in, and the sodium hypobromite formed was allowed to cool to 0°. The mixture of XI and XII (8.462 g) dissolved in 115 ml of 1,4-dioxane was dripped slowly into the reaction vessel with vigorous stirring under a nitrogen atmosphere. The addition of XI and XII took 50 min, and the ice bath was removed, making sure that the temperature of the solution did not rise above 30° at any time by reimmersing in the ice bath as needed. Under a nitrogen atmosphere, stirring was continued at room temperature for 4.5 hr, followed by heating at 60° for 30 min. Then 20% aqueous sodium bisulfite was added until the yellow color of the solution turned a cloudy white, which took 30 ml of the reagent; an additional 20 ml was added. The solution was acidified with 20% hydrochloric acid to pH 2, causing the temperature to rise to 70°. The reaction vessel was cooled to 15° and extracted 5 times with 150-ml portions of ether. The combined ether layers were extracted 4 times with 50-ml portions of 5% aqueous sodium hydroxide. The combined aqueous layers were acidified with 20% hydrochloric acid to pH 2 and extracted 4 times with 100-ml portions of ether. The ether solution was dried over magnesium sulfate and the ether removed on the rotary evaporator, leaving 3.3950 g of crude product (42% based on the amount of XI initially present). At this point impurities carried along from
previous synthetic steps were removed by crystallization from methanol-water, which gave white needles, mp 109-111° [lit (11) 110-111°]. The NMR spectrum (Figure 16) matches that reported by Thalacker (2) and is in agreement with structure VI.

**Methyl 2,4,4-Trimethyl-l-carboxylate (XIII)**

The general procedure presented in Organic Synthesis (12) was followed in preparing the methyl ester (XIII). A mixture of 14 ml of a 40% aqueous potassium hydroxide solution and 45 ml of ether in an unscratched 250-ml Erlenmeyer flask was cooled to about 5° in an ice bath (2). Nitrosomethylurea (12, p. 461; 30) (4.60 g) was added slowly and the ether layer turned a light yellow indicating the presence of diazomethane. The (upper) ether layer was carefully decanted off and a little ether was added to the residue which was again decanted. The ethereal diazomethane solution was added, slowly, to 0.919 g of the acid (VI) dissolved in 50 ml of ether until the yellow color of diazomethane persisted for several minutes and the evolution of nitrogen ceased. Excess diazomethane was decomposed by the dropwise addition of glacial acetic acid until the yellow color dissipated. The reaction mixture was washed 3 times with 25-ml portions of water, the ether layer was dried over magnesium sulfate, and the ether was removed on the rotary evaporator, leaving 0.929 g (99%) of a pleasant smelling liquid. Attempts at washing out traces of glacial acetic acid with 5% aqueous sodium bicarbonate solution seemingly resulted in hydrolysis of the ester (XIII). The GLC (168°, 18% GE-SE 30 on Chromasorb P) gave
only one peak so the reaction mixture was not purified before continuing on to the next step.

**β-Cyclolavandulol (IIc)**

Lithium aluminum hydride (0.258 g) and 35 ml of anhydrous ether were placed in a 200-ml, 3-necked flask equipped with a water condenser, nitrogen inlet, dropping funnel, and mechanical stirrer (2) Methyl ester (XIII, 0.885 g) dissolved in 35 ml of ether was dripped into the reaction vessel over a 20-min period with stirring under a nitrogen atmosphere. Reflux was noted and stirring continued for an additional 2 hr. Water (3.6 ml) was cautiously added, followed by 15% aqueous sodium hydroxide (3.6 ml), and then 10 ml of water. The ether layer was decanted and ether added 3 more times with shaking followed by decantation. The combined ether extracts were dried over magnesium sulfate and rotary-evaporated leaving 0.725 g (98%) of IIc. The cloudy appearance of the alcohol (IIc) could not be removed by repeated drying over magnesium sulfate, so it was assumed to be unreduced acid (VI).

**β-Cyclolavandulyl Bromide (IIIC)**

A 50-ml, 3-necked, pear-shaped flask equipped with a nitrogen inlet, dropping funnel, and water condenser was cooled to a -70° in a dry ice-acetone bath (2). To the reaction vessel was added β-cyclolavandulol (IIc) dissolved in 7 ml of anhydrous ether. With magnetic stirring 1.5 ml of phosphorous tribromide in 15 ml of anhydrous ether was dripped in slowly over a 30-min period. The dry ice bath was removed and the reaction mixture was allowed to warm to room temperature
and stirring was continued under a nitrogen atmosphere. Since nearly all of the ether evaporated, an additional 13 ml of anhydrous ether was added. Two phases were present with the lower phase being orange. A calcium chloride drying tube was added at the top of the condenser. After 5 hr, 50 ml of ether was added, followed by 60 ml of 27\% aqueous potassium hydroxide solution which must be added with caution due to the vigorous reaction. The ether layer was removed and the aqueous layer was washed three times with 30-ml portions of ether. The combined ether layers were dried over magnesium sulfate and the ether was removed on the rotary evaporator, leaving 0.227 g of IIIc (71\%) which was not purified further.

**Mono-sodium Salt (XVIh) of Bergaptol (XVIa) - First Preparation**

Initially it was believed that the di-sodium salt (XXIV) of bergaptol had been prepared. However, analysis of the products from this reaction would seem to indicate that the lactone ring did not open, and only the mono-sodium salt (XVIh) formed. Bergaptol (XVIa, 0.31 g, 0.155 mmol) was placed in a pointed centrifuge tube sealed with a serum cap. The system was flushed with argon and a solution of 7.0 mg (0.306 mmol) of sodium metal which had reacted with 1.6 ml of methanol (2:1 mole ratio of sodium methoxide to bergaptol) was added slowly with a syringe. The solution turned a dark yellow. The reaction mixture was heated in an oil bath for 70 min at up to 68° before all of the bergaptol dissolved. Heating was continued for 3 hr at 60-72° to make sure that the lactone ring had opened. The methanol was removed by passing
a strong stream of argon over the reaction mixture and heating the reaction vessel to 65°, leaving a dark reddish brown residue which was kept at all times under an argon atmosphere.

**Archangelin (XVIc) - First Preparation**

Spectrograde dimethylformamide (3.3 ml) was injected via syringe into the same reaction vessel used above containing the mono-sodium salt (XXIV) of bergaptol (31). The reaction vessel was cooled to a -78° in a dry ice-acetone bath. Still under an argon atmosphere, 0.0330 g of β-cyclolavandulyl bromide (IIIc) dissolved in 3.3 ml of spectrograde dimethylformamide was added slowly via syringe, shaking the reaction vessel occasionally. After the addition, the dry ice-acetone bath was removed, and the solution was allowed to warm to room temperature, followed by heating at 90° for 14 hr. After cooling to room temperature and still under argon, 5 ml of anhydrous ether was added via syringe and the ether layer turned green. Aqueous hydrochloric acid solution (1.6 ml, 0.1 N) was added to close the lactone ring which was believed to be open and the reaction mixture turned a reddish brown. For the first time since the beginning of the reaction, the reaction vessel was opened to the atmosphere, and the ether layer was separated. The pH of the water layer was 5. The water layer was extracted 4 times with 10-ml portions of ether and the combined ether layers were washed 3 times with water. After drying over magnesium sulfate, the ether was removed on the rotary evaporator, leaving 0.046 g. The TLC indicated only one major and one minor product as well as a small amount of unreacted bergaptol. The $R_f$ of the major product matched that of natural
archangelin. All three of these constituents were separated using preparative TLC employing 200 x 200 x 2 mm plates coated with silica gel PF-254 and eluting with low boiling petroleum ether:chloroform:ethyl acetate (8:5:12). All three compounds appeared to be various shades of green when sprayed with 30% sulfuric acid and heated gently on a hot plate. Synthetic archangelin (the major spot per TLC) was crystallized from methanol, giving white needles, mp 127-129° [lit (1) 131-132°]. The mixed melting point of synthetic and natural archangelin was 128-129°.

**Mono-sodium Salt (XXIV) of Bergaptol (XVIh) - Second Preparation**

Bergaptol (XVIa, 0.031 g) was placed in a 15-ml, round-bottomed flask equipped with an argon inlet, and a mercury reservoir between the reaction vessel and a calcium chloride drying tube. Methanol (0.2 ml) was injected into the reaction vessel and with magnetic stirring at 5° 3.5 mg of finely cut sodium metal dissolved in 1.0 ml of methanol (equimolar ratio of sodium methoxide and bergaptol) was injected slowly into the reaction vessel which was kept under an argon atmosphere at all times. The reaction was kept at 0° for 30 min during which time the argon flow was increased to drive off the methanol. After the methanol was removed a yellow solid remained.

**Archangelin (XVIc) - Second Preparation**

After cooling the mono-sodium salt (XXIVh) of bergaptol (XVIa) prepared above to -78° in a dry ice-acetone bath, 3.8 ml of spectrograde dimethylformamide was injected in, and 0.037 g of the bromide
(IIIc) dissolved in 3.8 ml of spectrograde dimethylformamide was injected slowly. After the addition, the solution was allowed to warm to room temperature slowly, where it was permitted to stand for 21 hr. At this time TLC indicated the presence of the same spots that were present from the first preparation of archangelin. There were about equal amounts of bergaptol and a spot corresponding to archangelin, and one other smaller spot. It would seem that the same products were obtained as before except the reaction had not gone to completion. Therefore, the reaction vessel was equipped with a water condenser and an argon inlet and, with magnetic stirring, heated for 24 hr at 90°. The reaction mixture was allowed to cool to room temperature before 5 ml of ether were added. At ice bath temperature 4 ml of 0.1 N aqueous hydrochloric acid solution was added to a pH of 5. The ether layer was removed and the aqueous layer was washed 3 times with 15-ml portions of ether. The combined ether layers were washed twice with 5-ml portions of water and then dried over magnesium sulfate. A small amount of activated charcoal removed most of the yellow coloration. The ether was removed on the rotary evaporator, leaving 28.1 mg of crude reaction product. The NMR spectrum (Figure 27) corresponded to that reported for natural archangelin (2).
PART II

STRUCTURE OF NICANDRENONE, AN INSECTICIDAL

PLANT STEROID DERIVATIVE
INTRODUCTION

In 1951 Gizycki and Kotitschke (32) isolated a compound they labeled "nicandrin" from the Peruvian weed *Nicandra physalodes*, a member of the Solanaceae family. They thought "nicandrin" was a glycoside, based on the observation that the optical rotation changes in a solution with emulsin. This is reported to indicate that the glycoside linkage has been hydrolyzed. However, they were unable to characterize a sugar in their reaction mixture. Their elemental analysis indicated 68.21% C and 7.85% H, leaving 23.85% O. They reported a molecular weight (Rast) of 470 and calculated a molecular formula of \( \text{C}_{27}\text{H}_{33}\text{O}_7 \) (68.31% C, 7.80% H, and 23.89% O).

It was noted that the plant, *Nicandra physalodes*, possesses strong insect repellent and mild insecticidal properties. The repellent substance can be extracted from the plant leaves with water and then partitioned into chloroform or ether. The extract has been shown to be highly toxic (33) to house flies and the hornworm which commonly forages on members of the Solanaceae family. Jacobson (34), however, failed to find any toxic activity in this particular plant, using houseflies, cockroaches, and milkweed bugs in his tests. Nalbandov, Yamamoto, and Fraenkel (35) found that the active constituent was fatal to houseflies.

Since it was suspected that the substance originally named "nicandrin" was an \( \alpha,\beta \)-unsaturated ketone from the position of its
carbonyl stretching band (1689 cm\(^{-1}\)) and that it was not a glycoside due to the presence of only one hydroxyl group, the name was changed to nicandrenone. In addition to the carbonyl band, most ketones show a peak in the region 1350-1200 cm\(^{-1}\) (36). Nicandrenone has a sharp peak at 1292 cm\(^{-1}\). The infrared spectrum of rotenone (XXXII), for comparison, has a carbonyl absorption at 1674 cm\(^{-1}\). The authors (35) imply that nicandrenone may be similar to rotenone. It was further suggested that most esters and lactones (saturated or unsaturated) show carbonyl absorption at frequencies higher than 1700 cm\(^{-1}\) (36).

Nicandrenone is reported to have a bitter taste (35) and is a white, crystalline substance melting at 102-105° (35). The melting point was probably taken on a sample having solvent of crystallization included in it as will be discussed shortly. Nicandrenone is optically active with \([\alpha]_D^{27} = +21.6°\) (C = 9, methanol). It is sparingly soluble in water, 5% hydrochloric acid solution, and 5% sodium hydroxide solution. After standing in a sodium hydroxide solution for
several hours a small amount of nicandrenone apparently dissolves or reacts, giving a bright yellow solution. Nicandrenone reacts with 85% phosphoric acid giving a cherry-red solution, and since this reaction is very sensitive it can be incorporated into a test for monitoring the separation of nicandrenone on column chromatography. At room temperature nicandrenone is soluble in chloroform, ethyl ether, methanol, ethanol, acetone, ethyl acetate, and dioxane, but sparingly soluble in carbon tetrachloride. It is soluble in hot benzene and crystallizes from this solvent.

Nicandrenone was reported to contain only carbon, hydrogen, and oxygen. Analyses for halogen, nitrogen, and sulfur by the usual methods gave negative results. The 2,4-dinitrophenylhydrazone of nicandrenone (35) was orange, but it failed to react with either the Tollens' or Schiff's reagents for aldehydes, again confirming that it is a ketone.

When nicandrenone is heated (35) with alcoholic alkali a dark orange-colored precipitate forms immediately which the authors suggested may indicate that it is a Y-pyrone derivative. Rotenone (XXXII), a naturally occurring insecticide with a dihydro-Y-pyrone ring, behaves in the same manner under identical conditions.

In the Legal test for unsaturated lactones, nicandrenone does not give the colors typical for this class of compounds (35). Nicandrenone gives brilliant colors when strong acids are added. The colors dissipate upon the addition of water.

Nicandrenone tenaciously retains solvents, especially chloroform and benzene, so that the elemental analyses are in error by the
amount of solvent present. A sample crystallized from benzene gave 72.63% C, 7.45% H, and 19.92% O (35). The molecular weight, determined on a chloroform solution in a vapor pressure osmometer, was 562. The molecular formula based on this information was presented as $\text{C}_{34}\text{H}_{42}\text{O}_7$, having a molecular weight of 562.7 and the following analytical values: 72.57% C, 7.52% H, and 19.91% O. This formula suggests a fused ring structure, possibly including at least one aromatic ring.

The infrared spectrum indicated a hydroxyl group present with a peak at 3520 cm$^{-1}$ (35). Quantitative determination (35) of the number of hydroxyl groups showed this group to constitute 2.95% of the compound which corresponds to one hydroxyl group per molecule.

The determination of terminal methyl groups indicated 7.79% of the compound was so constituted, which corresponds to three such groups per molecule (35).

Nicandrenone was not believed to contain any methoxy groups (35). It was suspected that the broad band in the infrared spectrum between 3000-2880 cm$^{-1}$ included olefinic (normally 3040-3010 cm$^{-1}$ (9, p. 73) C-H stretching bands. Aromatic compounds show C=C stretching vibrations between 1600-1500 cm$^{-1}$ (36) nicandrenone shows a sharp peak at 1505 cm$^{-1}$ but no other absorption in the aromatic region. This observation does not rule out the possibility that nicandrenone might be aromatic since this band in aromatic compounds is known to vary (36).

Large-membered rings containing ether linkages usually show absorption from 1150-1060 cm$^{-1}$ (36). Nicandrenone has an absorption band at 1085 cm$^{-1}$ with shoulders at 1105 and 1065 cm$^{-1}$.
The UV spectrum (35) of nicandrenone in 95% ethanol shows intense absorption at 217 nm ($\varepsilon = 17,670$) and a very broad band at 333 nm ($\varepsilon = 167$); $\alpha,\beta$-unsaturated ketones typically show similar absorption (37). The UV spectrum also included a number of sharp peaks at 261 ($\varepsilon = 326$), 267 ($\varepsilon = 450$), 276 ($\varepsilon = 416$), 278 ($\varepsilon = 273$). These last peaks are indicative of aromaticity in the molecule (37).

The NMR spectrum of nicandrenone exhibits no absorption above $\tau 8.9$ which indicates that the methyl groups present are close to double bonds, oxygen atoms, or aromatic rings, since they are shifted downfield (38, p. 51-66). It was believed that the absorption in the region $\tau 8.0-8.9$ was due to methyls and perhaps methylene groups. Based on color tests the repellent substance in Nicandra physolades was thought to be a steroid (39). Nicandrenone most likely is not a steroid or a triterpene (40) since it lacked much absorption between $\tau 8.0-8.5$ typical of these two classes of compounds. The peaks between $\tau 4.0-5.0$ were believed to be due to olefinic protons. The absorption in the region $\tau 2.4-3.5$ (4 to 6 protons) was thought to be due to aromatic protons (34) and possibly some olefinic protons shifted downfield somewhat from their usual position.

The $\gamma$-pyrone and one hydroxyl group accounted for 3 oxygens; the other 4 were suspected of being incorporated in ether linkages in the ring system.
Evidence will be presented here that nicandrenone has structure XXXIII (41) and is apparently the first natural steroidal derivative with ring D aromatic as shown in Figure 7.

The structure of nicandrenone was determined primarily by spectral methods, since the amount of pure nicandrenone available was small and attempts to make a heavy atom derivative for an X-ray study failed.

The overall approach to the following discussion will be to start with that portion of the molecule which is the simplest and best substantiated, and then proceed to the more difficult segments. Ring A (see XXXIIIa) is a logical starting point because the coplanarity of the conjugated system results in few hydrogen atoms and simple coupling patterns in the CMR and PMR spectra. After starting at the carbonyl in ring A, the discussion will proceed to the adjacent atoms and continue around the ring system until difficulty is experienced. Then the discussion will jump to Ring D, which is easily discussed since it is aromatic, with few hydrogens attached, no stereochemistry to worry about, and much evidence to indicate the substitution pattern and what types of atoms are bonded to it. After ring D, other prominent features of nicandrenone will be indicated, followed by a discussion of ring E. By examining the molecule in this way, when all the known
Figure 7. Numbering scheme (XXXIIIa), PMR shifts (τ), coupling constants (Hz), and CMR shifts (circled, ppm from TMS) for nicandrenone (XXXIIIb).
portions are eventually connected, few arrangements for the remainder of the molecule will be possible.

Comparison of the PMR spectrum (Figure 38) of nicandrenone recrystallized from benzene with that of material purified by TLC (Figure 39) indicated the presence of benzene in the former spectrum (sharp singlet at \[ \tau 2.6 \]). The earlier workers recrystallized their nicandrenone from benzene, and their NMR spectrum shows it to be present in their sample (35). This would seem to indicate that their elemental analysis and therefore molecular formula is in error by the amount of benzene of crystallization included in their nicandrenone. By integration of the PMR spectrum (Figure 38), it can be seen that a sample recrystallized from benzene contained about a 1:3 mole ratio of benzene to nicandrenone. The results from the elemental analysis of a sample crystallized from benzene were as follows: 72.635% C, 7.435% H, and 19.930% O (by difference). This analysis and those reported earlier for nicandrenone recrystallized from benzene (35) correspond fairly closely to a 1:4 ratio of benzene to nicandrenone (Calcd. 72.81% C, 7.36% H, 19.78% O).

Nicandrenone with time seems to form several impurities that were removed by preparative TLC. The plates were coated with silica gel PF-254 and eluted with freshly distilled ethyl acetate. Nicandrenone appears as a dark band against the fluorescent background of the added phosphor. Acetone was usually used to remove the nicandrenone from the silica gel. To remove any entrained acetone, the nicandrenone was heated to 100 ° for 24 hr under vacuum in a drying pistol. In this
way a fairly pure sample of nicandrenone, free of solvent or other impurities, was obtained.

The proton-decoupled CMR spectrum (Figure 40) of nicandrenone from which the benzene had been removed by preparative TLC as described above indicated that the molecule contained 28 carbons. Comparing the proton-decoupled CMR spectrum (Figure 40) to the off-resonance decoupled spectra (Figures 41 and 42) indicated the presence of 4 methyls, 4 methylenes, 12 methinyls, and 8 quaternary carbons, accounting for 32 hydrogens attached to carbon. Two hydroxyl hydrogens instead of the previously reported one (35) and 6 oxygens account for the molecular formula $\text{C}_{28}\text{H}_{34}\text{O}_{6}$ (calcd. % C 72.08, % H 7.35, and % O 20.57), consistent with the parent peak at m/e 466 in the mass spectrum. The molecular formula suggests a steroid origin with one additional carbon.

Nalbandov, Yamamoto, and Fraenkel (35) carried out color tests on nicandrenone which indicated to them that this substance may be a steroid.

Ring A

Starting with ring A, the $\alpha,\beta$-unsaturated carbonyl suggested by Nalbandov and coworkers was substantiated by the position of the carbonyl stretching band at $1670 \text{ cm}^{-1}$ (Figure 43), which is in the region for a conjugated ketone ($\sim 1675 \text{ cm}^{-1}$) (42, p. 42). Also, the 2,4-dinitrophenylhydrazone derivative of nicandrenone was orange rather than yellow, suggesting a conjugated carbonyl (35). The IR spectrum (Figure 43) lacks the bands at 2820 and 2720 $\text{ cm}^{-1}$ (42, p. 43) typical of the C-H stretching of an aldehyde, and the PMR spectrum (Figure 39) does
not show a peak in the region $\tau$ 0.0-0.7 (38, p. 62) for an aldehyde proton. Conclusive evidence for the presence of the $\alpha,\beta$-unsaturated keto group comes from the CMR spectra (Figures 40 and 41) which show a peak at -203 ppm in the region for a conjugated ketone [-196 to -210 ppm (43); conjugated aldehydes absorb at -192 to -195 ppm (43)]. Since the absorption is a singlet no hydrogens can be bonded to this carbonyl.

The PMR spectrum (Figure 39) shows a doublet at $\tau$ 4.13 ($J_{ab} = 10$ Hz, 1H) corresponding to the vinylic proton nearest to the carbonyl. At $\tau$ 3.43 is an 8-peak multiplet ($J_{ab} = 10$ Hz, $J_{bc} = 3$ Hz, $J_{bd} = 4$ Hz, 1H) which is the only other vinylic proton. This coupling can be explained by incorporating a methylene at $C_4$ having two nonequivalent hydrogens in a ring such as in partial structure XXXIV:

![XXXIV](image)

The PMR parameters (44) of the model compound XXXV compare favorably with those of nicandrenone. Assuming that nicandrenone is derived from a steroid, partial structure XXXIV can only be located in ring A. When irradiating at $\tau$ 7.39 (PMR, Figure 39-a) the multiplet at $\tau$ 3.43 collapses to a doublet ($J_{ab} = 10$ Hz). Upon irradiating at $\tau$ 7.29 (PMR, Figure 39-b) the multiplet at $\tau$ 3.43 almost appears as the B quartet
in an ABX grouping \( (J_{ax} = 10 \text{ Hz} \text{ and } J_{bx} = 3 \text{ Hz}) \), and the multiplet at \( \tau 4.1 \) appears as a doublet \( (J_{ab} = 10 \text{ Hz}) \). This would seem to indicate that one of the gem-hydrogens \( (H^c) \) absorbs at \( \tau 7.29 \) and the other \( (H^d) \) absorbs at \( \tau 7.39 \). Except for how rings A and B are joined, the discussion of ring A is almost complete.

**Ring D**

The benzene D ring that was suggested by previous workers (35) was substantiated by the CMR spectra (Figures 40-42) which show that there are only 8 carbons in the aromatic and olefinic region (-124 to -142 ppm) (43). Subtracting out two vinylic carbons leaves 6 carbons that could compose one benzene ring.

The PMR spectrum (Figure 39) shows a doublet at \( \tau 2.69 \) \( (J_{jk} = 8 \text{ Hz}, \text{ ortho coupling, } 1\text{H}) \) and a partially concealed multiplet at \( \tau 2.98 \) \( (J_{jk} = 8 \text{ Hz}, J_{k1} = 2 \text{ Hz}, \text{ meta coupling, } 1\text{H}) \). The doublet (PMR at \( \tau 3.02 \) \( (J_{k1} = 2 \text{ Hz}, 1\text{H}) \) belongs to the isolated aromatic hydrogen. The PMR coupling indicates that nicandrenone has a 1,2,4-trisubstituted aromatic ring. The PMR parameters of two model compounds, 1,2,4-trimethylbenzene (XXXVI) (45, #3417M) and thymol (XXXVII) (46, #270) were compared to nicandrenone to determine if oxygen or carbon atoms are attached to the aromatic ring. None of the aromatic hydrogens shown on partial structure XXXVIII absorb (PMR) far enough upfield to be adjacent to an oxygen-containing substituent. The CMR spectra (Figures 40-42) show that the 3 aromatic carbons absorbing between -124 and -129 ppm have hydrogens attached to them since they appear as doublets in the off resonance-decoupled spectra (Figures 41 and 42) and that the 3
carbon atoms absorbing from -135 to -142 ppm have alkyl substituents since alkyl-substituted aromatic carbons normally absorb between -135 and -145 ppm (43). No oxygen atoms are bonded directly to a carbon atom in a benzene ring since a carbon so situated would be shifted downfield considerably to about -154 to -165 ppm (47). The PMR and CMR spectra are thus consistent with partial structure XXXIX:

The molecular formula, $C_{28}H_{34}O_6$, requires 12 unsaturated sites for nicandrenone. Since neither the CMR nor PMR spectra indicate any other $sp^2$ hybridized carbons besides the 6 in the benzene ring, the 2 olefinic carbons, and the one carbonyl carbon, there must be 7 rings
present in nicandrenone. This suggests that the adjacent alkyl substituents on the benzene ring are probably part of another ring.

Side Chain and Ring E

At $\tau \ 8.75$ (Figure 39) is a methyl doublet ($J_{mn} = 7$ Hz) which is in the proper position for a methyl attached to a carbon bonded to an aromatic ring. The methyl doublet is more easily seen in the PMR spectrum (Figure 48) after Eu(fod)$_3$ had been added to a deuterochloroform solution of nicandrenone. The addition of the shift reagent clearly resolves the methyl absorption into 3 methyl singlets (3H for each) and one methyl doublet ($J_{mn} = 7$ Hz, 3H). The CMR spectrum (Figures 41 and 42) show a quartet at -14.10 ppm for a carbon bearing 3 protons that has been shifted somewhat downfield from the usual position for an aliphatic methyl at about -5 ppm. This could be due to the deshielding effect of the aromatic D ring.

The position of the methinyl attached to the methyl at $C_{21}$ was found by irradiating through the complex region $\tau \ 7.0-7.4$ making small changes in the irradiating frequency. Upon irradiating at $\tau \ 7.25$ the methyl doublet collapsed to a singlet (Figure 39-i), indicating that the methinyl at $C_{20}$ absorbs at $\tau \ 7.25$. Upon irradiating at the center of the methyl doublet at $\tau \ 8.75$, the complex absorption at about $\tau \ 7.2$ sharpens up (Figure 48-c). The CMR spectra (Figures 41 and 42) show two doublets at -43.21 ppm and -38.73 ppm, one of which might correspond to this methinyl carbon which has been shifted downfield due to its proximity to the aromatic ring.
Two oxygen atoms are accounted for in hydroxyl groups and one is in a keto group, leaving three oxygen atoms that must be in ether linkages. An important point is that examination of the CMR spectra indicates that there are no methylenes or methyls attached to oxygen. This considerably narrows the number of possible structures for nicandrenone. One methinyl (PMR, $\tau 5.04$, 1H; CMR, -92 ppm) is apparently attached to two other oxygen atoms in a hemiacetal grouping, because in some of the spectra (Figure 39) this peak appears as a doublet ($J_{op} = 7$ Hz) coupled to a $2^\circ$ hydroxyl hydrogen and in other spectra (Figure 38) it appears as a singlet. Further evidence that this methinyl is bonded to two oxygen atoms comes from the observed large chemical shifts induced in the PMR spectra (Figures 44-48) when the Eu(fod)$_3$ shift reagent is added to a deuterochloroform solution of nicandrenone. The methinyl doublet initially at $\tau 5.04$ shifts to about $\tau 3.0$. When deuterium oxide is added to a deuterochloroform solution of nicandrenone, the PMR spectrum (Figure 49) shows the disappearance of the doublet usually at $\tau 6.4$ ($J_{op} = 7$ Hz, 1H) for the $2^\circ$ hydroxyl hydrogen and the collapse of the methinyl doublet at $\tau 5.04$ to a sharp singlet.

From the CMR spectra (Figure 40-42) there is only one other methinyl attached to oxygen which is not part of an epoxide ring. This is indicated by the position of the 8-line multiplet ($J_{um} = 6$ Hz, $J_{us} = 11$ Hz, and $J_{ut} = 3$ Hz) for one hydrogen at $\tau 6.18$ in the PMR spectrum (Figure 39-c) which is in the usual position for a methinyl, ethereal hydrogen (9, p. 137). The CMR spectra (Figures 41 and 42) show a doublet at -68 ppm which is well situated for a methinyl carbon bonded to
an oxygen atom in an ether linkage which normally absorbs between -65 and -78 ppm (48).

Upon irradiating at \( \tau 8.5 \) the multiplet at \( \tau 6.18 \) appeared to partially collapse to a doublet (Figure 39-e, \( J_{um} = 6 \) Hz). This could arise if two nonequivalent protons which absorb at about \( \tau 8.5 \) are partially decoupled from the proton at \( \tau 6.18 \) by a fortuitous triple resonance experiment. This observation suggests that the two nonequivalent protons at about \( \tau 8.5 \) are possibly gem-hydrogens in a methylene group that is part of a ring. The PMR spectrum (Figure 39-f) shows a quartet at \( \tau 8.2 \) with the coupling constants \( J_{tu} = 3 \) Hz and \( J_{ts} = 14 \) Hz. Careful integration of the PMR spectrum between \( \tau 8.0-8.6 \) indicates the presence of 4 hydrogens not in methyl groups. The quartet at \( \tau 8.2 \) could account for one hydrogen, the quartet (\( J_{su} = 6 \) Hz, \( J_{ts} = 14 \) Hz) at \( \tau 8.4 \), the other gem-hydrogen, and a broadened methylene at \( \tau 8.16 \), the other two hydrogens. Upon irradiating at \( \tau 6.1 \), the quartet at \( \tau 8.2 \) collapses to a doublet (Figure 39-g, \( J_{st} = 14 \) Hz), the quartet at \( \tau 8.4 \) collapses to a doublet (Figure 39-g, \( J_{ts} = 14 \) Hz), and the multiplet at \( \tau 7.25 \) sharpens up. Again, this could be explained by gem-hydrogens of a methylene at \( C_{26} \). The CMR spectra (Figures 41 and 42) indicate a methylene triplet at -29 ppm which could correspond to \( C_{26} \). This methylene is shifted downfield slightly, due to the influence of two \( \beta \)-oxygen atoms.

The composition of the side chain containing the 6-membered ring was suggested by comparison of nicandrenone to the steroid withaferin A (XL):
which is obtained (49) from a Solanaceae plant as is nicandrenone. It is not difficult to imagine how the hemi-acetal ring structure of nicandrenone could be biogenetically derived from the 6-membered lactone of withaferin A (Figure 8):

Figure 8. Possible biogenetic pathway leading to the 6-membered hemi-acetal ring.
More likely, however, there is a common precursor for both nicandrenone and withaferin A:

![Diagram](image)

The aromatic ring D could arise from a normal steroid 5-ring such as in withaferin A by oxidation to the \( C_{18} \) alcohol followed by generation of a positive charge at \( C_{18} \) and then a 1,2-alkyl shift to give the tertiary carbonium ion, and then further oxidation; alternatively, one or two double bonds already present in the D ring would facilitate the ring expansion (Figure 9).

Good evidence for the location of the aromatic ring and composition of the side chain comes from the mass spectrum (Figure 50). A prominent parent peak is apparent with m/e 466. The peak at m/e 448 corresponds to \( P - H_2O \). The peak at m/e 430 could be \( P - 2H_2O \), and the large peak at m/e 418 is probably \( P - H_2O - 2CH_3 \). The peak at m/e 403 is most likely \( P - H_2O - 3CH_3 \), and at m/e 385 might be \( P - 2H_2O - 3CH_3 \). The third largest peak at m/e 323 results from the loss of 143 from the parent peak which very likely corresponds to the loss of \( C_7H_{11}O_3 \). This
peak very probably arises from cleavage of the side chain between $C_{20} - C_{22}$ to give a benzyl cation which rearranges to the corresponding tropylium ion. This would indicate that $C_{20}$ is not part of a ring. The loss of $C_7H_{11}O_3$ indicates that there are two unsaturated sites in the side chain, one most likely the 6-membered hemi-acetal ring (a favorable size for this grouping), and the other most likely an epoxide ring which accounts for five carbons and three oxygen atoms. The other two carbons are probably methyls and since all of the methyls in the molecule are either attached to a carbon bonded to oxygen or methyls on a double bond due to their downfield position in the PMR spectrum (Figure 49), these methyls are probably $\alpha$ to the epoxide ring. The PMR spectrum indicates two methyl singlets at $\tau 8.65$ and $\tau 8.67$ which are in the appropriate position for methyls $\alpha$ to an epoxide ring. The methyl group in propylene oxide (XVI) absorbs at $\tau 8.68$ (50).
Further evidence for the presence of a methyl α to an epoxide ring comes from the mass spectrum (Figure 50). The second largest peak at m/e 43 could be due to CH₃C=O which may arise as follows (51):

An epoxide ring with quaternary carbons at C₂₄ and C₂₅ is consistent with the CMR spectra (Figures 41 and 42), which have two singlets for quaternary carbons bonded to oxygen at -64 and -65 ppm (carbons bonded to ether oxygen atoms typically appear between -68 and -78 ppm) (48). The evidence presented is consistent with partial structure XLII:
The discussion of the side chain and ring E are now fairly complete.

The other hydroxyl proton sometimes can be seen in the PMR spectra (Figures 39 and 44) as a sharp singlet at about \( \tau 6.9 \) (1H) when it is not exchanging. This would indicate that there is a 3° hydroxyl group present. The CMR spectra (Figures 40-42) show the absorption of a quaternary carbon at -73 ppm which is indicative of a 2° or 3° hydroxyl carbon [1° hydroxyl carbons absorb between -56 and -68 ppm, 2° between -63 and -76 ppm, and 3° between -68 and -75 ppm (43)]. The addition of deuterium oxide to a sample of nicandrenone removes this signal from the PMR spectrum. Surprisingly, even after a large amount of \( \text{Eu(fod)}_3 \) shift reagent is added to a solution of nicandrenone, this 3° hydroxyl is only slightly shifted from its initial position at \( \tau 6.9 \), while the 2° hydroxyl proton is shifting from \( \tau 6.4 \) to -1.2. This most likely is due to steric hindrance between the bulky shift reagent and the sterically hindered 3° hydroxyl site. Perhaps 2° and 3° hydroxyl groups could be tentatively differentiated on this basis.

Assuming partial structures XXXIV and XLII leaves 9 carbons, 12 hydrogens, and 2 oxygen atoms yet to be located. There are 1 methyl, 2 methylenes, 4 methinyls, 2 quaternary carbons, one 3° hydroxyl and 1 oxygen atom in an ether linkage still to be accounted for. Of the 12 unsaturated sites in nicandrenone, 3 remain to be located and since the only carbonyl functional group as well as all of the double bonds have already been incorporated into partial structures XXXIV and XLII, there must be 3 more rings unaccounted for. Tentatively assuming a steroid
type structure suggests that there is probably one more epoxide ring and that the remaining methyl group is at C$_{10}$ and has the stereochemistry shown in XXXIII which is customary for steroids.

The structure for nicandrenone with the carbonyl at C$_{4}$ instead of at C$_{1}$ is ruled out due to the downfield position of the C$_{19}$ methyl at about $\tau$ 8.7 in the PMR spectrum (Figure 49).

**Rings B and C**

The only possible structures that are compatible with all of the data presented as well as the assumptions just made are XXXIII and XLIII through XLVII:
The PMR spectrum (Figure 39-c) contains a quartet centered at \( \tau 6.0 \) \((J_{ef} = 4 \text{ Hz}, J_{fg} = 2 \text{ Hz}, 1 \text{H})\). Upon irradiating at \( \tau 6.0 \), the doublet at \( \tau 6.85 \) \((J_{ef} = 4 \text{ Hz}, 1 \text{H})\) collapses to a singlet (Figure 49-a). Upon irradiating the doublet at \( \tau 6.85 \), the quartet at \( \tau 6.0 \) collapses to a singlet (Figure 44-a), indicating that both methinyls coupled to the methinyl at \( \tau 6.0 \) must absorb near \( \tau 6.85 \). However, upon irradiating the quartet (Figure 49) at \( \tau 6.95 \) \((J_{fg} = 2 \text{ Hz}, J_{h} = 11 \text{ Hz}, 1 \text{H})\), the quartet at \( \tau 6.0 \) collapses to a doublet (Figure 44-b, \( J_{ef} = 4 \text{ Hz} \)), thereby verifying that this is coupled to the quartet at \( \tau 6.0 \). The CMR spectra (Figures 40-42) show two very similar carbons at -56 and -57 ppm which are in the region for ether carbons and could very well correspond to \( C_6 \) and \( C_7 \). The methinyl at \( \tau 6.8 \) in the PMR spectrum (Figure 49) is too far upfield for an ordinary hydrogen attached to a carbon bonded to oxygen, so an epoxide is suggested since they normally absorb between \( \tau 7.0-7.8 \) (38, p. 55). If the doublet at \( \tau 6.8 \) is due to a hydrogen \( \sigma \) to an epoxide, then it is shifted downfield a small amount. This can be explained by deshielding due to the hydroxyl group at \( C_5 \). If the methinyl at \( \tau 6.0 \) is also a hydrogen \( \sigma \) to an epoxide, then it has been considerably shifted downfield. The epoxide hydrogen at \( C_7 \) in Figure 7 is nearly in the plane of the benzene ring which would account for its downfield position. Upon irradiating this hydrogen, a Nuclear Overhauser Effect of 20% was observed for the aromatic hydrogen at \( \tau 2.6 \) (compare Figures 49-b and 49-c). This confirms the spatial closeness of the hydrogens attached to \( C_7 \) and \( C_{15} \) in Figure 38 as well as indicating the position of the \(-C_9H_{19}O_3\) side chain on the aromatic ring.
The coupling constant of \( J_{ef} = 4 \) Hz is also typical of cis-1,2 hydrogens in an epoxide (46, #193; 52).

The carbon located at \( C_8 \) is situated \( \alpha \) to the benzene ring as well as an epoxide oxygen which would tend to shift its CMR signal downfield. Either of the CMR tertiary carbon signals at -43 or -39 ppm could correspond to \( C_8 \) though as discussed previously \( C_8 \) probably is the -39 ppm peak since the carbon at \( C_{20} \) is in closer proximity to more oxygen functions and therefore probably absorbs at -43 ppm.

By careful examination of the PMR spectrum (Figure 48) it appears that the methinyl responsible for the coupling constant of 11 Hz with the methinyl at \( C_8 \) (\( \tau \) 6.95) must lie upfield from it. Since the region between \( \tau \) 8.0-9.0 has already been explained, it seems reasonable that this methinyl absorbs somewhere in the complex region \( \tau \) 7.0-7.4. By careful integration of the PMR spectrum and by subtracting out all of the protons previously assigned, it appears that the methinyl corresponding to \( C_9 \) in XXXIII must absorb near \( \tau \) 7.3. The coupling constant, \( J_{hg} = 11 \) Hz, for the methinyl absorption at \( \tau \) 7.3 indicates that the two methinyls, \( H_h \) and \( H_g \), are trans di-axial to one another as in a fused ring system. The CMR spectra (Figures 40-42) indicate a carbon bearing one hydrogen absorbing at -32 ppm which suggests that it is more aliphatic in nature than the carbon located at \( C_8 \). This information is compatible with \( C_9 \) in XXXIII.

The CMR spectra (Figures 40-42) show two secondary carbons absorbing at -37 and -24 ppm. The lower field absorption was assigned to \( C_{12} \) in XXXIII due to the effect of the adjacent benzene ring. The
absorption at -24 ppm indicates a more aliphatic type methylene and has been assigned to C_{11}.

Upon irradiating at $\tau = 8.15$ (Figure 48) the complex absorption in the vicinity of $\tau = 7.15$ sharpens up. Careful integration of the PMR spectrum (Figure 38) suggests two unassigned protons at about $\tau = 7.1$ which could correspond to the methylene at C_{11} in XXXIII. Due to the complexity of absorption in the region about $\tau = 7.1$, the coupling constants for hydrogens attached to C_{9}, C_{11}, and C_{12} were not sorted out.

Nicandrenone (XXXIII) has 11 asymmetric centers. It most likely possesses the usual plant steroid configurations at C_{8}, C_{9}, C_{10}, and C_{20} as shown. The 6-3 ring junctures are most likely cis because of excessive strain in the trans configuration. The configuration at C_{22} is probably the same as in withaferin A (XL).

Two papers very recently appeared on the chemical constituents of Nicandra physalodes including X-ray structure determinations on two nicandrenone derivatives. This work (53, p. 1108, 1250) completely substantiates the structure XXXIII proposed here for nicandrenone and further elucidates the stereochemistry around the remaining asymmetric centers. They presented structure XLVIII (53, p. 1250) for nicandrenone:

\[ \text{XLVIII} \]
As suggested here, they also identified a steroid IL (53, p. 1108) which is a probable biogenetic precursor for nicandrenone:

We have isolated another compound from Nicandra physalodes referred to as Nic-2 which is in the process of being identified. It may very well be related to the structure XLVIII for nicandrenone.
EXPERIMENTAL

The experimental PMR spectra were run on 10% solutions of deuterochloroform with the Varian T-60 or HA-100 instruments, and the CMR spectra were run on 250 mg of nicandrenone dissolved in 2 ml of deuterochloroform with the Bruber 90 MHz instrument using tetramethylsilane (TMS) as an internal standard. All chemical shifts have been expressed in $\tau$ units.

The IR spectra were obtained with a Perkin-Elmer 337 Grating Infrared spectrophotometer with a KBr pellet.

Melting points were taken using a Thomas-Kofler micro hot stage instrument, model 6886-A, and are uncorrected.

Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer.

All experimental spectra (Figures 38 through 50) appear in the Appendix.
APPENDIX

ELECTRONIC AND MASS SPECTRA
Figure 10. PMR spectrum of 6-methyl-5-hepten-2-one (VII, CCl₄, 100 MHz).
Figure 11. PMR spectrum of 2,6-dimethyl-5-hepten-2-ol (VIII, CCl₄, 100 MHz).
Figure 12. PMR spectrum of 2,6-dimethyl-2,5-heptadiene (XVII, CCl₄, 60 MHz).
Figure 13. PMR spectrum of XIX (81%), XVIII (12%), IX and X (7%) (CCl₄, 100 MHz).
Figure 14. PMR spectrum of 1,5,5- and 1,3,3-trimethylcyclohexenes (IX and X, respectively, neat, 100 MHz).
Figure 15. PMR spectra of 1-acetyl-2,4,4- and 6-acetyl-1,3,3-trimethylcyclohexene (XI and XII, respectively, neat, 100 MHz).
Figure 16. PMR spectrum of \(1\)-carboxy-2,4,4-erimethylcyclohexene (VI, CDCl\(_3\), 100 MHz).
Figure 17. PMR spectrum of $\beta$-cyclolavandulol (IIc, neat, 60 MHz).
Figure 18. PMR spectrum of bergaptene (XVIe, CDCl$_3$, 100 MHz).
Figure 19. UV spectra of bergaptene (XVIe, solid line, 1.4 mg/100 ml ethanol) and isobergaptene (Ie, dotted line, 1.3 mg/100 ml ethanol).
Figure 20. IR spectra (KBr) of bergaptene (XVIe, upper) and isobergaptene (Ie, lower).
Figure 21. PMR spectrum of bergamottin (XVI, CDCl$_3$, 60 MHz).
Figure 22. IR spectra of bergamottin (XVf, KBr).
Figure 23. UV spectrum of bergamottin (XVI, 1.4 mg/100 ml ethanol).
Figure 24. PMR spectrum of limettin (XXI, CDCl₃, 60 MHz).
Figure 25. NMR spectrum of bergaptol (XVIa, DMSO-\textit{d}_6, 60 MHz).
Figure 26. NMR spectrum of XXII or XXIII (DMSO-$d_6$, 60 MHz).
Figure 27. PMR spectrum of synthetic archangelin (CDCl₃, 60 MHz).
Figure 28. PMR spectrum of natural archangelin (XVIc, CDCl₃, 60 MHz).
Figure 29. PMR spectrum of natural archangelin (XVIc, CDCl₃, 100 MHz).
Figure 30. UV spectrum of synthetic archangelin (XVIc, 1.6 mg/10 ml ethanol).
Figure 31. UV spectrum of natural archangelin (XVIc, 1.9 mg/100 ml ethanol).
Figure 32. IR spectrum of synthetic archangelin (KBr).
Figure 33. IR spectrum of natural archangelin (XVIc, KBr).
Figure 34. PMR spectrum of XXVI (CDCl$_3$, 60 MHz).
Figure 35. Mass spectrum of XXVI.
Figure 36. IR spectrum of XXVI (KBr).
Figure 37. PMR spectrum of isobergaptene (Ie, CDCl$_3$, 60 MHz).
Figure 38. PMR spectrum of nicandrenone (XXXIII, CDC13, 100 MHz).
Figure 39. PMR spectrum of nicandrenone (XXXIII, CDCl₃, 100 MHz) showing various decoupling experiments.
Figure 40. CMR spectrum of nicandrenone (XXXIII, CDCl₃, 90 MHz) with noise decoupling of protons.
Figure 41. CMR spectrum of nicandrenone (XXXII, CDCl₃, 90 MHz) with off-resonance decoupling.

- s = singlet
- d = doublet
- t = triplet
- q = quartet
s = singlet  
d = doublet  
t = triplet  
q = quartet

Figure 42. Expanded CMR spectrum of nicandrenone (XXXIII, CDCl₃, 90 MHz) with off-resonance decoupling.
Figure 43. IR spectrum of nicandrenone (XXXIII, KBr).
Figure 44. PMR spectrum of nicandrenone (XXXIII, CDCl₃, 60 MHz) with decoupling.
Figure 45. PMR spectrum of nicandrenone (XXXIII, Eu(fod)$_3$, CDCl$_3$, 60 MHz).
Figure 46. PMR spectrum of nicandrenone (XXXIII, Eu(fod)$_3$, CDCl$_3$, 60 MHz).
Figure 47. PMR spectrum of nicandrenone (XXXIII, Eu(fod)$_3$, CDCl$_3$, 60 MHz) with decoupling.
Figure 48. PMR spectrum of nicandrenone (XXXIII, Eu(fod)$_3$, CDCl$_3$, 60 MHz).
Figure 49. PMR spectrum of nicandrenone (XXXIII, CDCl$_3$, 100 MHz) showing enhancement due to Nuclear Overhauser Effect.
Figure 50. Mass spectrum of nicandrenone.
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