

year and a half of use they showed no loss in efficiency or sensitivity to AMPA or GLYPH. The extremely acidic mobile phase required for elution would not be compatible with the chemically bonded silica column packings which are prone to dissolution at such pH conditions. Reagent and HPLC pump maintenance over this period was limited to periodic flushings with deionized water to dissolve small amounts of crystalline deposits. Columns and pumps were stored for short periods (1 week) containing the mobile phase. Water was used for storage at longer periods.

Registry No. GLYPH, 1071-83-6; AMPA, 1066-51-9.

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Distribution of Lacinilene C and Lacinilene C 7-Methyl Ether in Cotton Plant Parts

Linda L. Muller, Jacqueline M. Simoneaux, Ralph J. Berni, and James H. Wall*

Lacinilene C (LC) and lacinilene C 7-methyl ether (LCME) were removed from nine cotton plant parts by exhaustive ether Soxhlet extraction and quantitated by high-performance liquid chromatography (HPLC). LCME was observed in extracts of all plant parts examined in quantities ranging from 92 $\mu\text{g/g}$ in the seed extract to 1159 $\mu\text{g/g}$ in the leaf extract. Values for LC contents varied from 23 $\mu\text{g/g}$ in the pedicel extract to 736 $\mu\text{g/g}$ in the leaf extract. LC, however, was not detected in the ether extracts of root or seed.

Stipanovic et al. (1975c) isolated lacinilene C (LC) and its 7-methyl ether (LCME) from *Gossypium hirsutum* L. bracts and revised the structure (Figure 1). Interest in LCME stems from its implication as a possible etiological agent of byssinosis, a clinical syndrome associated with inhalation of respirable dust generated during cotton processing in textile mills. Bioassays commonly used in studies of other lung diseases have been performed to ascertain the biological activity of LC and LCME. The naphthalenone, LCME, isolated from aqueous extracts of cotton dust, bracts, and stems, was identified by Stipanovic and Wakelyn (1975) as the yellow-fluorescing chemotaxin of the slow type (Lynn et al., 1974; Jeffs and Lynn, 1975; Kilburn et al., 1977; Ainsworth and Neuman, 1977; Northup et al., 1976; Ziprin and Greenblatt, 1979; Greenblatt and Ziprin, 1979a) which produced a proliferation of polymorphonuclear (PMN) leukocyte migration into airway lumen in vivo and in vitro (Kilburn et al., 1973; Lynn et al., 1974), inhibited luminol-dependent chemiluminescence of phagocytosing alveolar macrophages (Greenblatt and Ziprin, 1979b), and caused histamine release in sensitized rat mast cells (Ainsworth and Neuman, 1977; Northup et al., 1976). Lacinilene C has also been identified as an inhibitor of chemiluminescence of alveolar macrophages (Ziprin and Greenblatt, 1979; Greenblatt and Ziprin, 1979a). It has been postulated that the chemical

activity of both synthetic and natural LCME is cytokinetic rather than chemotactic toward leukocytes (Jeffs and Lynn, 1978). Other investigators found that synthetic LCME was both chemotactic and cytotoxic, but the cytotoxic effect predominates (Kilburn et al., 1979, 1981).

The functions of LC and LCME in the biosystem of the cotton plant is unknown. Kilburn et al. (1977, 1981) have speculated that LCME is a glycoside naturally occurring in cotton dust and bracts. Kilburn et al. (1979) also postulated that LCME appears to be an oxidation product and therefore related to senescence. He based this on reports of LCME in cotton dust and dried bracts but observed its absence in fresh green bract. However, LCME has been shown recently to be a natural product in fresh and dried green bracts (Stipanovic et al., 1981; Beier and Greenblatt, 1981). Other researchers (Essenberg et al., 1980) have indicated that the biosynthesis of LC and its recently identified precursor, 2,7-dihydroxycadalene (Stipanovic et al., 1981; Beier and Greenblatt, 1981), was induced in the cotton plant by infection and that the latter compound is a potent bactericide. Jeffs and Lynn (1975) speculated that the increased incidence of LCME in aged bracts and its absence from fresh plant material may also be linked to presence of contaminating microorganisms. It is well documented that other sesquiterpenoids such as hemigossypolone (Bell and Stipanovic, 1976), hemigossypol and 6-methoxyhemigossypol (Mace, 1976; Stipanovic et al., 1975a,b; Mace et al., 1974), hemigossypolone 7-methyl ether and the heliocides H₁, H₂, H₃, H₄, B₁, B₂, B₃, and B₄ (Stipanovic et al., 1977a,b, 1978; Bell et al., 1978), and the

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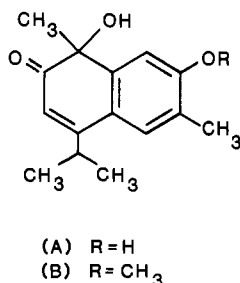


Figure 1. Structure of (A) lacinilene C and (B) lacinilene C 7-methyl ether.

triterpenoid gossypol (Veech, 1976) are toxic to the *Heliothis* spp. and act as fungotoxins to the *Verticillium* spp. These terpenoid compounds belong to a group of natural products produced by plants for defense which are subdivided into constitutive antibiotic systems and phytoalexins, the antibiotics synthesized in response to stress, injury, physiological stimuli, and the presence of infectious agents or products of such agents (Kuč, 1972; Bell, 1981).

Morey (1977) suggests that pharmacological agents can be expected to vary in content depending upon the physiological state of the plant part at the time of collection. The objective of the work presented here was to study the distribution of LC and LCME in ether extracts of cotton plant parts, thereby furnishing additional information as to their possible role in the biosystem of the cotton plant and their relationship to byssinosis.

EXPERIMENTAL SECTION

DES-056 (glanded) cotton plants in full growth were hand-harvested during the second gathering of cotton plants in field no. 6 at the U.S. Cotton Ginning Laboratory facilities in Stoneville, MS, in Oct 1979.

The plants were stored in ambient air in the laboratory for 2 weeks to ensure complete drying. This is comparable to conditions used in research studies. The individual cotton plant parts were removed by hand and stored in labeled containers until they could be ground with a Wiley mill through a 20-mesh screen by using dry ice to eliminate heat generated by the shearing action of the Wiley mill.

Ether Extractions. Diethyl ether was selected as the extraction solvent because of the solubility of LC and LCME, its low boiling point, and the fact that enzyme activity and oxidation and hydrolysis reactions might be minimized. Exhaustive diethyl ether Soxhlet extractions were carried out on 0.6–5.0 g cotton plant part samples depending on sample availability. Each sample was folded in Whatman filter paper to prevent loss of fine particulates and placed in an ether-washed, single-thickness paper extraction thimble and exhaustively extracted with diethyl ether in the dark to avoid photodegradation (Muller et al., 1981b; Wall et al., 1980b). Extraction time varied depending on the sample type and size; estimated extraction was two to five cycles per 30 min. Factors affecting the ether-soluble extraction time are the number and rate of Soxhlet extractor cycles and the density of material packed in the thimble. Extraction progress was monitored by thin-layer chromatography (TLC) of an aliquot of solvent taken before respiponing into the boiling flask. The TLC solvent was 80:19:1 chloroform–acetone–formic acid and detection was accomplished with fluorescence on exposure to long wave UV light. The extracts were concentrated on a Büchi Roto-Vap to a known volume and stored under nitrogen at -4°C until high-performance liquid chromatographic (HPLC) analyses could be performed.

Standards. Isolation of pure LC and LCME standards by preparative and TLC of an extract of cotton gin trash

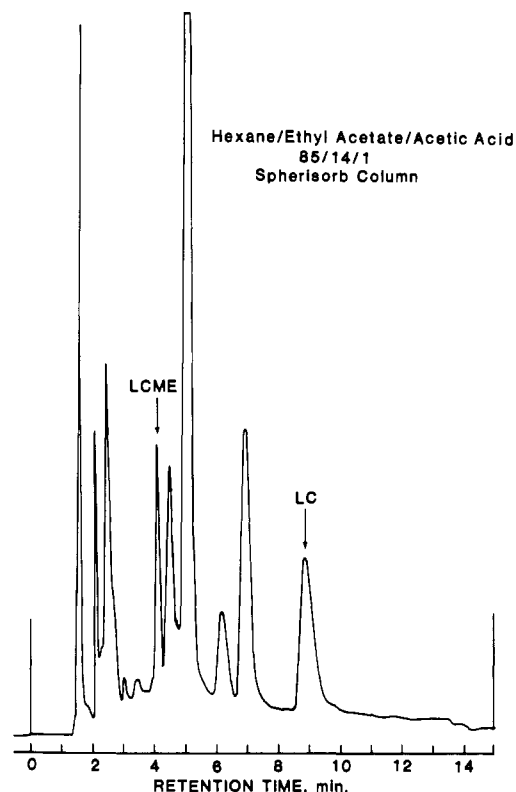


Figure 2. HPLC chromatogram of the separation of LC and LCME in the ether extract of cotton bract.

was similar to that previously reported for LCME (Wall et al., 1980a,b).

HPLC Analyses. Waters Associates liquid chromatography grade solvents were used for all HPLC analyses. The HPLC system consisted of a Waters Model 204 liquid chromatograph equipped with a U6K septumless injector, a Model 6000-A pump, and an Alltech spherisorb column packed with $5\ \mu\text{m}$ of activated silica. The separations were performed by using isocratic elutions with 85:14:1 hexane–ethylacetate–acetic acid. Operating pressures ranged from 300 to 400 psi. The spherisorb column was purged regularly along the recommended lines of a general silica column cleanup procedure (Waters Associates, 1976) to reduce pressure buildup due to contamination of the column. Separation was effected at a flow rate of 1.0 mL/min and recorded at a chart speed of 1 cm/min throughout the analyses. Sample injection size varied from 15 to 300 μL depending upon the particular plant part extract to be examined, with 20 μL the most frequently used quantity. LC and LCME were monitored at 340 nm with a Waters Model 440 fixed UV absorption detector and quantitated by integration of peak area with a Hewlett-Packard lab-data acquisition system, Series 3350. Figure 2 represents a typical HPLC chromatogram of the separation of LC and LCME in the ether extract of cotton plant parts analyzed in this study.

The peaks identified as LC and LCME in the HPLC chromatogram were collected and analyzed by two-dimensional TLC. Both appeared as a single yellow fluorescent compound with chloroform–acetone–formic acid (80:19:1) used as the first solvent system and benzene–methanol (90:10) used as the second on Mallinckrodt silica G-60 plates when viewed under long wave UV light. No other compounds were apparent when the plate was exposed to short wave UV light, iodine vapors, or sulfuric acid spray.

Gram-Negative Bacteria/Endotoxin Analyses. Analyses for Gram-negative bacterial counts and Limulus

Table I. Lacinilene C and Lacinilene C 7-Methyl Ether Contents in DES-056 Cotton Plant Parts^a

plant part	LC		LCME	
	$\mu\text{g/g}$	% distribution	$\mu\text{g/g}$	% distribution
bract	371	23.5	599	16.2
leaf	736	46.7	1159	31.4
pedicel	23	1.5	278	7.5
pericarp	147	9.3	329	8.9
petiole	126	8.0	254	6.9
root	ND ^b		253	6.9
seed ^c	ND		92	2.5
sepal	101	6.4	530	14.4
stem	73	4.6	195	5.3
total	1577	100.0	3689	100.0

^a Mean based on four determinations. ^b Not detected. ^c Delintiered.

amebocyte lysate analysis for endotoxin levels for correlation with LC and LCME contents were performed under contract by Dr. Janet J. Fischer of the School of Medicine, University of North Carolina at Chapel Hill, according to her protocols.

RESULTS AND DISCUSSION

Table I shows the content and percent distribution of LC and LCME in cotton plant parts. The data indicate LCME is found in significant quantities throughout the cotton plant parts examined. Lacinilene C, however, is found in only certain plant parts; it was not detected in the root or seed. The largest levels of LCME were found in leaves (1159 $\mu\text{g/g}$), bracts (599 $\mu\text{g/g}$), and sepals (530 $\mu\text{g/g}$). These plant parts are extremely friable and have been reported as the major portion of the plant debris in cotton (Morey et al., 1976a,b; Morey and Raymer, 1978). LC was also most abundant in leaves (736 $\mu\text{g/g}$) and bracts (371 $\mu\text{g/g}$). The LC content in sepals was somewhat lower (101 $\mu\text{g/g}$) by comparison. It is interesting to note that the level of LC in pedicels is 23 $\mu\text{g/g}$, whereas in the petiole, the LC content is 126 $\mu\text{g/g}$. The LCME contents, however, are comparable—278 $\mu\text{g/g}$ in pedicels and 254 $\mu\text{g/g}$ in petioles. Lacinilene C and LCME contents for cottonseed (not detectable and 92 $\mu\text{g/g}$, respectively) correlate closely with results of HPLC analysis of a Sweetwater high-volume sampler cottonseed oil mill dust (Muller et al., 1981a). Those values of 77 $\mu\text{g/g}$ LCME and no detectable LC suggest that the vegetative matter present in the cottonseed oil mill dust is predominantly from the seed.

A correlation between LC, LCME, and microorganism contamination has been suggested (Essenberg et al., 1980; Jeffs and Lynn, 1975). Gram-negative bacteria and endotoxin values for the individual plant parts are given in Table II. The Gram-negative bacterial counts for the bract (888 cfu/mg), pedicel (519 cfu/mg), sepal (253 cfu/mg), and pericarp (90 cfu/mg) indicate that bacterial contamination is concentrated in an area associated with the cotton boll. The low value of Gram-negative bacteria (38 cfu/mg) for the leaf does not correlate with the large amount of LC and LCME present. The level of endotoxin in bract and pedicel was 25 ng of LPS/mg, while only 0.3 ng of LPS/mg was found in the leaf. Linear regression analyses of the data show no correlation between either LC or LCME contents and Gram-negative bacteria or endotoxin levels in the plant parts of this particular study.

A preliminary TLC investigation (Muller, 1981) of ether extracts of fresh green and air-dried green bract hand-picked at anthesis from Deltapine 61 cotton grown at SRRRC indicates the presence of LC and LCME. This

Table II. Gram-Negative Bacteria and Endotoxin Levels in DES-056 Cotton Plant Parts

plant part	Gram-negative bacteria, cfu/mg ^a	endotoxin, ng of LPS/mg ^b
bract	888.0	25.0
leaf	38.0	0.3
pedicel	519.0	25.0
pericarp	90.0	2.5
petiole	5.0	2.5
root	1.3	2.5
seed ^c	6.4	0.2
sepal	253.0	2.5
stem	2.5	2.5

^a Colony-forming units. ^b Lipopolysaccharide. ^c Delintiered.

finding is further supported by Stipanovic et al. (1981), who found the lacinilenes in young and mature green bract in six commercial cultivars, and Beier and Greenblatt (1981), who found LC, LCME, and their precursors in dried green bracts. Disparities exist among present findings and previous reports that LC and LCME were not found in leaf, stem, or root tissue and that LCME was only found in field-dried bracts or cotton dust (Stipanovic and Wakelyn, 1975; Jeffs and Lynn, 1975, 1978). Several factors could contribute to these differences. The solvent used to extract LC and LCME plays an important role and could account for some of the differences in concentration of LC and LCME reported in the literature (Stipanovic et al., 1981; Beier and Greenblatt, 1981; Gilbert et al., 1980). Muller et al. (1981b) compared the LCME content in cotton leaves by extraction with diethyl ether, acetonitrile, and water and found that water was the least effective solvent for quantitative removal of LCME (67 $\mu\text{g/g}$ as compared to 1159 and 1311 $\mu\text{g/g}$). Stipanovic et al. (1981) used 30% aqueous methanol to extract LC, LCME, and their respective cadalene precursors from green and field-dried cotton bracts. The earlier methods of extraction of LCME commonly used were water extractions followed by ether or chloroform partitions. Varietal differences should also be considered as well as physiological age.

Stipanovic et al. (1981) also reports *Verticillium* wilt-diseased tissue as well as healthy tissue contained the lacinilenes. He further suggests the lacinilenes are formed enzymatically in situ and by autoxidation in dried tissue and during extraction and purification. Bell and co-workers (Bell and Stipanovic, 1976; Bell, 1980) postulates that light mediates the chemical defense system by inducing synthesis of unique enzymes and mediates and redirects terpenoid biosynthesis in certain tissue. These possibilities could account for only approximately 15% of the amount of LC and LCME reported in this investigation. We have found acetonitrile will extract approximately 85% of the exhaustive ether extraction value but with only 15 min from sample grinding to HPLC injection (Muller et al. 1981b).

The biological functions of LC and LCME are unknown. The work presented in this investigation provides valuable quantitative information on the distribution of LC and LCME in the cotton plant. Whether LC and LCME are phytoalexins or related to senescence is a question to be answered by additional investigations concerning ontogenetic changes and defense mechanisms of cotton plants.

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Registry No. LC, 41653-72-9; LCME, 56362-72-2.

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Tissue Residue Regulatory Method for the Determination of Lasalocid Sodium in Cattle Liver Using High-Performance Liquid Chromatography with Fluorometric Detection

George Weiss,* Nancy R. Felicito, Maurice Kaykaty, Gloria Chen, Ann Caruso, Edythe Hargroves, Connie Crowley, and Alex MacDonald

A method has been developed for the assay of lasalocid sodium in cattle liver at the 25-ppb level. Ten grams of liver tissue was extracted with acetonitrile, which was then washed with hexane, and an aliquot was blown down to dryness with nitrogen. The residue was brought up in an aliquot of water saturated with the mobile phase, which was then extracted with the mobile phase. This extract was analyzed by HPLC using two 25-cm Whatman Partisil 10 columns in series using a basic mobile phase. Detection was by fluorescence (excitation at 310 nm, emission at 430 nm). Peak heights were used for quantitation.

Lasalocid, or antibiotic X-537A (Figure 1), is a carboxylic acid ionophore. Its discovery (Berger et al., 1951) and

structure and chemistry (Westley et al., 1970, 1973; Johnson et al., 1970) have been described. The ability of ionophores to mitigate the transport of mono- and divalent ions across lipid membranes has aroused considerable interest and has led to the discovery of interesting biological activities. It has also led to attempts by synthetic chemists

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