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THE TAXONOMICALLY SIGNIFICANT CONSTITUENTS OF TWO COMPOSITAE PLANTS,
PART I: ASTER SPINOSUS BENTH. (SPINY ASTER). PART II: ARTEMISIA CARRUTHII WOOD VAR. WRIGHTII (GRAY) BLAKE (CARRUTH SAGEBRUSH).

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THE TAXONOMICALLY SIGNIFICANT CONSTITUENTS OF TWO
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BENTH. (SPINY ASTER). PART II: ARTEMISIA
CARRUTHII WOOD VAR. WRIGHTII (GRAY)
BLAKE (CARRUTH SAGEBRUSH)

by

JEFFREY CHANDLER SPITZER

A Dissertation Submitted to the Faculty of the
DEPARTMENT OF CHEMISTRY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

1966
I hereby recommend that this dissertation prepared under my direction by Jeffrey Chandler Spitzer entitled The Taxonomically Significant Constituents of Two Compositae Plants. Part I: Aster spinosus Benth. (Spiny Aster). Part II: Artemisia carruthii Wood. var. wrightii (Gray) Blake. (Carruth Sagebrush), be accepted as fulfilling the dissertation requirement of the degree of Doctor of Philosophy.

After inspection of the dissertation, the following members of the Final Examination Committee concur in its approval and recommend its acceptance:

This approval and acceptance is contingent on the candidate's adequate performance and defense of this dissertation at the final oral examination. The inclusion of this sheet bound into the library copy of the dissertation is evidence of satisfactory performance at the final examination.
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SIGNED: Jeffrey C. Spitzer
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ABSTRACT

Part I

Steam distillation of *Aster spinosus* Benth., a spiny aster found in Southern Arizona, yielded a yellow-brown oil and solid mixture. A petroleum ether solution of this material readily deposited a white, crystalline compound, which was shown to be cis-lachnophyllum ester by spectral data and by mixed melting point with an authentic sample. The taxonomic value of cis-lachnophyllum ester is discussed.

Part II

Steam distillation of leaves and flowers of *Artemisia carruthii* Wood. var. *wrightii* (Gray) Blake, a sagebrush, yielded chamazulene as an artifact. The naturally occurring precursor of chamazulene was shown to be the sesquiterpene lactone, matricin, by chromatographic and spectral comparison with an authentic sample. Some stereochemical conclusions were drawn from nuclear magnetic resonance data. The possible use of matricin and other sesquiterpene lactones in chemotaxonomy is discussed.
Part I

*Aster spinosus* Benth. (Spiny Aster)
INTRODUCTION

**Historical.**—The first naturally occurring acetylenes were investigated by Arnaud and by Semmler. The former proposed the correct structure for tariric acid (I), while the latter, due to an unexplained disbelief in the existence of natural acetylenes, assumed the incorrect allenic structure (II) for carlina oxide. The correct formula (III) was finally deduced by Pfau and his co-workers, who observed a $\text{C=\text{C}}$-band at 2235 cm$^{-1}$ in the Raman spectrum.

cis-Lachnophyllum ester (IV) from *Lachnophyllum gossypinum* Bge. was the first naturally occurring polyacetylene to be described. This was followed by erythrogenic acid, for which Castille proposed either structure V or VI, and which Jones later defined as VI. In 1941 Sorensen and Stene isolated a polyacetylene from *Matricaria inodora* L., and this compound was finally shown to be the methyl...
ester of cis, cis-2, 8-decadiene-4, 6-diynoic acid (VII). The trivial name "matricaria ester" was given to this compound, which seems to be the most frequently occurring polyacetylene in the Compositae family.

At this point the pure chemistry of polyacetylenes was investigated. The Jones and Bohlmann groups developed useful synthetic routes to a variety of polyacetylenic compounds and compiled electronic spectral data which facilitated the identification of new natural products. The importance of this work was soon recognized when it was demonstrated that polyacetylenes isolated from micro-organisms (fungi) possessed marked antibiotic activity. Mycomycin (VIII) was one of the first of these antibiotics to be characterized.

Distribution. At present there are three principal natural sources of acetylenic compounds, namely, seed oils, fungi, and plants of the Compositae and Umbelliferae families. The seed oils contain
acetylenic acids (as glycerides), examples being tariric acid (I) from various *Picramnia* species and ximenynic (santalbic) acid (IX) from several *Ximenia* species. Except for *Picramnia* compounds, all the glyceride acids with triple bonds seem to occur in the order Santalales.

\[
\text{CH}_3-(\text{CH}_2)_5-\text{CH}=\text{CH}-\text{C}≡\text{C}-(\text{CH}_2)_7-\text{CO}_2\text{H}
\]

IX

Fungal acetylenes have been discovered in Actinomycetes but are most common in Basidiomycetes (*Agaricaceae* and *Polyporaceae* families). These compounds possess a variety of functional groups, including the unusual allene linkage (e.g., mycomycin). Some examples are agrocybin (X), junipal (XI), and the nitrile (XII).

\[
\text{HOCH}_2-\text{C}≡\text{C}-\text{C}≡\text{C}-\text{C}≡\text{C}-\text{CONH}_2
\]

X

\[
\text{CH}_3-\text{C}≡\text{C}-\text{S}-\text{CHO}
\]

XI

\[
\text{HO}_2\text{C}-\text{CH}=\text{CH}-\text{C}≡\text{C}-\text{C}≡\text{C}-\text{CN}
\]

XII

The most common natural acetylenes are the C\textsubscript{10} esters and alcohols from *Compositae* and *Umbelliferae* plants. In the *Compositae* family nearly thirty species of the genus *Erigeron* alone have been shown to contain matricaria ester (VII), and most of these contain lachnophyllum ester (IV) also. Several other polyacetylenes, including hydrocarbons, alcohols, aldehydes, ketones, glycols, chlorohydrins,
furans, epoxides, and aromatic compounds have been isolated from numerous genera of the composites. Two species of the Umbelliferae, Circuta virosa and Enanthe crocata, contain highly toxic glycols (e.g., XIII and XIV);

\[
\text{XIII} \quad \text{HO-(CH}_2\text{)}_3\text{-(C≡C)}_2\text{-(CH=CH)}_3\text{-CHOH-(CH}_2\text{)}_2\text{CH}_3
\]

\[
\text{XIV} \quad \text{HOCH}_2\text{CH=CH-(C≡C)}_2\text{-(CH=CH)}_2\text{-(CH}_2\text{)}_2\text{CHOH-(CH}_2\text{)}_2\text{CH}_3
\]

and similar compounds with simple functional groups and odd-numbered carbon chains have been found in other genera of this family.

A few other acetylenes are known from sources other than the above, but these have yet to be investigated to any appreciable extent. Certainly the list of these interesting constituents, which numbers well over a hundred, is far from complete. It is probable that not many seed oils have been screened for acetylenes. In the case of the fungal compounds the investigations were limited by the search for antibiotics. The most extensive efforts have been directed at the Compositae family, from which many of the acetylenes are readily obtainable by steam distillation, and therefore it is not surprising that most of these compounds have been found here.

**Isolation and Characterization.** -- Both solvent extraction (e.g., with acetone) and steam distillation have been used to obtain acetylenic constituents from plants. The resulting mixtures of several compounds
are often subjected to chromatography on alumina in order to isolate the acetylene. In some cases, however, it is possible to extract a steam distillate with petroleum ether and crystallize the material directly from this solvent.

Ultraviolet spectroscopy can be used most advantageously to detect the presence of conjugated double and triple bonds. Besides the characteristic absorption patterns, the molar absorptivities are usually high ($>10^4$), thus enabling even microgram quantities to be detected. Some typical UV spectra are shown in Fig. I-1.

Once the existence of a conjugated system has been demonstrated (usually with the crude extract), infrared spectroscopy can determine the presence or absence of triple bonds. However, because acetylenic absorption in the infrared (ca. 2100-2300 cm$^{-1}$) is often weak, it is advisable to separate the extract at least partially into its components in order to increase the relative amount of acetylene. It is often possible to determine the complete structure of a pure polyacetylene merely from IR, UV, and NMR data plus the elemental analysis.

**Synthetic Methods.**—Several of the naturally occurring polyacetylenes have been identified by unequivocal synthesis. For this purpose three general synthetic methods have been developed. The first$^{13,14}$ is based on the rearrangement of acetylenic dichlorides in strong base. The chain is lengthened by reaction with formaldehyde
Fig. I-1. - Ultraviolet Spectra of Polyacetylenes

A: \( \text{CH}_3 - \text{CH} = \text{CH} - \text{C} = \text{C} = \text{C} = \text{C} = \text{CH} - \text{CO}_2 \text{CH}_3 \) (cis, cis) (Ref. 32)

B: \( \text{C}_6\text{H}_5 - \text{C} = \text{C} = \text{C} = \text{C} = \text{C} = \text{CH}_3 \) (Ref. 32)

C: \( \text{CH}_3 - \text{C} = \text{C} = \text{C} = \text{C} = \text{CH} = \text{CH} = \text{CO}_2 \text{CH}_3 \) (Ref. 33)

D: \( (\text{CH}_3)_3 \text{C} - (\text{C} = \text{C})_4 - \text{C} (\text{CH}_3)_3 \) (Ref. 34)
The second method employs oxidative coupling between two terminal acetylenes. An example is the synthesis of cis-lachnophyllum ester (IV).

The third route avoids the mixture of products obtained in the second. By making one reactant the bromide, only one polyacetylene is produced.

As many as eight triple bonds have been introduced into a molecule by use of these methods. However, unless the terminal R and R' groups are bulky (e.g., phenyl or tert-butyl) the molecule is highly unstable and cannot be isolated. In fact, if R = R' = H, only a triyne can be synthesized.
Finally, it might be mentioned that the Wittig reaction offers an excellent method of forming an ene-yne group. The acetylene function can be either in the phosphorus ylide or the aldehyde.

\[
\begin{align*}
CH_3CH_2-CH≡CH-CH=P(C_6H_5)_3 + HC≡C-CHO & \rightarrow \\
CH_3CH_2-(CH≡CH)_2-C≡CH & \xrightarrow{\text{Br-C≡C-CH=CH-CH}_2\text{OH}} \\
& \xrightarrow{\text{C}^+} \\
CH_3CH_2-(CH≡CH)_2-(C≡C)_2-C≡CH & \text{CH=CH-CH}_2\text{OH}
\end{align*}
\]

**Biosynthesis.** --Two problems are involved in proposing a biosynthetic scheme for polyacetylenes: the origin of the carbon skeleton and the formation of the triple bonds. The first has been solved to a large extent, while the second remains a matter of speculation. Bu’lock and his co-workers have shown that polyacetylenic chains are built in essentially the same manner as fatty acids. This pathway can be outlined as follows:

\[
\begin{align*}
\text{CH}_3\text{COSCoA} & \xrightarrow{[\text{CO}_2\text{I}]} \text{HO}_2\text{C-CH}_2-\text{COSCoA} \xrightarrow{\text{CH}_3\text{COSCoA}} \\
\text{CH}_3\text{COCH}-\text{COSCoA} & \xrightarrow{\text{CO}_2\text{H}} \text{CH}_3\text{CHOHCH}-\text{COSCoA} \\
\text{CH}_3-\text{CH=C-COSCoA} & \xrightarrow{\text{CO}_2\text{H}} \text{CH}_3\text{CH}_2\text{CH=COSCoA} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{COSCoA} & \xrightarrow{\text{reacts further with malonyl-CoA}}
\end{align*}
\]
In accordance with this scheme acetate $-^{14}\text{C}$ was incorporated into alternate carbon atoms of matricaria ester (VII) from a fungus. On the other hand, malonate $-^{14}\text{C}$ was incorporated into carbons 2, 4, 6, and 8 of XV but not into 9 or 10 (which come from acetyl-CoA directly).

\[
\text{CH}_3\text{-CH}=\text{CH}-(\text{C}≡\text{C})_2\text{-CH}=\text{CH}-\text{CO}_2\text{CH}_3
\]

VII

\[
\text{CH}_3-(\text{C}≡\text{C})_3\text{-CH}=\text{CH}-\text{CH}_2\text{OH}
\]

XV

The occurrence of odd-numbered fatty acids is not unknown, but their frequency is much greater among polyacetylenic acids. Gardner, Lowe, and Read\textsuperscript{24} showed that such acids can arise by decarboxylation of even-numbered chains. In their experiment cell-free extracts of a fungus converted XVI to XVII. No $\alpha,\beta$-acetylenic aldehyde or alcohol

\[
\text{HO}_2\text{C}-(\text{C}≡\text{C})_3\text{-CH}=\text{CH}-\text{CH}_2\text{OH} \rightarrow \text{H}-(\text{C}≡\text{C})_3\text{-CH}=\text{CH}-\text{CH}_2\text{OH}
\]

XVI XVII

was found, thereby lending support to the direct decarboxylation reaction.

The problem of triple-bond formation is connected with that of double-bond formation, for which several hypotheses have been advanced. Schoenheimer and Rittenberg showed that saturated fatty acids can be dehydrogenated by living systems but did not propose a mechanism.\textsuperscript{25} One possibility is direct desaturation at a specific site, thus:
An alternate route is $\alpha, \beta$-dehydrogenation (a well-known reaction) followed by double bond migration, i.e.,

$$\text{CH}_3\text{(CH}_2\text{)}_m\text{-CH}_2\text{CH}_2\text{-CO}_2\text{H} \quad \downarrow \quad \text{CH}_3\text{(CH}_2\text{)}_m\text{-CH}=\text{CH}-\text{(CH}_2\text{)}_n\text{-CO}_2\text{H}$$

1) protonation
2) hydride shifts

Lynen has proposed that double bonds could arise from dehydration of known hydroxylated intermediates to $\beta, \gamma$-unsaturated compounds, as illustrated below. These could then be built up via the usual acetate-malonate pathway with the double-bond left behind.

$$\text{R-CH}_2\text{-CHOH-CH}_2\text{COSCoA} \quad \rightarrow \quad \text{R-CH}=\text{CH-CH}_2\text{COSCoA}$$

The mechanism of triple-bond formation is unknown at present. The obvious possibility that acetylenes are synthesized by simple dehydrogenation of olefins is thermodynamically feasible, the second dehydrogenation being nearly as exothermic as the first. *

---

*This process involves reaction of a compound with molecular oxygen to produce a dehydrogenated compound and water.
On the other hand, Jones has suggested a concerted decarboxylation-elimination on compounds such as XVIII. Fleming and Harley-Mason

\[
\text{CH}_3\text{COSCoA} + \text{HO}_2\text{C-CH}_2\text{COSCoA} \rightarrow \text{CH}_3\text{COCH-CO}_2^- \text{COSCoA} \\
\text{1) enolization} \\
\text{2) phosphorylation}
\]

reacts further

\[
\text{reacts further} \quad \text{CH}_3\text{C}≡\text{C- CO}_2^- \text{COSCoA} \quad \text{CH}_3\text{C}≡\text{C- CO}_2^- \text{COSCoA}
\]

with malonyl-CoA

\[
\text{carried out a similar reaction in vitro with sulfonate derivatives (XIX) but were unsuccessful with a phosphate (XX).}
\]

\[
\text{R=C= C(CO}_2\text{Et)}_2 \quad \text{OSO}_2\text{-C}_6\text{H}_5\text{-p-Br} \xrightarrow{\text{dilute base}} \text{R=C≡C- CO}_2\text{Et} \\
\text{R=C≡C- CO}_2\text{Et} \quad \text{R=C≡C-CO}_2\text{Et} \\
(R=C_6\text{H}_5\text{-CH=CH-}, \text{CH}_3\text{-CH=CH-}, \text{CH}_3\text{- (CH=CH)}_2^-)
\]

\[
\text{C}_6\text{H}_5\text{-C= C(CO}_2\text{Et)}_2 \quad \text{OPO(OEt)}_2 \xrightarrow{\text{dilute base}} \text{hydrolysis products, no acetylene.}
\]

\[
\text{XX}
\]
Fig. I-2. -- *Aster spinosus* Benth.
EXPERIMENTAL

Melting points were determined in capillary tubes with a Mel-Temp apparatus. Infrared spectra were obtained on a Beckmann IR-4 spectrophotometer, ultraviolet spectra on a Cary model 11 recording spectrophotometer, and nuclear magnetic resonance spectra on a Varian A-60 spectrometer. Microanalyses were performed by C. F. Geiger, Ontario, California.

Aster spinosus Benth. (Fig. 1-2) was collected in August along the banks of the San Pedro River in southern Arizona. The long, green overground shoots (1 kg.) were steam distilled from a large iron can, the distillate passing through two condensers into an ice-cooled receiver. Approximately one gram (0.1%) of a yellow-brown oil and solid mixture was obtained. When this mixture was dissolved in petroleum ether and left overnight in the refrigerator, white crystals (needles) appeared, which melted at 32.7-33.0° after one recrystallization. Calculated for C₁₁H₁₂O₂: C, 74.98; H, 6.88. Found: C, 74.92; H, 6.95. The compound gave positive permanganate, tetranitromethane, and hydroxamate tests.

Vapor phase chromatography of the volatile oil on a column of 20 per cent carbowax on chromosorb at 170° yielded irreproducible results. Decomposition may have occurred on the column. Paper
chromatography afforded virtually no separation with the following solvent systems:

- petroleum ether (100-115°C)
- n-butanol saturated with 2% ammonium hydroxide
- acetic acid-water (1:5)
- ethyl acetate
- ethyl acetate saturated with water
- benzene-dioxane-acetic acid (90:25:4)
- benzene-methyl ethyl ketone-2% formic acid (9:1:1)
- benzene-dioxane-triethylamine (1:1:1)

Thin-layer chromatography on silica gel G (Research Specialties Co.) gave the best results (see Results and Discussion).
RESULTS AND DISCUSSION

The infrared spectrum of the purified material is shown in Fig. I-3. Most significant are bands at 2245 and 2150 cm\(^{-1}\) (C=\(\equiv\)C stretching), 1735 cm\(^{-1}\) (C=O stretching of an ester), and 1610 cm\(^{-1}\) (C=C stretching). Bands at 1210 and 1170 cm\(^{-1}\) are also associated with an ester group.

The ultraviolet spectrum is reproduced in Fig. I-4. Positions and molar absorptivities (\(\epsilon\)) of the maxima are listed in Table I-1, along with those recorded by Sorensen\(^{29}\) for cis-lachnophyllum ester. The discrepancy in the \(\epsilon\) values is due to the fact that Sorensen's spectrum was determined on the crude essential oil.

<table>
<thead>
<tr>
<th>(\lambda_{\text{max}}) ((\mu))</th>
<th>(\log \epsilon)</th>
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<tbody>
<tr>
<td>Observed</td>
<td>Literature(^{a})</td>
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<tr>
<td>225.3</td>
<td>225.0</td>
</tr>
<tr>
<td>276.0</td>
<td>275.0</td>
</tr>
<tr>
<td>292.0</td>
<td>291.6</td>
</tr>
<tr>
<td>310.5</td>
<td>310.0</td>
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</table>

\(^{a}\)Reference 29.
Fig. I-3. --Infrared Spectrum of cis-Lachnophyllum Ester in Carbon Tetrachloride
Fig. I-4. -- Ultraviolet Spectrum of **cis**-Lachnophyllum Ester in Hexane ($6.17 \times 10^{-3}$ gram/liter)
The NMR spectrum is shown in Fig. 1-5, and the assignments are listed in Table 1-2. Both vinyl protons have the same chemical shift.

**TABLE I-2. —Nuclear Magnetic Resonance Data for cis-Lachnophyllum Ester.**

| \( \text{CH}_3-\text{CH}_2-\text{CH}_2-\text{C}=\text{C}-\text{C}=\text{C}-\text{CH}=\text{CH}-\text{CO}_2\text{CH}_3 \) |
|-----------------|-----------------|-----------------|
| A               | B               | C               |
| D               | D               | E               |

<table>
<thead>
<tr>
<th>( \delta \text{ (p.p.m.)}^a )</th>
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<th>No. of Protons</th>
<th>Assignment</th>
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<tr>
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<tr>
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<td>1</td>
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<td>D</td>
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In \( \text{CCl}_4 \) and relative to tetramethyilsilane.

An authentic sample of cis-Lachnophyllum ester was obtained from Professor Sorensen. The melting point was 32-33\(^\circ\) and was not depressed upon admixture with the \textit{A. spinosus} acetylene.

Fig. 1-6 shows the thin-layer chromatogram of the essential oil from \textit{A. spinosus}. Obviously, there are many other compounds present besides cis-lachnophyllum ester. By spotting the oil several times on two plates, running the chromatogram, dissolving the
Fig. I-5.--Nuclear Magnetic Resonance Spectrum of \textit{cis}-Lachnophyllum Ester in Carbon Tetrachloride
Fig. 1-6.--Thin-layer Chromatogram (V-Shape Technique) of *A. spinosus* Oil.

Adsorbent: silica gel G; solvent system: hexane-ethyl acetate (9:1); visualization: sulfuric acid followed by heating five minutes at 90°; colors: 1-purple-brown, 2-green-yellow, 3-purple-brown, 4-yellow (*cis*-lachnophyllum ester), 5-green-yellow, 6-red-purple, 7-red, 8-red-purple, 9-purple-brown
compounds off the silica gel with hot chloroform or methanol, and determining the infrared spectra, it was possible to demonstrate that the oil contained no other acetylenic compounds. However, other acetylenes may be present during different periods of the growing season.

Williams, Smirnov and Goljmov proved the structure of cis-lachnophyllum ester (IV) chemically by the reactions outlined in Fig. 1-7. The cis configuration of the double bond was shown by degradation to maleic acid. Finally, the unequivocal synthesis by Jones confirmed the structure. The infrared and nuclear magnetic resonance data presented here are in excellent agreement with these conclusions.
Fig. I-7. --Degradation of cis-Lachnophyllum Ester
BIOLOGICAL ACTIVITY

Impure cis-lachnophyllum ester has previously been tested for physiological activity on mice, dogs, frogs, and guinea pigs. The L.D.₅₀ (dose required to kill 50 per cent of the test animals) in mice was 1.5 mg./10g. for subcutaneous and 0.75 mg./kg. for intraperitoneal injection. A dose of 0.5 mg./kg. excited respiration and reduced blood pressure in dogs. The amplitude of the heart beat in frogs was sharply reduced by a 0.001 per cent solution of the acetylene. The tonus of guinea pig intestine was repressed by 0.0002 and 0.00005 per cent solutions.

In the present investigation purified cis-lachnophyllum ester was found moderately effective in inhibiting the growth of Erwinia carnegiana, a bacterium from saguaro and cholla cacti. No quantitative work was carried out. The compound was also tested for antitumor activity against a human epidermoid carcinoma of the nasopharynx. The E.D.₅₀ (calculated effective dose which inhibits the growth of the treated cells 50 per cent as compared to the growth of control cells) was 2.5 µg./ml. This result indicated that cis-lachnophyllum ester was cytotoxic but not sufficiently active to warrant further testing.
TAXONOMICAL CONSIDERATIONS

The present investigation represents the first isolation of cis-lachnophyllum ester (IV) from the genus Aster. Shortly afterward, Bohlmann discovered this compound in Aster novi belgii, L. \(^{30}\) Hitherto, IV had been observed only in Lachnophyllum and Erigeron.

In an investigation of 31 species of Erigeron and 7 species of Aster, Sorensen \(^{31}\) showed that the former group all contained cis, cis-matricaria ester (VII) and nearly all contained cis-lachnophyllum ester (IV), whereas the latter were devoid of these compounds. Only one species of Aster, A. tripoleum, contained a polyacetylene, an ester of trans, trans-matricarianol (XXI). One species of Erigeron, E. khorassanicus Boiss., contained neither IV nor VII; but some modern botanists have reassigned this plant to the genus Conyza on purely botanical grounds. The chemical evidence appears to support the reclassification.
The three genera, Aster, Erigeron, and Conyza, are very difficult to distinguish by classical botanical tests. Sorensen has argued that chemical evidence, based on the presence or absence of IV and VII, can assist the botanist in assigning a difficult species to the above genera. As an example he cites the controversy over whether the two plants, *E. peregrinus* and *E. salsuginosus glacialis*, originally assigned to Erigeron, should be placed in Aster. Chemically, *E. peregrinus* contains both IV and VII and should therefore be in Erigeron. The other plant, however, contains neither of these compounds (but does have *trans*, *trans*-matricarianol) and so should be placed in Aster.

The finding of this investigation and that of Bohlmann apparently disprove Sorensen's arguments. Obviously, if cis-lachnophyllum ester (IV) exists in both Erigeron and Aster, then its presence cannot be used to distinguish between the two. On the other hand, matricaria ester, (VII) was not found in Aster spinosus and was not mentioned in Bohlmann's report on Aster novi belgii. Therefore, this compound may have taxonomic value. Finally, the genus Conyza should be investigated along with several more species of Aster so that definite conclusions can be reached.
Part II

*Artemisia carruthii* Wood, var. *wrightii* (Gray) Blake.

(Carruth Sagebrush)
INTRODUCTION

Background. -- The sesquiterpene lactones comprise an interesting class of naturally occurring farnesol derivatives. They were investigated originally because of medicinal properties (e.g., santonin (I) is widely used as an antihelminthic, while others have shown antiphlogistic activity) and later because of relationship to azulenes. Now they are studied merely as curious and variegated natural molecules. Future work may indicate some utility in chemotaxonomy.

This discussion will pertain only to the guaianolide lactones, i.e., compounds possessing the guaiane skeleton (II). Other sesquiterpene lactones have been found with eudesmane (III), eremophilane (IV), and
germacrane (V) skeletons. Examples of these are santonin (I), ivalin (VI),
eremophilanolide (VII), costunolide (VIII), and pyrethosin (IX).

The guaianolides can be divided into three classes according to the
ease of aromatization to azulene derivatives. First are the ketolactones
(e.g., helenalin, matricarin), in which the keto group must be reduced
prior to aromatization. Second are those compounds (e.g., flexuosin A,
pseudoivalin) which can be converted to azulenes directly by heating with
sulfur or selenium. Finally, the so-called true proazulenes (e.g.,
matricin, artabsin) can be converted to azulenes simply by steam dis-
tillation from dilute acid.

The perhydroazulenic sesquiterpene lactones are widely distributed
throughout the Compositae family. So far they have been found in the
tribes Ambrosiae, Heliantheae, Helenieae, Anthemideae, Cichorieae,
Cynareae, and Carduaceae. Their possible utilization in taxonomy will
be discussed later. Recently, Sorm and his co-workers discovered a guaianolide in an *Umbelliferae* genus, but its structure has not yet been fully elucidated.  

Table II-4 contains a complete list of all the guaianolides characterized to date. Several of the compounds have undergone structure revision in the past five years as a result of reinvestigation by nuclear magnetic resonance techniques. For example, the structures of tenulin (X), helenalin (XI), and balduilin (XII) had to be changed from XIII, XIV, and XV, respectively. In another case the structure of arborescin was first believed to be XVI, later revised to XVII, and finally by the use of NMR and NMDR established as XVIII.
Isolation. -- Several methods of extraction have been used to obtain sesquiterpene lactones, the following being the most common.

1. The ground plant material is extracted with petroleum ether, the petroleum ether solution extracted with two per cent aqueous potassium bicarbonate in order to separate the lactones from the lipids and other water-insoluble compounds, and the lactones finally extracted from the bicarbonate solution into ethyl ether. The ether solution is dried and evaporated, thus leaving a yellow, syrupy residue.  

2. The ground plant material is extracted with ethyl ether, the solution concentrated, and an equal volume of petroleum ether added. This mixture is then extracted with 50 per cent aqueous ethanol and the ethanolic solution concentrated and extracted with ether. The ether is then dried and evaporated.

3. The ground plant material is extracted with chloroform, the solvent evaporated, and the residue dissolved in ethanol. Small quantities of acetic acid and lead acetate are added and the suspension left to settle. (The lead acetate is used to remove chlorophyll, tannins,
and some flavonoids.) The clarified solution is then filtered, concentrated, and extracted with chloroform. After the chloroform has been dried and evaporated, a brown, gummy residue is left.\textsuperscript{12}

The methods used in the present investigation are described in the Experimental section.

It is sometimes possible to crystallize the desired lactone directly from the gummy residues of the extraction. However, it is more often necessary to use column chromatography on alumina or silica gel to separate the different constituents. Countercurrent distribution has been used less often.

**Characterization.** Instead of treating the structure proofs of individual compounds, only a few general aspects will be discussed. In all cases both physical and chemical techniques were employed, but in the more recent work nuclear magnetic resonance spectroscopy has been the most powerful tool.

The guaianolide skeleton can easily be demonstrated by aromatization to azulene derivatives. As has already been pointed out, keto-lactones require initial reduction before the selenium treatment. The yields of chamazulene (XIX) are as high as 70 per cent, except in the case of those compounds with rearranged skeletons (i.e., methyl group at C-5 instead of C-4), which afford only traces of XIX. It should be noted that the angular methyl group can often be demonstrated by its NMR absorption, which is usually farther upfield than
that of other methyl groups (δ = 0.74, 0.90, 1.05, and 1.13 p.p.m. in XX, 13 XXI, 14 and XXIII, 15 respectively).

The above structures illustrate that the γ-lactone ring can be closed either to C-6 or C-8. Several methods have been used to distinguish between these possibilities, the choice depending upon the substitution pattern of the molecule. Herz used NMR spectroscopy with pulchellin XXI after demonstrating the presence of an abnormal skeleton. 13 If the lactone ring were closed to C-6, the absorption of the proton on the carbon bearing the lactone ether oxygen would be merely a doublet. In fact, however, this proton, which absorbs at approximately 4 p.p.m., is the complex multiplet expected from formula XXI.
White and Winter hydrogenated achillin (XXIV) to the dihydro derivative (XXV) and then produced the dieneone (XXVI) by treatment with base.\textsuperscript{16} The dieneone chromophore, easily detected by its ultraviolet spectrum ($\lambda_{\text{max}} 285m\mu, \log \epsilon = 4.18$), could not have formed had the lactone ring been closed to C-8.

Herz and Watanabe reduced parthenin (XXVII) with lithium aluminum hydride and then aromatized the product to artemazulene (XXVIII).\textsuperscript{17} This indicated a C-6 lactone ring closure. On the other hand, mexicanin E (XXIX) was eventually converted to linderazulene (XXXI), thus proving a C-8 ring closure.\textsuperscript{18} The oxygenated azulenes, XXXI and XXVIII, are formed when the diols XXX and its C-6 counterpart, obtained in the LiAlH$_4$ step, are heated with selenium. These aromatic compounds can be identified by the melting points of.
their trinitrobenzene adducts, as can other azulene derivatives.

Another method of determining the orientation of the lactone ring may soon be based on biogenetic considerations. (See section on taxonomy).

**Stereochemistry.** -- The stereochemistry of the guaianolides has presented a challenging problem. In several cases either the relative or absolute configurations have been determined by chemical and/or physical techniques. Some examples will be discussed below.

Herz and his co-workers carried out a five-step reaction sequence with pulchellin (XXI). Formation of lactone XXXII showed that the C₅-C₆ side chain was cis to the C₄ hydroxyl group. The C₄ hydroxyl was shown to be cis to the C₂ hydroxyl by synthesis of cyclic
sulfite and carbonate derivatives. Finally, the Hudson-Klyne rule (vide infra) was used with compounds XXXIII and XXXII to elaborate the absolute stereochemistry at C₂ (see XXXIII). These data allowed a more detailed structure (XXIa) to be drawn for pulchellin.

Sorm partially elucidated the stereochemistry of artabsin (XXXIV) by degradation to (XXXVI), a product of known configuration obtained from isophotosantonin lactone acetate (XXXV).
The empirical Hudson-Klyne rule\textsuperscript{20} has been used to find the absolute configuration of the carbon atom bearing the lactone ether oxygen. If the stereochemistry of this carbon atom relative to other centers is known, then other absolute configurations can be assigned.

To employ the Hudson-Klyne rule one determines the molecular rotation \([M]_D = [\alpha]_D \times \frac{\text{mol. wt.}}{100}\) of a lactone and subtracts that of the open-chain hydroxyacid or a suitable derivative (e.g., an alkali salt). If the difference is positive, then when the lactone is rotated to fit
XXXVII the proton on C-1 will be below the plane of the ring (XXXVIIa); if this difference is negative, the proton in question will be above the plane of the ring (XXXVIIb). Both γ- and δ-lactones fused to 5-, 6-, and 7- membered rings have been shown to follow this rule.

The application of the Hudson-Klyne rule to the stereochemistry of pulchellin (XXI) has already been mentioned. In this case the difference between the molecular rotations of XXXIII and XXXII was negative, thus implying a β-hydrogen at C^2. Sorm used the rule to find the absolute configuration at C^6 in artabsin (XXXIV). The result here was in agreement with that obtained later by chemical transformations.

The technique of optical rotatory dispersion was applied to tenulin (X) and helenalin (XI). However, the incorrect structures (XIII) and (XIV) were assumed, and so the arguments, which were based on comparisons with steroid models, are invalid. The lack of suitable model systems has reduced the applicability of ORD to the guaianolide series; but the method has much potential, especially with respect to the configurations at C^1 and C^5.

Nuclear magnetic resonance and double resonance were employed to determine the relative stereochemistry of globicin (XXXVIII). The arguments used will be described in the Results and Discussion section.
Finally, X-ray analysis must be mentioned as perhaps the most reliable method of determining stereochemistry. This technique has been applied to $\xi$-sigerin (XXXIX), $^{24}$ a natural guaianolide, and to isophotosantonin lactone acetate (XXXV), $^{25}$ a synthetic product.

**Biosynthesis.** --The guaianolides, like other sesquiterpenes, are derived from farnesol (XL). Hendrickson has outlined a sequence which in some cases predicts the relative stereochemistry of the final product. $^{26}$ After removal of the hydroxyl group from farnesol, the ring can close in either of two positions to form carbocation ion XLIa or b. The former will be favored. If the ion XLIa is now hydrated, the alcohol XLII will be produced (forms a, b, c, and d all being equivalent). This alcohol, as can be seen from formulas c and d, has its double bonds suitably oriented for a concerted cyclization either to XLIII or XLIV (R = H or OH). Were such a concerted
cyclization to occur, the resulting heavy-lined bonds would be parallel; and the relative stereochemistry of the product would be as indicated.

According to Hendrickson\textsuperscript{26} all sesquiterpenes of known stereochemistry and derived from XLIV possess the configurations predicted from the foregoing arguments. There are no guaiane (from XLIII) terpenes whose stereochemistry is known at all the pertinent positions. (In most compounds only two or three of the predictable positions are asymmetric.) However, in cases where the partial stereochemistry
has been elucidated (e.g., XXXIV, XXXVIII, and partheniol (XLV)\textsuperscript{27}),

![Chemical Structure](image)

the results tend to substantiate the above mechanism. These considerations will be referred to later.

**The "True" Proazulenes.** -- Those guaianolides which can be converted to chamazulene simply by steam distillation from dilute acid are known as true proazulenes. Up to now only five have been characterized: arborescin (XVII),\textsuperscript{9} artabs'\textsuperscript{n} (XXXIV),\textsuperscript{19} globicin (XXXVIII),\textsuperscript{23} absinthin (XLVI),\textsuperscript{28} and matricin (XLVII).\textsuperscript{29} As might be expected,

![Chemical Structures](image)

the investigations of these compounds were prompted by the discovery of chamazulene (or compounds rapidly oxidized to chamazulene by air) in the essential oils of plants. Further study revealed that azulenes were not present as such in the plants but were artifacts of the steam distillation.
Arborescin was the first to be isolated in crystalline form. This was followed rapidly by artabsin, matricin, and absinthin. Globicin was isolated in 1960. The original structures proposed for arborescin, artabsin, and absinthin, which were based on infrared, ultraviolet, and chemical evidence, were incorrect and had to be revised when NMR spectroscopy became available. This tool was used to great advantage with globicin, especially in the elucidation of the stereochemistry. The structure of matricin, which is substantiated in the present investigation, was derived almost entirely from chemical evidence. The reactions involved will be outlined in the Results and Discussion section.

The present work was initiated after the discovery that Artemisia carruthii, a sagebrush native to Arizona, yielded a blue oil on steam distillation. It was believed that the plant might contain one or more new proazulenes in quantities sufficient for characterization.
EXPERIMENTAL

**Apparatus.** -- The following instruments were used to obtain physical properties: a Mel-Temp melting point apparatus, a Bendix type 143A automatic polarimeter equipped with a 500 watt light source and a filter to isolate the D line of sodium, a Beckmann IR-4 infrared spectrophotometer, Cary models 11 and 14 ultraviolet spectrophotometers, and a Varian A-60 nuclear magnetic resonance spectrometer.

Vapor phase chromatography was done with a F & M flame detector apparatus and a 1/4" x 5' column of 20 per cent carbowax on chromosorb. A constant temperature of 150° was used. Thin-layer chromatography was done on 8" square glass plates coated 1/4 mm thick (1 mm. for preparative work) with Research Specialties Co. silica gel G. The chromatographic tanks were saturated overnight with the solvent to be used. Plates were heated to 100° for about 30 minutes just before use. Paper chromatography was done on Whatman #1 paper in tanks saturated with solvent. Column chromatograms were run in glass columns of various sizes with Baker reagent grade alumina (pH 6.6) or Research Specialties Co. plain silica gel (untreated).

**Location and Description of the Plant.** -- *Artemisia carruthii* Wood var. *wrightii* (Gray) Blake is a sagebrush native to mountainous regions
in Southern Arizona. Plants used in this investigation were obtained on Mt. Graham near the Hospital Flat camping area (elevation: ca. 9000 ft.).

The plant is shown in Fig. II-1. Numerous three-pronged leaves impart a shaggy appearance to the species and afford a means of recognition. Small buds appear at the end of the green stem and produce yellow flowers at maturity. The highest yield of sesquiterpene lactones is obtained from plants collected in late July. Thereafter, the yield decreases until almost no lactonic material can be obtained from plants harvested in September.

Steam-distillation. --Previous work with *A. carruthii* had revealed the presence of chamazulene (XIX) in the steam-distillate. However, no quantitative work had been done; and the exact location of the proazulene in the plant had not been determined.

The leaves, stems, and roots of *A. carruthii* were separated and steam-distilled individually from 2 M sulfuric acid. The steam-volatile oil was extracted into ether, the solution dried over magnesium sulfate, and the ether evaporated. The residue was subjected to vapor-phase chromatography and the percentage of chamazulene determined by cutting out and weighing the peaks. A total of 13 well-defined peaks appeared in the spectrum of the leaf-oil, and the peak due to chamazulene was located by comparison with an authentic sample.

Of the three anatomical portions of the plant only the leaves yielded a significant amount of volatile oil. One hundred grams of
Fig. II-1. -- *Artemisia carruthii* Wood var. *wrightii* (Gray) Blake
leaves yielded 0.145 gram of oil, one-fourth of which was chamazulene (0.036% of the leaves). The stems and roots afforded only minor quantities of an oil which was colorless. *

The azulenic fraction of the leaf oil could be purified by extraction of the dilute ether solution with a little concentrated sulfuric acid, dilution of the acid with water, and back-extraction into pentane. Paper chromatography of the concentrated pentane solution revealed the presence of chamazulene only (determined by comparison with an authentic sample). In this chromatography the stationary phase was paper impregnated with paraffin oil, and the mobile phase was 50 per cent aqueous phosphoric acid saturated with petroleum ether. Detection was accomplished by irradiation with an ultraviolet lamp.

**Extraction.** Two extraction procedures were used, each one giving somewhat different results.

a. Prior to the discovery that the proazulenes were absent from the stems and roots, the entire dried plants were ground in a Wiley mill for extraction. Three hundred and fifty grams of the ground material was then placed in a large beaker and soaked in chloroform overnight. The dark green slurry was filtered and the chloroform evaporated overnight. The recovered chloroform was used to extract

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*In line with this observation was the discovery that the leaves had an intensely bitter taste (characteristic of many sesquiterpene lactones), whereas the stems and roots had no distinct taste.*
the plant further. Next, the residue from the evaporation was taken up in 100 ml. of 95 per cent ethanol, and 300 ml. of water was added to precipitate a large quantity of black tar. Filtration of the tar left a tan suspension as the filtrate. Celite and Nuchar were then added to the suspension and the resulting mixture filtered through a mat of Celite. (At this point the turbidity was gone, and the solution was yellow or brown. If the solution was colorless, the Celite-Nuchar combination had removed too much of the lactone; if the turbidity was still present, then the chlorophyll had not been removed entirely. A small amount of chlorophyll was tolerable, for it could be separated later by chromatography.) Finally, the yellow filtrate was extracted into chloroform and the chloroform solution concentrated and stored in the refrigerator. The yield of brown, gummy extract varied from four to four and one half grams. When proficiency had been gained, the time required was about three hours.

b. In the second procedure 300 grams of leaves were set out to dry for two days, after which period the weight was only 108 grams. This material was placed in a large Soxhlet and extracted with pentane for six days. The orange-brown pentane solution was concentrated on a rotary evaporator, during which process much non-lactonic, solid material separated. This solid was filtered off and the pentane evaporated from the filtrate. The yield was one and one half grams of brown gum. Steam-distillation of the gum afforded a large quantity
of blue oil. The remainder of the leaves was steam-distilled, yielding more blue oil. Thus, the pentane had extracted a significant amount of azulenogenic material, but also had left behind a large amount. This observation was later explained by the thin-layer chromatographic results.

**Thin-layer Chromatography (TLC).**--The most rapid and reliable method of examining the extracts was TLC. Fig. II-2 shows chromatograms of the pentane extract along with arborescin, globicin, artabsin, and matricin (four of the five known "true" proazulenes). Only those spots which turned purple after sulfuric acid treatment are shown, for this reaction appeared to be characteristic of the "true" proazulenes. It can be seen that pentane extracted several azulene precursors, among which was a small quantity of matricin. The large spot at the top of the pentane extract chromatogram was actually composed of eight to ten compounds, as was shown by eluting the material from the plate and rechromatographing it in hexane-ethyl acetate (8:2). The chromatogram in Fig. II-2 indicates that artabsin may have been present in the pentane extract but in an amount insufficient for further study. It must be mentioned that several spots of different colors appeared on the chromatogram of the pentane extract, but most of these overlapped each other and were difficult to distinguish.
Fig. II-2. —Thin-layer Chromatogram of Proazulenes.

If after the pentane extraction the leaves were extracted with chloroform (as described above), matricin was the only proazulene obtained. This fact was revealed by TLC of the concentrated chloroform extract, which exhibited only one purple spot ($R_f$ identical to that of matricin). However, a UV-fluorescent compound was also present and overlapped the top of the matricin spot.

In order to isolate a larger quantity of matricin, preparative TLC was employed. Chromatographic plates coated one mm. thick with silica gel G were streaked with a concentrated solution of the chloroform extract and run in 90:1 chloroform-methanol. The location of the fluorescent compound (vide supra) was determined with an ultraviolet lamp, and the adsorbent just below this area was scraped off the plate into a test tube. Methanol or chloroform was then used to elute the matricin from the adsorbent (methanol affording a better yield). In this manner it was possible to work up enough matricin for a melting point, an optical rotation, and spectral analysis. The presence of the fluorescent compound precluded higher yields of matricin. None of the solvent systems which separated matricin from the other plant compounds could separate it from the fluorescent compound.

**Column Chromatography.**—In another attempt to obtain a higher yield of the lactone, column chromatography was employed. Several unsuccessful experiments were conducted with alumina as
the adsorbent and eluents ranging in polarity from hexane to methanol. The lactone (not known to be matricin at this point) apparently decomposed on the column, an observation already reported by Sorm et al.\textsuperscript{10}

With the success of the TLC experiments, it was reasonable to expect that a column of finely ground silica gel would be effective in isolating the matricin. After many trials with different eluents and column preparations, a procedure was found which gave fair results. The directions are as follows:

Fill a 2" x 27" column (teflon stopcock) with chloroform, push a plug of glass wool to the bottom with a long glass rod, and add a small amount of clean sand. With a magnetic stirrer prepare a homogeneous slurry of silica gel (plain) in chloroform, pour this into the column, and begin draining. As the gel settles, prepare more of the slurry and add it little by little, while the column drains. In this way the gel settles to a consistent mass, which appears gray and translucent. Finally, add a small amount of sand at the top to protect the surface of the adsorbent. About 300 grams of silica gel should be used. The column can stand indefinitely if the solvent is not permitted to fall below the level of the sand.

Before applying the extract, drain the column to within one half cm. of the sand. Now add one to two grams of extract in five or six ml. of chloroform, drain the column slightly, add a little more chloroform, and drain until all the extract has gone through the sand. Then fill the column to the top with chloroform, attach a
siphon arrangement, and complete the chromatography.

The chlorophyll not removed in the extraction procedure travels rapidly down the column. Other minor constituents follow. The progress of the matricin can be followed by irradiation with an unshielded ultraviolet lamp, for the fluorescent material mentioned previously is easily observed. As on TLC plates the matricin and the fluorescent compound overlap. By collecting the eluate immediately after the fluorescent band leaves the column, about 15 mg. of matricin can be obtained. The elution should be followed by TLC in order to ascertain that the matricin has been isolated.

The chromatography is a slow progress. Approximately five days are required for the lactone to travel the length of the column. However, the use of a siphon to refill the column continuously simplifies the procedure so that no supervision is needed for up to 20 hours at a time.

**Paper Chromatography.**--The plant extracts could not be analyzed by paper chromatography. No solvent system was found which could separate the numerous components efficiently. Also, visualization with sulfuric acid could not be achieved on paper. The solvent systems tried were the following:

1. 5 per cent sulfuric acid
2. 30 per cent acetic acid
3. 8:2 petroleum ether-toluene saturated with 8:2 methanol-water
8:2 petroleum ether-chloroform saturated with 8:2 methanol-water
ethyl acetate saturated with water
4:1:5 butanol-acetic acid-water
water saturated with ethyl acetate
water saturated with isoamyl acetate

The sprays used for visualization were the following:

one per cent potassium permanganate in one per cent sulfuric acid
Stahl spray: a five per cent solution of p-dimethylaminobenzaldehyde in a 1:1 mixture of glacial acetic acid and 85 per cent phosphoric acid (one part) plus water (four parts).
ferric hydroxamate: a mixture of equal volumes of 1 M hydroxylamine hydrochloride and 1 M potassium hydroxide both in methanol, followed by a one per cent solution of ferric chloride in 2.6 M hydrochloric acid.

Physical Measurements. -- The infrared and nuclear magnetic resonance spectra were determined in cavity cells and microcells, respectively. The more sensitive ultraviolet instrument required no special sample container. If a chloroform solution of matricin (say, from the IR determination) was treated with an equal volume of pentane and left overnight in the refrigerator, a small quantity of matricin, sufficient for a melting point, precipitated in non-crystalline form. The matricin used for the optical rotation determination was
dissolved directly off a TLC plate into chloroform. The solution was run in a one-cm. Cary cell along with an appropriate dextrose standard.
RESULTS AND DISCUSSION

The results of this investigation indicate that the principal chamazulenogenic lactone in *A. carruthii* is matricin (XLVII). Evidence for this conclusion is presented below.

At no time was the matricin isolated in pure condition. The compound was very easily oxidized or polymerized on standing and was most frequently obtained as a light brown gum. A small amount could be precipitated in solid form (see Experimental section), but even this was tan and non-crystalline. Similar difficulties had been experienced by other workers.\(^{32,38}\)

For these reasons no formula analysis was obtained. However, the melting point of 152-6\(^\circ\) (decomposition) was close to the literature\(^{32}\) value of 158-60\(^\circ\). The specific rotation, \([\alpha]_D^{30} -122^\circ\) (c = 0.074 in chloroform), also was in reasonable agreement with the literature\(^{32}\) value of \([\alpha]_D^{20} -131^\circ\) (c = 1.96 in chloroform).

Chromatographic Comparison.--An authentic sample of matricin, received from Dr. Z. Cekan,\(^*\) was a brown solid and contained two impurities. A paper chromatogram performed by Dr. Cekan showed identical R\(_f\) values for matricin and the principal lactone.

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\(^*\) to whom the author is greatly indebted.
from *A. carruthii* (R_f = 0.82 in isopropyl ether saturated with water; Stahl's reagent used for spray). Thin-layer chromatography in various solvent systems also suggested the identity of the two compounds. Table II-1 gives these results.

**TABLE II-1.**--Thin-layer Chromatogram of Matricin and the Principal *A. carruthii* Lactone

<table>
<thead>
<tr>
<th>Solvent</th>
<th>R_f of both Lactones</th>
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<tbody>
<tr>
<td>90:1 CHC_l_3-CH_3OH</td>
<td>0.22</td>
</tr>
<tr>
<td>45:1 CHC_l_3-CH_3OH</td>
<td>0.50</td>
</tr>
<tr>
<td>9:1 CHC_l_3-acetone</td>
<td>0.98</td>
</tr>
<tr>
<td>19:1 CHC_l_3-acetone</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**Spectral Comparison.**--The ultraviolet, infrared, and nuclear magnetic resonance spectra of the principal *A. carruthii* lactone were all superimposable on those of matricin. The UV spectrum (Fig. II-3) exhibited a maximum at 242 m (ε = 11,200). The IR spectrum (Fig. II-4) contained the expected bands at 3600 cm^{-1} (hydroxy), 1780 cm^{-1} (γ-lactone), and 1748 cm^{-1} (acetoxy).

**Confirmation of Sorm's Structure.**--The NMR spectrum (Fig. II-5) has not been reported previously and is in complete agreement with structure XLVII, which Sorm had deduced almost entirely by chemical means. These chemical experiments are outlined here in order to show that other structures were possible.
Fig. II-3. -- Ultraviolet Spectrum of Matricin in Ethanol (18.0 x 10^{-3} gram/liter)
Fig. II-4. --Infrared Spectrum of Matricin in Chloroform
Fig. II-5. -- Nuclear Magnetic Resonance Spectrum of Matricin in Deuteriochloroform
Preliminary work had established that matricin possesses two conjugated double bonds, hydroxy and acetoxy functions, and a γ-lactone ring. Conversion to chamazulene suggested the guaiane skeleton (II). The problem was to determine the positions of the functional groups.

That the lactone ring is closed to C-6 was demonstrated by formation of XLVIII (Fig. II-6) and subsequent aromatization to artemazulene (XXVIII). The position of the acetoxy group was shown by formation of XLIX and aromatization to both XXVIII and XXXI. The tertiary nature of the hydroxy group was shown by its resistance to oxidation. The hydrogenolysis on treatment of matricin with hydrogen and platinum in acetic acid suggested that the hydroxy group is allylic to a double bond. Finally, production of a non-conjugated ketoguaianolide from L proved that the hydroxy group is not at positions 7 or 11.

The case for placing the hydroxy function at C-4 consisted mainly of negative evidence, much of which was tenuous. Position 5 was eliminated because periodic acid failed to attack XLIX, but this result could have been a stereochemical consequence. Position 1 was considered unlikely because it was felt that both the original double bonds would then have to be in the cyclopentane ring, a situation which should lead to hydrogenolysis of the lactone hydroxyl (unobserved). However, structures such as LI and LII cannot be ruled out by this argument. Position 10 was also eliminated, for the authors believed that the formic acid dehydration (Fig. II-6) would yield a
Fig. II-6. -- Chemical Transformations of Matricin
ketoguaienolide with a conjugated carbonyl. If the dehydration occurred in the other direction, however, the resulting double bond (between C-1 and C-10) would not be in conjugation with the ketone. Finally, no attempt was made to eliminate the possibility of an exocyclic methylene group, which could rearrange to a methyl group during steam distillation.

Other structures which could fit the chemical data are LI-LV along with several others (e.g., LVI and LVII) with exocyclic methylene groups.
The NMR results rule out the above structures. Table II-2 lists the NMR peaks and their assignments. The presence of four methyl absorptions precludes an exocyclic methylene group. Two sets of vinyl peaks eliminate structures LI, LII, and LV, which have fewer than two vinyl protons. The triplet at $\delta = 4.12$ p.p.m., due to the proton on C-6, would be a doublet if formulas LIII or LIV were correct.

**TABLE II-2.---Nuclear Magnetic Resonance Spectrum of Matricin in CDCl$_3$**

<table>
<thead>
<tr>
<th>$\delta$(p.p.m.)$^a$</th>
<th>Multiplicity</th>
<th>Assignment</th>
<th>No. of Protons$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.36</td>
<td>2</td>
<td>C-13</td>
<td>6</td>
</tr>
<tr>
<td>1.43</td>
<td>1</td>
<td>C-14</td>
<td></td>
</tr>
<tr>
<td>1.90</td>
<td>1</td>
<td>C-15</td>
<td></td>
</tr>
<tr>
<td>2.14</td>
<td>1</td>
<td>OAc</td>
<td>11 or 12</td>
</tr>
<tr>
<td>2.0 - 3.3</td>
<td>-</td>
<td>C-5,7,9,11,-OH(?)</td>
<td></td>
</tr>
<tr>
<td>4.12</td>
<td>3</td>
<td>C-6</td>
<td>1</td>
</tr>
<tr>
<td>~4.9</td>
<td>-</td>
<td>C-8</td>
<td>1</td>
</tr>
<tr>
<td>5.94</td>
<td>2</td>
<td>C-3</td>
<td>1</td>
</tr>
<tr>
<td>6.33</td>
<td>2</td>
<td>C-2</td>
<td>1</td>
</tr>
</tbody>
</table>

$^a$Relative to tetramethylsilane.

$^b$Determined with a planimeter.

**Stereochemical Considerations.---**The stereoisomeric relationship between achillin and desacetoxymatricarin (LVIII) (see Table II-4)
shows that there are at least two series of compounds differing in configuration at carbons 5, 6, 7, or 11. Although the nature of the difference is not known, hydroxyachillin and acetoxyachillin have been correlated with achillin, while matricarin and desacetylmatricarin have been correlated with desacetoxymatricarin. Another compound, artilesin (Table II-4), may possess a third variation of the 5-6-7-11 area or may differ at C-8, which bears an acetoxy group. Stereoisomers such as the above are sometimes found in the same plant.

The absolute configuration at positions 5, 6, 7, and 11 has been deduced for artabsin (XXXIV) and arborescin (XVIII), which were correlated with isophotosantonin lactone acetate (XXXV) by chemical transformation. The relative configuration of globicin (XXXVIII) has been established by NMR and NMDR methods. In the case of globicin, H-6 appeared as a triplet in the NMR spectrum because of coupling to H-5 and H-7 with both J values equal to 10 c.p.s. Also, H-7 was coupled to H-11 with J = 11 c.p.s. In view of the Karplus relationships between coupling constant and dihedral angle, it
could be stated that the dihedral angles between protons at positions 5 and 6, 6 and 7, and 7 and 11 were either $0^\circ$ (cis and eclipsed) or $150-180^\circ$ (trans). Dreiding models indicated that an angle of $0^\circ$ was highly unlikely at any of the pertinent locations. Therefore, an all-trans relative stereochemistry was preferred for globicin. An all-trans arrangement was also found for artabsin and arborescin, and it is probable that the absolute configuration of all three lactones is the same at positions 5, 6, 7, and 11.

In the present investigation an attempt was made to deduce the relative configuration at positions 5, 6, 7, and 11 in matricin. The NMR spectrum (Fig. II-5) possessed a triplet at $\delta = 4.12$ p.p.m. due to H—6. The coupling constant of 10 c.p.s. suggested a trans-trans arrangement between protons on positions 5, 6, and 7 by analogy with globicin. In order to obtain the coupling constant between H—7 and H—11, however, it is necessary to eliminate the effect of the methyl group on C—11. The double resonance technique offers the best hope of solving the problem. Application of a second frequency at $\delta = 1.2-1.5$ p.p.m. (C—11 methyl group) might cause the appearance of a doublet in the 2.3-3.0 p.p.m. region (H—11 split only by H—7). The coupling constant of this doublet would then indicate the stereochemical relationship between H—7 and H—11. This experiment was not carried out due to lack of the necessary apparatus.
**Test for "True" Proazulenes.** It has already been mentioned that thin-layer chromatography of the pentane extract of *A. carruthii* demonstrated the presence of other "true" proazulenes in the plant. This type of compound could readily be identified by spraying the plate with concentrated sulfuric acid, which produced a blue or purple color. Arborescin, artabsin, globicin, and matricin all turned blue or purple after acid treatment, whereas 23 other sesquiterpene lactones, not "true" proazulenes, did not (Table II-3). Another technique used to identify proazulenes on a TLC plate consisted of spraying with 2 M sulfuric acid, placing the silica-coated glass face-up on a hot plate, and covering it with a piece of clean glass. A micro-scale steam distillation then occurred, causing a blue spot to appear at the site of the proazulene.

**TABLE II-3. Spot Reactions of Lactones with Sulfuric Acid**

<table>
<thead>
<tr>
<th>Blue or Purple</th>
<th>Colorless or Brown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arborescin</td>
<td>Arctiopicrin</td>
</tr>
<tr>
<td>Artabsin</td>
<td>Balchanolide</td>
</tr>
<tr>
<td>Globicin</td>
<td>Balduilin</td>
</tr>
<tr>
<td>Matricin</td>
<td>Coronopolin</td>
</tr>
<tr>
<td></td>
<td>Costunolide</td>
</tr>
<tr>
<td></td>
<td>Damsin</td>
</tr>
<tr>
<td></td>
<td>Dehydrocostus lactone</td>
</tr>
<tr>
<td></td>
<td>Flexuosin A</td>
</tr>
<tr>
<td></td>
<td>Helenalin</td>
</tr>
<tr>
<td></td>
<td>Hydroxybalchanolide</td>
</tr>
<tr>
<td></td>
<td>Hydroxyeremophilenolide</td>
</tr>
<tr>
<td></td>
<td>Isoalantolactone</td>
</tr>
<tr>
<td></td>
<td>Isobalchanolide</td>
</tr>
<tr>
<td></td>
<td>Isotenulin</td>
</tr>
<tr>
<td></td>
<td>Ivalin</td>
</tr>
<tr>
<td></td>
<td>Lactucin</td>
</tr>
<tr>
<td></td>
<td>Parthenin</td>
</tr>
<tr>
<td></td>
<td>Pinnatifidin</td>
</tr>
<tr>
<td></td>
<td>Pulchellin</td>
</tr>
<tr>
<td></td>
<td>Saussurea lactone</td>
</tr>
<tr>
<td></td>
<td>Telekin</td>
</tr>
<tr>
<td></td>
<td>Tenulin</td>
</tr>
<tr>
<td></td>
<td>Xanthinin</td>
</tr>
</tbody>
</table>
TAXONOMICAL CONSIDERATIONS

All the compounds in Table II-4 were isolated from the Compositae family, which is composed of about 13 tribes. The chemical differences between lactones from different tribes may be highly significant. For example, compounds 1-26 (Table II-4) are found in the Gaillardia and/or Helium genera of the Helenieae tribe; compounds 27-41 are found in the Artemisia and/or Matricaria and/or Achillea genera of the Anthemideae tribe. It is apparent that Helenieae compounds all possess skeleton LIX with a rearranged methyl group * and the lactone ring closed to C-8. In addition, there is rarely a functional group at C-10, whereas C-11 is usually unsaturated. No Helenieae lactone has both a functional group at C-10 and a saturated C-11.

* Mexicanin E and its dihydro derivative have lost this methyl group entirely.
On the other hand, all guaianolides from the Anthemideae tribe have skeleton LX with no rearranged methyl groups and the lactone ring closed to C-6. In all but one compound (arbiglovin) a functional group is present at C-10. Only two compounds (arbiglovin and estafiatin) are unsaturated at C-11.

Thus, the guaianolides appear to have much potential value in chemotaxonomy. To be sure, only a few genera of the Helenieae and Anthemideae tribes have been examined for sesquiterpene lactones, and the generalizations to the whole tribes may prove unwarranted. Nevertheless, biogenetic relationships such as the above may be of use to the botanist in classifying Compositae plants or to the chemist in determining structural formulas.
### Table II-4: Sesquiterpene Lactones of the Guaianolide Type

<table>
<thead>
<tr>
<th>NAME</th>
<th>STRUCTURE</th>
<th>M. P.</th>
<th>$[\alpha]_D^b$</th>
<th>GENERA</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenulin</td>
<td><img src="image1" alt="Structure" /></td>
<td>196-8°</td>
<td>$-22E$</td>
<td>Helenium, Leptopoda</td>
<td>6</td>
</tr>
<tr>
<td>Isohelenalin</td>
<td><img src="image2" alt="Structure" /></td>
<td>257-9</td>
<td>$+43C$</td>
<td>Helenium</td>
<td>40</td>
</tr>
<tr>
<td>Mexicanin A</td>
<td><img src="image3" alt="Structure" /></td>
<td>138-9</td>
<td>$-27C$</td>
<td>Helenium</td>
<td>7</td>
</tr>
<tr>
<td>Mexicanin C</td>
<td><img src="image4" alt="Structure" /></td>
<td>251-2</td>
<td>$-80C$</td>
<td>Helenium</td>
<td>39</td>
</tr>
<tr>
<td>Mexicanin I</td>
<td><img src="image5" alt="Structure" /></td>
<td>257-9</td>
<td>$+43C$</td>
<td>Helenium</td>
<td>40</td>
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<tr>
<td>NAME</td>
<td>STRUCTURE</td>
<td>M. P.</td>
<td>[α]_{D}</td>
<td>GENERA</td>
<td>REF.</td>
</tr>
<tr>
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<td>--------------------</td>
<td>-------</td>
<td>---------</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Mexicanin D</td>
<td><img src="image" alt="structure" /></td>
<td>225-6°</td>
<td>+107C</td>
<td>Helenium</td>
<td>7</td>
</tr>
<tr>
<td>Mexicanin E</td>
<td><img src="image" alt="structure" /></td>
<td>100-1</td>
<td>-47C</td>
<td>Helenium</td>
<td>18</td>
</tr>
<tr>
<td>Dihydro-mexicanin E</td>
<td><img src="image" alt="structure" /></td>
<td>133-5</td>
<td>-188C</td>
<td>Helenium</td>
<td>57</td>
</tr>
<tr>
<td>Linifolin A^c</td>
<td><img src="image" alt="structure" /></td>
<td>195-8</td>
<td>+30C</td>
<td>Helenium</td>
<td>41</td>
</tr>
<tr>
<td>Balduilin</td>
<td><img src="image" alt="structure" /></td>
<td>231-2</td>
<td>+57C</td>
<td>Balduina</td>
<td>7</td>
</tr>
<tr>
<td>Linifolin B</td>
<td><img src="image" alt="structure" /></td>
<td>149</td>
<td>-</td>
<td>Helenium</td>
<td>41</td>
</tr>
<tr>
<td>Amarilin</td>
<td><img src="image" alt="structure" /></td>
<td>195-8</td>
<td>+5C</td>
<td>Helenium</td>
<td>43</td>
</tr>
<tr>
<td>NAME</td>
<td>STRUCTURE</td>
<td>M. P.</td>
<td>$[\alpha]_D$</td>
<td>GENERA</td>
<td>REF.</td>
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<tr>
<td>Aromatin$^c$</td>
<td><img src="image1" alt="Structure" /></td>
<td>159°</td>
<td>-6C</td>
<td>Helenium</td>
<td>44</td>
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<tr>
<td>Aromaticin</td>
<td><img src="image2" alt="Structure" /></td>
<td>232-4</td>
<td>+18C</td>
<td>Helenium</td>
<td>44</td>
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<tr>
<td>Flexuosin A</td>
<td><img src="image3" alt="Structure" /></td>
<td>220-2</td>
<td>+12C</td>
<td>Helenium</td>
<td>47</td>
</tr>
<tr>
<td>Flexuosin B</td>
<td><img src="image4" alt="Structure" /></td>
<td>110-</td>
<td>+44C</td>
<td>Helenium</td>
<td>47</td>
</tr>
<tr>
<td>Thurberilin</td>
<td><img src="image5" alt="Structure" /></td>
<td>162</td>
<td>+20C</td>
<td>Helenium</td>
<td>58</td>
</tr>
<tr>
<td>Pulchellin</td>
<td><img src="image6" alt="Structure" /></td>
<td>165-8</td>
<td>-36C</td>
<td>Gaillardia</td>
<td>13</td>
</tr>
<tr>
<td>Pulchellin B</td>
<td><img src="image7" alt="Structure" /></td>
<td>215-8</td>
<td>+93E</td>
<td>Gaillardia</td>
<td>46</td>
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</table>
### TABLE II-4. --Continued

<table>
<thead>
<tr>
<th>NAME</th>
<th>STRUCTURE</th>
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<th>[α]D</th>
<th>GENERA</th>
<th>REF.</th>
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<tr>
<td>Pulchellin C</td>
<td><img src="image1" alt="Structure" /></td>
<td>199-202°</td>
<td>+125E</td>
<td>Gaillardia</td>
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<tr>
<td>Pulchellin E</td>
<td><img src="image2" alt="Structure" /></td>
<td>181-3</td>
<td>+44E</td>
<td>Gaillardia</td>
<td>58</td>
</tr>
<tr>
<td>Gaillardilin</td>
<td><img src="image3" alt="Structure" /></td>
<td>197</td>
<td>-2C</td>
<td>Gaillardia</td>
<td>58</td>
</tr>
<tr>
<td>Spathulin</td>
<td><img src="image4" alt="Structure" /></td>
<td>var.</td>
<td>+17E</td>
<td>Gaillardia</td>
<td>58</td>
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<tr>
<td>Fastigilin A</td>
<td><img src="image5" alt="Structure" /></td>
<td>176-7</td>
<td>-81C</td>
<td>Gaillardia</td>
<td>58</td>
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<td>Fastigilin B</td>
<td><img src="image6" alt="Structure" /></td>
<td>254-6</td>
<td>-97C</td>
<td>Gaillardia</td>
<td>58</td>
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<td>Fastigilin C</td>
<td><img src="image7" alt="Structure" /></td>
<td>196-8</td>
<td>-86C</td>
<td>Gaillardia</td>
<td>58</td>
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TABLE II-4. --Continued

<table>
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<th>NAME</th>
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<th>M. P.</th>
<th>[α]&lt;sup&gt;b&lt;/sup&gt;</th>
<th>GENERA</th>
<th>REF.</th>
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<td>Matricin</td>
<td><img src="image1" alt="Structure" /></td>
<td>158-160°</td>
<td>-131C</td>
<td>Matricaria Artemisia</td>
<td>29</td>
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<tr>
<td>Artabsin</td>
<td><img src="image2" alt="Structure" /></td>
<td>129-132</td>
<td>-49C</td>
<td>Artemisia</td>
<td>19</td>
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<tr>
<td>Arborescin</td>
<td><img src="image3" alt="Structure" /></td>
<td>145</td>
<td>+63C</td>
<td>Matricaria Artemisia</td>
<td>9</td>
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<tr>
<td>Globicin</td>
<td><img src="image4" alt="Structure" /></td>
<td>148-150</td>
<td>+66C</td>
<td>Matricaria</td>
<td>23</td>
</tr>
<tr>
<td>Absinthin</td>
<td><img src="image5" alt="Structure" /></td>
<td>182-3</td>
<td>+180C</td>
<td>Artemisia</td>
<td>28</td>
</tr>
<tr>
<td>Anabsinthin</td>
<td><img src="image6" alt="Structure" /></td>
<td>210</td>
<td>+111M</td>
<td>Artemisia</td>
<td>28</td>
</tr>
<tr>
<td>NAME</td>
<td>STRUCTURE</td>
<td>M. P. [α] D</td>
<td>GENERA</td>
<td>REF.</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Estafiatin</td>
<td><img src="image" alt="Structure" /></td>
<td>104-6° -10C</td>
<td>Artemisia</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Matricarinc</td>
<td><img src="image" alt="Structure" /></td>
<td>190-1 +24C</td>
<td>Matricaria&lt;br&gt;Achillea</td>
<td>49</td>
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<tr>
<td>Acetoxy-achillin</td>
<td><img src="image" alt="Structure" /></td>
<td>193-4 +116C</td>
<td>Achillea</td>
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<tr>
<td>Artilesin</td>
<td><img src="image" alt="Structure" /></td>
<td>- -</td>
<td>Artemisia</td>
<td>49</td>
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<tr>
<td>Desacetylmaticarinc</td>
<td><img src="image" alt="Structure" /></td>
<td>123-5 -</td>
<td>Artemisia&lt;br&gt;Achillea</td>
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<tr>
<td>Hydroxy-achillin</td>
<td><img src="image" alt="Structure" /></td>
<td>161-2 +110M</td>
<td>Achillea</td>
<td>16</td>
<td></td>
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<tr>
<td>Desacetoxy-maticarinc</td>
<td><img src="image" alt="Structure" /></td>
<td>202-3 +55X</td>
<td>Artemisia</td>
<td>56</td>
<td></td>
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<tr>
<td>(Leukodin)</td>
<td><img src="image" alt="Structure" /></td>
<td>144-5 +160C</td>
<td>Achillea</td>
<td>16</td>
<td></td>
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<tr>
<td>Achillin</td>
<td><img src="image" alt="Structure" /></td>
<td>201-3 +190C</td>
<td>Artemisia</td>
<td>58</td>
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<tr>
<td>Parthenin</td>
<td><img src="image" alt="Structure" /></td>
<td>163-6 +7C</td>
<td>Parthenium</td>
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<tr>
<td>NAME</td>
<td>STRUCTURE</td>
<td>M. P.</td>
<td>$[\alpha]^b$</td>
<td>GENERA</td>
<td>REF.</td>
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<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Ambrosin</td>
<td><img src="image1" alt="Structure" /></td>
<td>145-6° -15C</td>
<td>Parthenium</td>
<td>Ambrosia 12</td>
<td></td>
</tr>
<tr>
<td>Coronopolin$^c$</td>
<td><img src="image2" alt="Structure" /></td>
<td>177-8 -30E</td>
<td>Parthenium</td>
<td>Ambrosia 15</td>
<td></td>
</tr>
<tr>
<td>Damsin</td>
<td><img src="image3" alt="Structure" /></td>
<td>111 -72C</td>
<td>Ambrosia 45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geigerinin</td>
<td><img src="image4" alt="Structure" /></td>
<td>202-3 -11E</td>
<td>Geigeria 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geigerin</td>
<td><img src="image5" alt="Structure" /></td>
<td>192 -64C</td>
<td>Geigeria 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudo-ivalin</td>
<td><img src="image6" alt="Structure" /></td>
<td>122-3 -145C</td>
<td>Iva</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Dihydro-pseudo-ivalin</td>
<td><img src="image7" alt="Structure" /></td>
<td>oil -</td>
<td>Iva</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>
TABLE II-4. --Continued

<table>
<thead>
<tr>
<th>NAME</th>
<th>STRUCTURE(^a)</th>
<th>M.P.</th>
<th>([\alpha]_D)(^b)</th>
<th>GENERA</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cynaropicrin</td>
<td><img src="image" alt="structure" /></td>
<td>glass</td>
<td>-</td>
<td>Cynara</td>
<td>51</td>
</tr>
<tr>
<td>Lactucin</td>
<td><img src="image" alt="structure" /></td>
<td>213-7</td>
<td>+49M</td>
<td>Lactuca</td>
<td>52</td>
</tr>
<tr>
<td>Carpesia lactone</td>
<td><img src="image" alt="structure" /></td>
<td>liq.</td>
<td>-</td>
<td>Carpesium</td>
<td>54</td>
</tr>
<tr>
<td>Dehydrocostus lactone</td>
<td><img src="image" alt="structure" /></td>
<td>63-4</td>
<td>-14E</td>
<td>Saussurea</td>
<td>55</td>
</tr>
</tbody>
</table>

[FOOTNOTES FOR TABLE]

a) \(R_1 = \text{COCH}=\text{C(CH}_3\text{)}_2; \quad R_2 = \text{COC(CH}_3\text{)}=\text{CH-CH}_3; \quad R_3 = \text{COC(CH}_2\text{OH)}=\text{CH}_2.\)

b) Specific rotations were determined at 20-30\(^\circ\)C. The solvent code is:
   - C = chloroform,
   - E = ethanol,
   - M = methanol,
   - X = not given.

c) These compounds are stereoisomers.
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Part I

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Part II


29. Z. Čekan, V. Herout, and F. Šorm, Chem. and Ind., 1234 (1956).


58. W. Herz, personal communication.
