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NEUTRAL DITERPENOIDS OF *HELIANTHUS ANNUUS*[1]

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ABSTRACT.—The saponified extract of the ligule flowers of *Helianthus annuus* afforded the two esters of *ent*-kaur-16-en-19-oic and *ent*-trachyloban-19-oic acids with thujanol (**1** and **2**). The following diterpenoids were also identified: *ent*-kaur-16-en-19-al, *ent*-trachyloban-19-al, *ent*-kauran-16β-ol, *ent*-kauran-16α-ol, *ent*-kauran-16β,19-diol, *ent*-atisan-16α-ol, and *ent*-atisan-16β-ol. Loliolide acetate (**3**) was isolated from an acetylated portion of the same extract as well as from the extract of flowers of *Calendula officinalis*.

In the course of the investigation of pentacyclic triterpenoids present in the ray flowers of *Helianthus annuus* L. and *Calendula officinalis* L. (Compositae) (2), several neutral diterpenoids were isolated and identified in the saponified extract of the first plant. Compounds described in this communication are present as minor diterpenoids accompanying *ent*-kaur-16-en-19-oic and *ent*-trachyloban-19-oic acids, isolated previously from the same species (3). These newly identified compounds complement the long list of diterpenoids recently detected in other *Helianthus* species (4-6, and references therein).

Diterpenoid acids isolated from sunflower exhibit antimicrobial (7) and insecticidal (5,8) properties. *Gibberella* transforms *ent*-trachyloban-19-oic acid into cyclogibberellins (9,10) which, if formed by the soil flora, may contribute to the known alleopathic property of the sunflower plant (11).

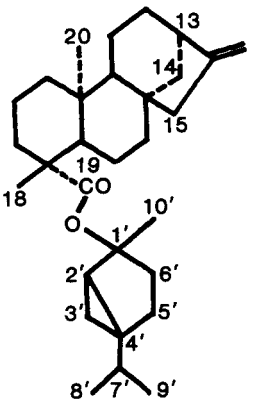
RESULTS AND DISCUSSION

A silica gel column separation of the least polar fraction of the saponified extract followed by preparative separation on silica gel-$AgNO_3$ afforded two isomeric compounds with the apparent composition of a triterpenoid diketone $C_{30}H_{46}O_2$ (ν max 1715 cm^{-1}). Mass spectral analysis, however, revealed the presence of a monoterpenoid alcohol moiety (abundant fragment ions at *m/z* 136, 121, 93, and 91, characteristic for bicyclic monoterpenoids) esterified with two different diterpenoid acids. The fragment ion at *m/z* 302 ($C_{20}H_{30}O_2$), and subsequent eliminations were analogous to those observed for *ent*-kaur-16-ene-19-oic and *ent*-trachyloban-19-oic acids. Moreover, both ir as well as pmr spectra were in accord with the presence of these diterpenoid fragments and pointed to the structures **1** and **2**.

The exact correspondence of carbon chemical shifts with those of *ent*-trachyloban-19-oic and *ent*-kaur-16-en-19-oic acid methyl esters (12,13) was observed (Table 1). Ten additional signals, identical for both compounds, were assigned to the thujanol fragment based on comparison with the published data for this monoterpene alcohol (14) corrected by the predictable acylation shifts. The proton spectra showed the same set of the methyl and cyclopropyl proton signals fully corroborating the presence of this monoterpenoid moiety. The absolute configuration of the monoterpenoid fragment remains to be established.

Esters **1** and **2** are very stable toward alkaline hydrolysis. This stability is typical for esters of axial carboxylic acids. On the other hand, LAH reduction produced *ent*-kaur-16-en-19-ol and *ent*-trachyloban-19-ol from both esters in addition to identical C_{10} products, which were detected by capillary gc.

[1]Part 12 in the series: "Terpenes of Compositae Plants"; for part 11, see Pyrek (1). Results presented in part at the 23rd Annual Symposium of Phytochemical Society of North America, Tucson, AZ, 1983.



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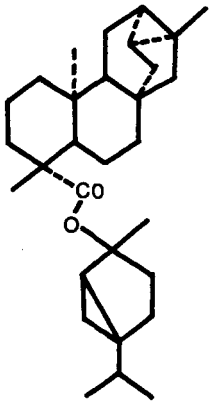

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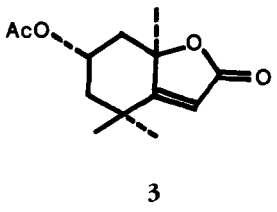

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Compounds **1** and **2** represent the rare example of a naturally occurring ester composed of two different terpenoid moieties. Esters composed of two diterpenoids were recently isolated from *Helianthus radula* (Pursh) T. & G. (6).

The least polar fraction of the saponified extract also afforded two aldehydes identified as *ent*-kaur-16-en-19-al and *ent*-trachyloban-19-al by reduction to the corresponding primary alcohols.

Mono-, di- and tri-hydroxylated fractions of the extract are primarily composed of pentacyclic triterpenoids and the separation of minor diterpenoid constituents was relatively difficult. The set of four isomeric tertiary alcohols, *ent*-kauran-16β-ol and *ent*-kauran-16α-ol, *ent*-atisan-16α-ol (major tertiary alcohol), and *ent*-atisan-16β-ol (trace component), was isolated from the monohydroxylated fraction either by taking advantage of their resistance toward oxidation or the relative volatility. These alcohols were purified by hplc and efficiently analysed by capillary gc and gc-ms. Only *ent*-kauran-16β-ol has been isolated from *Helianthus* species (4,6) but the presence of other isomers has been suspected (4). The search by gc-ms demonstrated the widespread occurrence of all four compounds in the *Helianthus* genus (15). Their thorough spectral identification and correlation, performed for substances isolated from *H. annuus*, is reported in this paper.

Dehydration with either $SOCl_2$ or Ac_2O in pyridine afforded the corresponding hydrocarbons. The yield of the acetylation versus dehydration is distinctly different for each epimer and may serve as a diagnostic reaction. The two epimeric *ent*-atisan-16-ols were mentioned as products of the skeletal rearrangement and were only partially characterized (16,17). Their unambiguous differentiation was obtained by the comparison of $Eu(fod)_3$ effect on the pmr spectrum. Four and five signals were shifted downfield for *ent*-atisan-16α-ol and *ent*-atisan-16β-ol, respectively. The diagnostic difference was in the relative magnitude of the induced shift of 15-methylene protons. The signal of *ent*-15α-H was easily identified based on the additional long-range coupling with *ent*-14β-H [prochirality (18): H_S-14]. This *ent*-15α-H signal had a higher magnitude of the induced shift in the case of the major *ent*-atisanol, thus assigned as *ent*-16α-ol, and lower in the case of the minor isomer *ent*-atisan-16β-ol.

Another known diterpene was isolated from the acetylated polar fractions as a monoacetate. It was dehydrated to acetates of *ent*-kaur-15-en-19-ol and *ent*-kaur-16-en-19-ol. The comparison of europium-induced shifts with those of the two 16-epimeric *ent*-kauranols, behavior of the corresponding diol upon acetylation, and cmr data (Table 1) confirmed its structure as *ent*-kauran-16β,19-diol.

The separation of the acetylated polar fraction afforded loliolide acetate (**3**). The

TABLE 1. ^{13}C-Chemical Shifts of Diterpenoids Isolated from *Helianthus annuus* ($CDCl_3$)

C-	*ent*-kauran-16α-ol	*ent*-kauran-16β-ol	*ent*-kauran-16β,19-diol 19-mono-acetate	*ent*-atisan-16α-ol	**1**	methyl *ent*-kaur-16-en-19-oate	**2**	methyl *ent*-trachyloban-19-oate	thujanol[a]
1	38.96	37.88	37.44	39.83	41.12	40.89	39.63	39.5	
2	18.81	18.76	18.03	18.91	19.33	19.25	19.00	18.8	
3	42.37	42.27	36.42	42.42	38.45	38.21	39.95	38.1	
4	33.39	33.50	37.05	33.15	44.38	43.89	44.30	43.7	
5	56.47	56.47	56.76	56.61	57.19	57.20	57.19	57.0	
6	20.22	20.61	20.57	18.32	22.13	22.02	22.06	21.8	
7	40.66	40.61	42.32	38.18	41.64	41.43	38.52	39.3	
8	44.61	45.50	45.25	33.98	55.30	55.24	52.96	52.7	
9	57.49	57.15	57.05	51.44	55.30	55.24	52.96	52.7	
10	39.59	39.60	39.20	37.83	39.80	39.51	39.00	38.6	
11	19.10	18.13	18.13	24.22	18.48	18.48	17.78	19.7	
12	26.91	27.05	27.76	39.59	33.19	33.19	24.73	24.2	
13	47.25	49.30	48.95	23.39	43.98	43.89	20.56	20.5	
14	42.37	42.27	42.32	27.57	39.82	39.75	33.25	33.1	
15	58.08	58.47	57.93	58.08	49.19	49.07	50.62	50.4	
16	77.69	79.35	79.05	72.03	155.55	155.56	22.50	22.4	
17	32.52	24.52	24.37	30.52	102.99	103.05	20.76	20.5	
18	33.69	33.69	27.44	33.49	29.12	28.78	29.15	28.7	
19	21.74	21.69	67.10	21.78	177.00	177.86	177.00	177.8	
20	17.74	17.88	18.13	14.03	16.47	15.48	13.35	12.3	
1′					88.09		88.10		80.6
2′					31.62		31.69		34.4
3′					12.10		12.10		13.3
4′					33.80		33.50		34.7
5′					24.66		24.47		26.0
6′					34.35		34.42		36.7
7′					32.53		32.54		32.2
8′					19.65		19.65		20.0
9′					19.52		19.52		20.1
10′					24.66		24.73		25.0
Me(Ac)			20.81						
CO(Ac)			171.3						

[a]Data from Bohlmann *et al.* (14).

same substance was also isolated from the saponified extract of the ray flowers of *C. officinalis*.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were measured using hot microscope stage and are uncorrected. Optical rotations were measured using JASCO DIP-4 digital polarimeter with $CHCl_3$ solutions in a microcell. Capillary gc analyses were performed using Hewlett-Packard model 5880 A instrument and 22 m SE-54 column, 0.25 mm i.d., temperature program 100° to 250°, 4°/min, 70 KPa N_2). Retention is given as methylene unit (MU) calculated by coinjection of C_{10}-C_{30} *n*-hydrocarbons. For the capillary gc-ms the column was introduced directly to the ion source of a Finnigan 3200 instrument. Tlc separation of monohydroxylated diterpenoids was performed using silica gel plates developed twice in C_6H_6-EtOAc (98:2); preparative and analytical hplc separations were performed using 5μ silica gel column, 4.6 mm × 15 cm, hexane-EtOAc (16:1) as solvent and refractive index detector. The pmr and cmr spectra were obtained using a JEOL instruments at 90, 100, and 270 MHz; TMS signal was used as internal standard, and chemical shifts are recorded in δ ppm units.

ISOLATION AND SEPARATION OF DITERPENOIDS.—Flowers of *H. annuus* L. are available as a commercial product of Herbapol, Poland [see Pyrek (1,19)]. The extraction of sunflower ray flowers, saponification, and silica gel column chromatographic separation of the neutral fraction was described before (1,19). The fraction eluted before monohydroxylated compounds was submitted to molecular distillation at 50-90°, 10^{-3} torr. Volatile (3.5 g) and nonvolatile parts (5.3 g) were obtained.

SEPARATION OF THUJANOL ESTERS OF DITERPENOID ACIDS.—The nonvolatile part of the nonpolar fraction was separated on alumina activity III and silica gel-$AgNO_3$ columns to give esters **1** (53 mg) and **2** (78 mg); tlc, C_6H_6-hexane (1:1), silica gel: Rf 0.57 and 0.60 respectively, silica gel-$AgNO_3$: Rf 0.40 and 0.90, respectively.

THUJANOL ESTER OF *ENT*-KAUR-16-EN-19-OIC ACID (**1**).—Compound **1** had mp 128-131°; ir, ν max (film) 3050, 1715, 1655, 880 cm^{-1}; eims (probe, 70 eV) *m/z* 438 (19, M^+, $C_{30}H_{46}O_2$, measured: 438.3486, calcd.: 438.3498), 423 (7), 302 (7, $C_{20}H_{30}O_2$, measured 302.2240, calcd.: 302.2246), 287 (7), 257 (36), 241 (10), 136 (98, $C_{10}H_{16}$, measured: 136.1249, calcd.: 136.1252), 121 (45), 105 (31), 93 (100), 91 (52), 81 (98); M* for: 302↦259, 302↦287, 246↦231, 231↦213, 136↦93, 121↦93, and 93↦91; pmr (100 MHz, CCl_4) 4.74 and 4.67 (two bs, 16-H_2), 2.59 (bs, 13-H), 1.47 (s, 10′-Me), 1.11 (s, 18-Me), 0.91 (s, 20-Me), 0.94 and 0.89 (two d, J=6 Hz, 8′-Me and g′-Me), 0.25-0.75 (ABC m, 2′-H and 3′-H_2); (270 MHz, $CDCl_3$, assignments as above): 4.80 (bs), 4.75 (bs), 2.65 (bs), 2.14 (bd, J=13.5 Hz, 15-H), 1.52 (s), 1.18 (s), 0.97 (s), 0.96 (d), 0.91 (d), 0.61 (dd, J=5 and 3 Hz), 0.42 (dd, J=5 and 8 Hz).

Found: C, 81.87; H, 10.31. $C_{30}H_{46}O_2$ requires: C, 82.14; H, 10.57%.

The LAH reduction of ester **1** (dioxane, 90°, 20 h) produced three major products as shown by capillary gc (MU): 10.40 (7%), 10.58 (44%), 10.94 (1%), and 23.39 (48%, identical by gc-ms with *ent*-kaur-16-en-19-ol). The *ent*-kaur-16-en-19-ol purified by preparative tlc (C_6H_6-EtOAc, 95:5) was identical with the authentic substance, mp and mmp 140-143°.

THUJANOL ESTER OF *ENT*-TRACHYLOBAN-19-OIC ACID (**2**).—Compound **2** had mp 132-135°; ir ν max (film) 1715 cm^{-1}; eims (probe, 70 eV) *m/z* 438 (29, M^+), 423 (9), 302 (33), 287 (15), 257 (27), 246 (21, M-136-56, characteristic for trachylobane derivatives), 231 (11), 136 (79), 121 (42), 105 (35), 93 (100), 91 (47), 81 (60); M* for 302↦287, 136↦93, and 93↦91. Pmr (270 MHz, $CDCl_3$) 1.51 (s, 10′-Me), 1.14 (s, 18-Me), 0.94 and 0.91 (two d, J=6 Hz, 8′-Me and 9′-Me), 0.93 (s, 20-Me), 0.82 (dd partially overlaped) 0.59 (dd, J=5 and 3 Hz) and 0.40 (dd, J=8 and 5 Hz, 2′-H and 3′-H_2).

The ester **2** was reduced with LAH in THF at 60° for 20 h to give four major products according to capillary gc (MU): 10.40 (34%), 10.58 (13%), 10.94 (9%), and 22.90 (42%, identical by gc-ms with *ent*-trachyloban-19-ol). The *ent*-trachyloban-19-ol purified by preparative tlc (as before) was identical with the authentic substance, mp and mmp 126-129°.

ENT-KAUR-16-EN-19-AL.—This compound was obtained either by the direct column chromatography of the nonpolar fraction on silica gel column and alumina activity III or by the separation of the volatile part (more-polar aldehyde, 0.5 g) mp 87-100°. It was identified based on ir and nmr and reduced (with $NaBH_4$ in EtOH) to *ent*-kaur-16-en-19-ol, mp 144-146°. [α]D −64.5°; lit. (3) mp 143-144.5°, [α]D −78°, identical by ir comparison with authentic material.

ENT-TRACHYLOBAN-19-AL.—This less-polar aldehyde was obtained from the same fraction as an oil, 0.5 g; identical with authentic material by ir and nmr comparison. It was reduced with $NaBH_4$ in EtOH to *ent*-trachyloban-19-ol, mp 125-130°, [α]D −42.0°, lit. (3) mp 130-131°, [α]D −38.0°, identical with authentic material by ir comparison.

SEPARATION OF HYDROXYLATED DITERPENOIDS.—The monohydroxylated fraction (13 g) obtained from the saponified extract separated on silica gel column was oxidized with Jones' reagent in Me_2CO. The mixture of four unchanged diterpenoid tertiary alcohols (0.9 g) was separated from less-polar 3-oxo-triterpenoids on silica gel column. The following four components were purified by repeated column and hplc chromatography.

ENT-KAURAN-16β-OL.—This compound had the following chromatographic characteristics: Rf: 0.30, Rv: 11.5 ml; MU: 22.32; mp 216-218°. $[\alpha]_D$ −48.5°; lit. (20) mp 214-216°, $[\alpha]_D$ −45°; pmr (100 MHz, $CDCl_3$) 0.81, 0.85, 1.03, and 1.36 four Me singlets; Eu(fod)$_3$ induced shifts (relative to 17-Me, 100): H-13 (112), *ent*-H-14β (44), *ent*-H-14α (98), *ent*-H-15β (112), *ent*-H-15α (62), 20-Me (5), 18-Me and 19-Me (5 and 17); cmr in Table 1; eims (probe, 15 eV) *m/z* (rel. int.) 290 (M^+) (23), 275 (21), 272 (82), 257 (66), 232 (100, M-CH_2=C(OH)CH_3), 217 (26), 123 (87), 94 (57). Acetylation of this monoalcohol (pyridine-Ac_2O 1:1, 57°, 3 h) produced no diacetate (<0.2%) and *ent*-kaur-15-ene (9.2%) and *ent*-kaur-16-ene (4.7%). The dehydration (pyridine-$SOCl_2$) of this alcohol produced the mixture of *ent*-kaurenes in addition to chlorinated diterpenoids (capillary gc-ms). The *ent*-kaur-15-ene and *ent*-kaur-16-ene were separated by preparative tlc on $AgNO_3$-silica gel and compared with authentic substances. The same alcohol (mp and mmp 218-220°, identical by tlc and gc-ms) was obtained from *ent*-kaur-16-ene as the sole product of the standard reaction of oxymercuration-demercuration [Hg(OAc)$_2$ in THF, followed by $NaBH_4$-NaOH].

ENT-KAURAN-16α-OL.—This compound had the following chromatographic characteristics: Rf: 0.47; Rv: 7.5 ml; MU: 22.22; mp 146-147.5°, $[\alpha]_D$ −57.7°; lit. (21) mp 151-152°; pmr (100 MHz, $CDCl_3$) 0.81, 0.86, 1.03, and 1.31 four Me singlets; Eu(fod)$_3$ induced shifts (as before): *ent*-9α (30), *ent*-11α (90), 13-H (90), *ent*-14β (31), *ent*-14α (58), *ent*-15β (90), *ent*-15α (103), 20-Me (10), 18-Me and 19-Me (2 and 18); cmr in Table 1; eims (probe, 15 eV) *m/z* (rel. int.) 290 (M^+) (17), 275 (30), 272 (100), 257 (50), 232 (55), 217 (27), 123 (86), 94 (57). It was dehydrated to the same set of products separated and identified as in the case of previous compound. Acetylation (conditions as before) produced 13.3% of acetate with no dehydration.

ENT-ATISAN-16α-OL.—This compound was the major component of the fraction and had the following chromatographic characteristics: Rf: 0.42; Rv: 8.8 ml; MU: 22.15; mp 132-143° (from Me_2CO) mp 102-104° (from EtOH-H_2O), $[\alpha]_D$ −40.0°; lit. (16) mp 108°; pmr (100 MHz, $CDCl_3$) 0.83, 0.86, 0.94, and 1.27 four Me singlets; Eu(fod)$_3$ induced shifts (as before): *ent*-11α (90), 12-H (112), *ent*-H-15β (66), *ent*-H-15α (92), 20-Me (11), 18-Me and 19-Me (4 and 19); cmr in Table 1; eims (probe, 15 eV) *m/z* (rel. int.) 290 (M^+) (1), 275 (5), 272 (34), 257 (100), 244 (5), 232 (6). Acetylation (conditions as before) occurred at very low yield (1.6%) with limited dehydration to *ent*-atis-15-ene (0.5%) and *ent*-atis-16-ene (0.8%). These hydrocarbons obtained by dehydration (pyridine-$SOCl_2$, accompanied by two chlorinated atisanes identified by capillary gc-ms) were separated by preparative tlc, $AgNO_3$-silica gel: *ent*-atis-15-ene, mp 80-81°, $[\alpha]_D$ −79.0°; lit. (22) mp 84-85°, $[\alpha]_D$ −74°; pmr (100 MHz, CCl_4): 5.52 (bs, 15-H), 2.23 (b, 12-H), 1.73 (d, J=1 Hz, 17-Me), 0.94, 0.86, and 0.82 three Me singlets; cmr in Table 1; eims (probe, 15 eV) *m/z* (rel. int.) 272 (M^+) (30), 257 (60), 244 (100), 229 (20). *Ent*-atis-16-ene, $[\alpha]_D$ negative, (c <0.05); pmr (90 MHz, CCl_4) 4.48 (q, J=2 Hz, 17-H), 4.65 (q, J=2, H-17), 2.18 (br, H-12), 0.95, 0.85, and 0.82 three Me singlets. The above tertiary alcohol was identical (hplc, capillary gc-ms) with one of the two products of the oxymercuration—demercuration of *ent*-atis-16-ene.

ENT-ATISAN-16β-OL.—This compound was the minor component of the monoalcohol fraction and had the following chromatographic charactertistics: Rf: 0.30; Rv: 10.7 ml; MU: 22.10; mp 175°, lit. (17) mp 174-176°. This alcohol was identical by hplc and capillary gc-ms comparison with the second product of the mercuration-demercuration of *ent*-atis-16-ene. Pmr (270 MHz, $CDCl_3$) 0.788, 0.816, 0.922, and 1.252 four Me singlets, 1.82 (tt, J=11.4 and 3.1 Hz, *ent*-H-14β (?)), 1.99 (tq, J=13.2 and 3.2 Hz *ent*-H-13α); eims (gc-ms, 22 eV) *m/z* (rel. int.) 290 (M^+) (5), 275 (37), 272 (18), 257 (78), 232 (100, M-CH_2=C(OH)CH_3), 217 (25). Acetylation (conditions as before) occurred at the low yield (1.6%) with extensive dehydration to *ent*-atis-15-ene (7.4%) and *ent*-atis-16-ene (11%).

19-MONOACETATE OF *ENT*-KAURAN-16β,19-DIOL.—This compound was isolated by the additional chromatography of the acetylated (pyridine, Ac_2O) polar fraction from the first separation of the whole saponified extract on silica gel column. Pmr (100 MHz, $CDCl_3$) 4.30 and 3.95 (d and bd 19-H_2, J=11.3 Hz), 2.07 (s, Ac), 1.37 (s, 17-Me), 1.07 (s, 18-Me), 0.95 (s, 20-Me); Eu(fod)$_3$ induced shifts: H-13 (111), *ent*-H-14β (49), *ent*-H-14α (100), *ent*-H-15β (111), *ent*-H-15α (64), 20-Me (28), 18-Me (31), 19-H_2 (70) Me (Ac) (66); cmr in Table 1; eims (probe, 15 eV) *m/z* (rel. int.) 348 (M^+) (6), 330 (60), 315 (12), 290 (20, M-CH_2=C(OH)CH_3), 288 (15), 275 (22), 270 (17), 257 (65), 242 (10), 230 (15), 43 (100). It was hydrolyzed to *ent*-kauran-16β,19-diol, mp 202-204°, $[\alpha]_D$ −38.2°; lit. (23) mp 200-201°, $[\alpha]_D$ −43°; eims (probe, 20 eV) *m/z* (rel. int.) 306 (M^+) (2), (308 when dissolved in MeOD), 288 (18), 275 (100), 248 (9), 243 (7), 229 (7), 217 (16). The above monoacetate was dehydrated with pyridine/$SOCl_2$ to acetates of *ent*-

kaur-15-en-19-ol and *ent*-kaur-16-en-19-ol separated by preparative tlc on silica gel-$AgNO_3$ and directly compared with authentic substances by ir and ms. Acetylation (conditions as for monoalcohols) of the diol did not produce diacetate and extensive dehydration was observed by capillary gc.

LOLIOLIDE ACETATE (**3**).—This compound was isolated from the acetylated polar fraction, mp 86-87.5°. The identical acetate was obtained from the acetylated polar fraction obtained from the saponified extract of *C. officinalis* [preparation of this extract was described before (1)]. Its identification was based on $[\alpha]_D$, ir, uv, nmr, and ms spectra identical with those reported (24, 25).

Found: C, 66.63, H, 7.70. $C_{13}H_{18}O_4$ requires: C, 66.54, H, 7.62%.

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