Constituents of *Chrysothamnus paniculatus* (Compositae): Chrysothame, a New Diterpene, and 6-Oxogrindelic Acid

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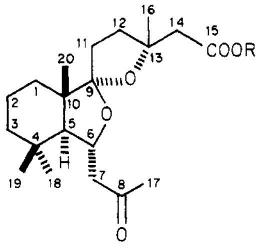
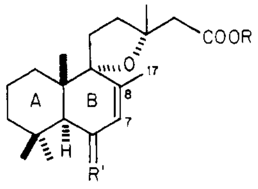
An ether extract of *Chrysothamnus paniculatus* (Compositae) gave, upon further fractionation, two crystalline diterpenes, chrysothame (1) and 6-oxogrindelic acid (2). The identity of chrysothame (1), which is new, is deduced from spectroscopic evidence and by chemical transformation to its methyl ester (1a). NMR and mass spectral data are given for 2 for the first time.

Chrysothamnus nauseosus, rabbit-brush, was investigated during the early 1900s as a source of rubber. This plant is currently being investigated as a source of rubber, resin, and oil.[1] It has been shown to contain insecticidal polyacetylenes[2] and various labdane diterpenes.[3,4] Other *Chrysothamnus* species have received very little attention, although *C. parryi* has been reported to contain polyacetylenes.[5]

As a result of screening plants of the Southwest as sources of renewable energy,[6] *C. paniculatus* (Gray) Hall, family Compositae, tribe Astereae, was selected for additional chemical evaluation. Hall and Clements (1923)[7] place it in the section Punctati. It occurs in the Mohave and Sonoran desert area from southwestern Utah and southern Nevada to western Arizona and southeastern California. The plant is a shrub growing to a height of over 2 m, found along roadside and in dry desert washes. The material used in this study (McLaughlin and Bowers 2550) was collected in southern Nevada, 16 miles west of Searchlight, on 22 October 1980. We report herein the isolation and identification of a new diterpene acid, chrysothame (1), as well as 6-oxogrindelic acid (2), from this source.



1, R = H
1a, R = Me



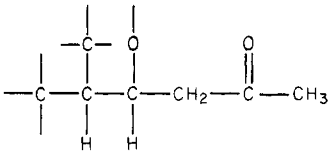
2, R = H; R' = O
2a, R = Me; R' = O
3, R = H; R' = H_2

Table I. ^{13}C NMR Chemical Shifts (δ, $CDCl_3$) for Chrysothame (1), Chrysothame Methyl Ester (1a), 6-Oxogrindelic Acid (2), and Methyl 6-Oxogrindelate (2a)

atom	1	1a	2	2a
C-1	35.8	36.2	38.9	38.4
C-2	19.3	19.4	18.1	18.1
C-3	41.8	42.0	43.0	43.0
C-4	32.6	32.7	32.6	32.5
C-5	57.7	57.2	56.6	56.4
C-6	74.1	73.5	200.1	200.2
C-7	47.3	48.1	154.3	154.9[a]
C-8	208.6	208.1	130.0	129.5[a]
C-9	118.3	117.6	90.6	89.8
C-10	46.8	46.5	45.6	45.4
C-11	30.8	30.8	28.5	28.6
C-12	31.4	31.2	32.9	32.8[a]
C-13	81.8	81.4	82.5	82.6
C-14	52.3	52.5	47.6	47.7
C-15	171.9	171.6	174.2	171.3
C-16	26.5	26.0	28.9	27.6
C-17	30.4	30.4	21.7	21.6
C-18	34.2	34.3	33.7	33.6[a]
C-19	22.3	22.2	20.9	20.9
C-20	17.9	18.1	19.8	19.8
OMe		51.3		

[a] Misassigned in ref 8; they did not have an off-resonance spectrum.

Chrysothame, $C_{20}H_{32}O_5$ by high-resolution mass spectroscopy, was formulated as 1 on the basis of spectroscopy. The IR spectrum of 1 contained bands typical of carboxyl, *gem*-dimethyl, and aliphatic ketone groups. The ^{1}H NMR spectrum showed five methyl singlets (δ 0.93, 1.00, 1.02, 1.22, 2.23; the last is α to a carbonyl group) and a methylene singlet (δ 2.68). Irradiation of a downfield methinyl proton [δ 4.35 (ddd, J = 10.7, 6.3, 5.5 Hz); next to oxygen] caused a methylene multiplet at δ 2.73 to collapse to an AB quartet (J = 15.8 Hz) and a methinyl doublet at δ 1.74 (J = 10.7 Hz) to collapse to a singlet. This, and loss of the elements of acetone from $M^{+\cdot}$ in the mass spectrum, led to the following structural fragment:



$$-\underset{|}{\overset{|}{C}}-\underset{\underset{H}{|}}{\overset{\overset{|}{-C-}}{C}}-\underset{\underset{H}{|}}{\overset{\overset{|}{O}}{C}}-CH_2-\overset{\overset{O}{\|}}{C}-CH_3$$

^{13}C NMR (Table I) proved informative. Comparison with the spectrum of 6-oxogrindelic acid (2), which occurs in the same plant, showed similarities at C-13 and differences at C-9. The C-13 singlet in 2 absorbs at δ 82.5 and in 1 at δ 81.8, suggesting retention of this portion. However, the C-9 singlet in 2 is at δ 90.6, whereas the C-9 singlet in 1 is at δ 118.3, requiring another adjacent oxygen. This leads to the bicyclic ether structure 1 as depicted. The stereochemistry at C-5, C-10, and C-13 in 1 is assumed

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(1) Ostley, W. *Biomass Digest* **1981**, *3*, 4.
(2) Rose, A. F.; Butt, B. A.; Jermy, T. *Phytochemistry* **1980**, *19*, 563.
(3) Bohlmann, F.; Dutta, L.; Robinson, H.; King, R. M. *Phytochemistry* **1979**, *18*, 1889.
(4) Rose, A. F. *Phytochemistry* **1980**, *19*, 2689.
(5) Bohlmann, F.; Zdero, L.; Robinson, H.; King, R. M. *Phytochemistry* **1979**, *18*, 1519.
(6) McLaughlin, S. P.; Hoffmann, J. J. *J. Econ. Botany* **1982**, in press.
(7) Hall, H. M.; Clements, F. E. *Carnegie Inst. Washington Publ.* **1923**, *No. 326*, 157-234.

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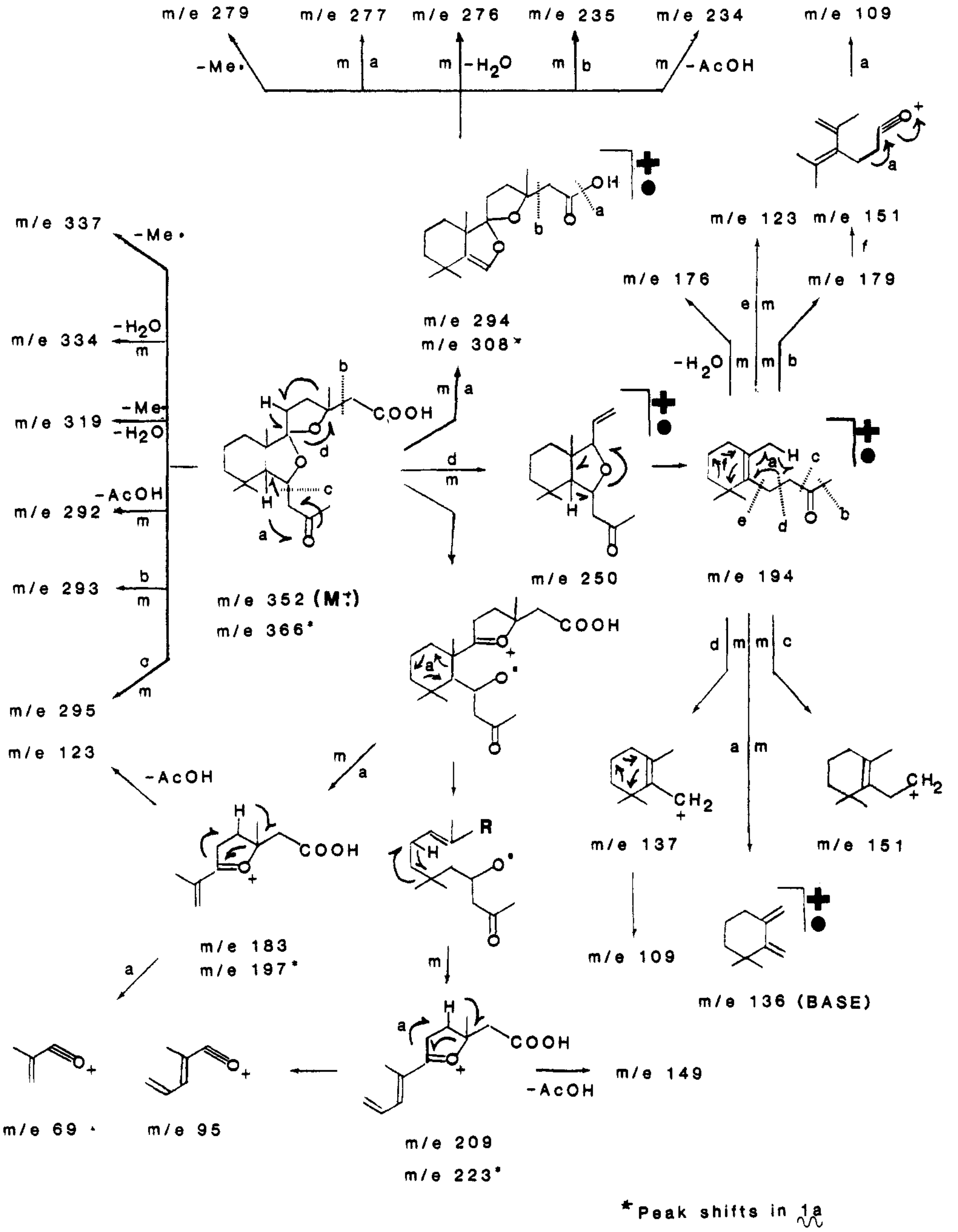
Scheme I. Major Fragment Ions in the Mass Spectrum of Chrysothame (1)



*Peak shifts in 1a

to be the same as in 2. The configuration at C-6 is clearly as shown from the large magnitude of $J_{5,6}$ (10.7 Hz). The configuration at C-9 is presumably as shown since the ^{13}C NMR shifts of 1 and its methyl ester (1a) differ appreciably at C-6 and C-7, indicating these carbons can closely approach the COOR group.

^1H–^1H decoupling experiments showed the remaining proton absorptions to consist of four strongly coupled protons at δ 1.7–2.3 (C-11, C-12 methylenes) and six strongly coupled protons at δ 1.0–1.7 (C-1, C-2, and C-3 methylenes).

The mass spectrum of chrysothame (1; Scheme I) provided supporting evidence for this structure. The fragmentations shown were verified by high-resolution exact-mass measurements and, where indicated by m, were substantiated by metastable peak study. The spectrum of 1 differs considerably from that of 2. The retro Diels–Alder rearrangement in 2 and grindelic acid (3)[9] leading to the base peaks at *m/e* 210 and 196, respectively, was not observed in 1. The base peak at *m/e* 136 in 1 shows the A ring to be unoxidized as in 2 and 3. An intense peak at *m/e* 294 (63%) corresponding to the loss of acetone from $M^{+\cdot}$ via McLafferty rearrangement strongly supported structure 1.

A possible biogenetic route to 1 and 2 from grindelic acid (3), the major constituent of this plant, via 6β-hydroxygrindelic acid (4, found in a plant of the same family[8]) is shown in Scheme II.

Experimental Section

See ref. 10 for a description of the analytical procedures used.

Isolation of Chrysothame (1) and 6-Oxogrindelic Acid (2). Dried *C. paniculatus* was ground in a Wiley mill and stored at −10 °C prior to extraction. The ground material (575 g) was suspended in ether at room temperature for 60 h and filtered, and the filtrate was vacuum dried. The resulting ether-soluble

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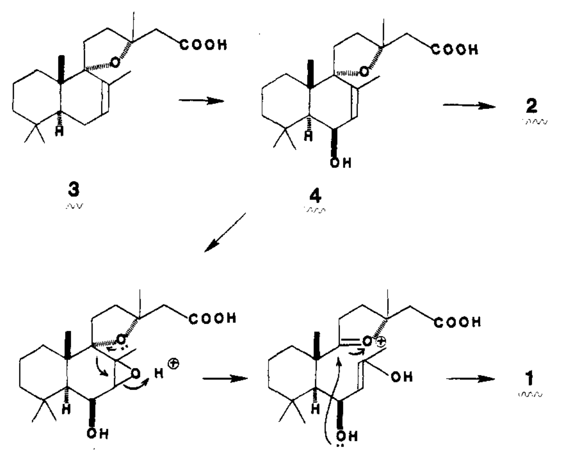
[8] Rose, A. F.; Jones, K. C.; Haddon, W. F.; Dreyer, D. L. *Phytochemistry* **1981**, *20*, 2249.

[9] Bruun, T.; Jackman, L. M.; Stenhagen, E. *Acta Chem. Scand.* **1962**, *16*, 1675.

Scheme II. Biosynthesis of 1 and 2 from Grindelic Acid (3)



residue (45 g) was extracted with isopropyl ether by being stirred mechanically at room temperature for 1 h and was left in the freezer overnight and filtered, and the filtrate was vacuum dried. The resulting isopropyl ether soluble syrup was partitioned between petroleum ether and 20% aqueous MeOH, and the lower aqueous MeOH phase (27 g), after drying under vacuum, was subjected to EM SiO_2 60 (900 g) column chromatography. The column was eluted with methylene chloride followed by methylene chloride containing gradually increasing amounts of MeOH, and several 1 L fractions were collected. Fractions 2–4 showed essentially a single spot, corresponding to grindelic acid (**3**), which was separated by preparative TLC (3.7% of dry plant); its identity was established by mass spectrometry.

Fraction 6 (2.17 g), which displayed two major spots on TLC, was subjected to preparative TLC (PF-254 SiO_2 60), using hexane/ether/AcOH (40:10:1) as the developing solvent system. Evaporation of the solvent from the fraction containing the higher R_f spot gave an oily residue (0.76 g), which on treatment with isopropyl ether gave colorless crystals of 6-oxogrindelic acid (**2**, 0.6% of dry plant). The fraction containing the lower R_f spot (0.37 g), after removal of the solvent under vacuum, was resubmitted to preparative TLC (PF-254 SiO_2 60) to remove impurities, using hexane/ether/AcOH (40:10:1.2) as the developing solvent. Crystallization from benzene/petroleum ether gave colorless crystals of chrysothame (**1**, 0.4% of dry plant).

Chrysothame (1). This compound had the following: mp 108–109 °C; $[\alpha]^{25}{}_D$ −16.6° (*c* 1.76, $CHCl_3$); IR (KBr) 3000–2500, 1710 (br), 1425, 1375, 1250, 1090, 1070, 1015, 910 cm^{-1}; ^1H NMR (described in the text); ^{13}C NMR (Table I); mass spectrum, *m/e* 352 ($M^{+}\cdot$, 12.3), 337 (2.1), 334 (2.1), 319 (1.3), 295 (14.8), 294 (63.1), 279 (10.8), 277 (6.1), 276 (12.2), 266 (9.2), 251 (9.7), 250 (6.6), 235 (15.9), 210 (11.5), 209 (72.8), 196 (21), 195 (9), 194 (54.7), 183 (62.9), 179 (24.4), 177 (11.3), 176 (30.7), 165 (14.4), 161 (34.8), 159 (25.2), 151 (50.1), 141 (36.4), 137 (36.5), 136 (100), 135 (13.5), 133 (18.1), 125 (23.5), 124 (25.4), 123 (41.3), 109 (73.7), 95 (86.5), 81 (63.8), 78 (64.1), 69 (89.1), 55 (47.5). The IR, ^1H NMR, ^{13}C NMR, and mass spectra were in accord with structure **1**.

Anal. Calcd for $C_{20}H_{32}O_5$: mol wt, 352.2250. Found: mol wt, 352.2245 (high-resolution mass spectroscopy).

Chrysothame Methyl Ester (1a). Esterification of 1 (50 mg) with diazomethane yielded **1a** as an oil, which was purified by preparative TLC. No attempt was made to crystallize the sample, whch was homogeneous as judged from TLC. **1a**: IR ($CHCl_3$) 1730, 1715, 1230 cm^{-1}; ^1H NMR (similar to 1 except COOH absorption at δ 5.6 (br s) replaced by COOMe singlet at δ 3.64); ^{13}C NMR (Table I); mass spectrum, *m/e* 366 ($M^{+}\cdot$, 10.9), 351 (2.3), 348 (1.4), 335 (6.5), 308 (43.6), 293 (18.7), 290 (13.9), 280 (10.1), 265 (7.9), 250 (4.8), 235 (23.9), 223 (63.7), 210 (24.8), 197 (49.9), 194 (45.3), 179 (20), 176 (24.9), 173 (20), 165 (12.1), 161 (23.6), 155 (32.1), 151 (33.7), 141 (8.9), 137 (22.7), 136 (60.7), 135 (10.3), 125 (13.6), 124 (14.5), 123 (25), 122 (14.3), 121 (20.3), 109 (41.4), 107 (16), 95 (42.5), 81 (29.3), 69 (41), 55 (28.6), 43 (100), 41 (52.9). The IR, ^1H NMR, ^{13}C NMR, and mass spectra were in accord with structure **1a**.

6-Oxogrindelic Acid (2). This compound had the following: mp 208–210 °C (lit.[11] mp 208–210 °C); $[\alpha]^{25}{}_D$ −83.1° (*c* 2.43, $CHCl_3$); IR ($CHCl_3$) 3000–2500, 1713, 1668, 1410, 1385, 1378, 1238, 1168, 1138, 1090, 1015, 980, (25), cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.67 (1 H, m), 2.73, 2.57 (2 H, q, $J_{AB} = 14.7$ Hz), 2.69 (1 H, s), 1.9–2.3 (4 H, m), 1.98 (3 H, d, $J = 1.1$ Hz), 1.0–1.9 (6 H, m), 1.45 (3 H, s), 1.17 (3 H, s), 1.11 (3 H, s); ^{13}C NMR (Table I); mass spectrum, *m/e* 334 ($M^{+}\cdot$, 6.5), 319 (2.4), 306 (3.6), 291 (1.2), 263 (2.0), 234 (2.4), 219 (2.1), 210 (100), 201 (3.8), 192 (22.6), 183 (4.5), 164 (15.1), 151 (6.6), 150 (17.6), 149 (6.4), 136 (5.4), 135 (7.3), 123 (8.6), 121 (6.2), 111 (65.5), 110 (25), 109 (12.2), 95 (9.6), 91 (8.5), 82 (71.4), 69 (11.2), 67 (10.4), 55 (13.4). The IR, ^1H NMR, ^{13}C NMR, and mass spectra were in accord with structure **2**.

Anal. Calcd for $C_{20}H_{32}O_4$: mol wt, 334.2144. Found: mol wt, 334.2136 (high-resolution mass spectroscopy).

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Registry No. 1, 80865-69-6; **1a**, 80865-70-9; 2, 59219-63-5; **2a**, 80865-71-0; **3**, 1438-57-9.

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[10] Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Bates, R. B. *J. Org. Chem.* **1981**, *46*, 4267.

[11] Mangoni, L.; Belardini, M. *Gazz. Chim. Ital.* **1962**, *92*, 983.

Synthetic Studies of *trans*-Clerodane Diterpenoids and Congeners: Stereocontrolled Total Synthesis of (±)-Avarol

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A stereocontrolled total synthesis of (±)-avarol, a sesquiterpenoid hydroquinone, has been accomplished in eight steps, by a flexible route which is potentially useful in the synthesis of related natural products containing a functionalized bicyclo[4.4.0]decane skeleton such as *trans*-clerodanes. The originally assigned stereochemistry for this natural product has been confirmed through correlation with a degradation product of ilimaquinone. Preliminary model studies on the employed methodology are also presented.

Recently, a number of terpenoids containing a functionalized bicyclo[4.4.0]decane skeleton with a characteristic array of asymmetric centers have been isolated. They include, apart from several *trans*-clerodane diterpenoids

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