Constituents of *Chrysothamnus paniculatus* (Compositae). 2. Chrysolic Acid, a New Labdane-Derived Diterpene with an Aromatic B Ring

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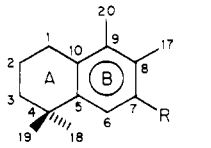
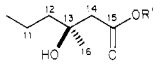
An ethyl acetate extract of *Chrysothamnus paniculatus* (Compositae) gave, upon separation of acid constituents followed by methylation and chromatography of the methylated product, the methyl ester of a new diterpene, chrysolic acid (**1a**), whose identity was established from spectroscopic evidence and biogenetic considerations. It is the first labdane-derived diterpene with an aromatic B ring.

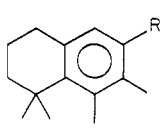
We have previously reported[1] the isolation and characterization of a new diterpene, chrysothame, and two known diterpenes, grindelic acid and 6-oxogrindelic acid, from *Chrysothamnus paniculatus* (Compositae). We now report the structure determination of the methyl ester (**1b**) of another new diterpene, chrysolic acid (**1a**), isolated from the same plant. The procedure described in the Experimental Section was employed to isolate the remaining major diterpene acid constituents (as methyl esters) of *C. paniculatus*.



1, R =



a, R' = H
b, R' = Me



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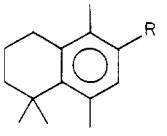

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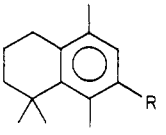

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Methyl chrysolate, $C_{21}H_{32}O_3$ by high-resolution MS, was shown to be **1b** on the basis of spectroscopy. Structure **1b** is consistent with the IR spectrum, which suggested the presence of an intramolecular hydrogen-bonded hydroxyl (3540 cm^{-1}; did not form either a Me_3Si or acetyl derivative under normal reaction conditions), an ester (1730 cm^{-1}), a phenyl ring with an isolated H (1600, 1568, 875 cm^{-1}), and a *gem*-dimethyl (1380, 1360 cm^{-1}) group.

The NMR spectra (Table I) showed the presence of an aromatic ring, which bears two methyl groups, one hydrogen, a $CH_2CH_2CMe(OH)CH_2CO_2Me$ group, and a $CH_2CH_2CH_2CMe_2$ grouping fused to two ortho positions. The arrangement of these groups on the aromatic ring was not apparent until a shift reagent experiment was performed with $Eu(fod)_3$ (Table I, last two columns): after all of the hydrogens on the large side chain, the largest shifts were observed for an aryl methyl group (C-17) and the aryl hydrogen (C-6), indicating these groupings to be ortho to the large side chain. Evidence in support of the four structures (**1b–4b**) that contain this structural feature came from a ^1H–^1H decoupling experiment in which it was found that irradiation of the aryl hydrogen increased by 50% the intensity of the aryl methyl peak (C-20), which was less affected by the shift reagent, whereas the intensity of the other aryl methyl peak (C-17) increased by only 20%; these results are only consistent with structures with

Table I. NMR Parameters for 1b in $CDCl_3$

C	$\delta(^{13}C)$	$\delta(^1H)$	$\Delta\delta(^1H)$ with $Eu(fod)_3$ low concn[e]	$\Delta\delta(^1H)$ with $Eu(fod)_3$ high concn[f]
1	28.9 (t)[a]	2.63 (t, J = 6.6 Hz)	0.00	0.03
2	19.8 (t)	1.81 (m)	0.01	0.03
3	43.4 (t)	1.59 (m)	0.01	0.04
4	33.8 (s)			
5	137.4 (s)[b]			
6	125.1 (d)	7.03 (s)	0.01	0.19
7	143.4 (s)[b]			
8	132.5 (s)[b]			
9	135.0 (s)[b]			
10	131.4 (s)[b]			
11	28.5 (t)[a]	2.70 (m)	0.06	*d*
12	38.9 (t)	1.71 (m)	0.09	*d*
13	71.0 (s)			
14	45.0 (t)	2.53 (d, J = 15.6 Hz)	0.09	*d*
		2.61 (d, J = 15.6 Hz)	0.10	*d*
15	173.3 (s)			
17	26.7 (q)	1.35 (s)	0.07	*d*
17	15.7 (q)[c]	2.20 (s)	0.01	0.16
18				
19	32.1 (q)	1.28 (s)	0.00	0.03
20	15.4 (q)[c]	2.14 (s)	0.00	0.04
OMe	51.6 (q)	3.72 (s)	0.02	0.20

[a-c] Values with same letter may be interchanged. [d] Shifts unknown due to severe line broadening. [e] To 19 mg of 1b in 0.6 mL of $CDCl_3$ was added three drops of a solution of 20 mg of $Eu(fod)_3$ in 1.5 mL of $CDCl_3$. [f] Nine more drops of same solution as in footnote *e* added.

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(3) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Bates, R. B. *J. Org. Chem.* **1981**, *46*, 4267.

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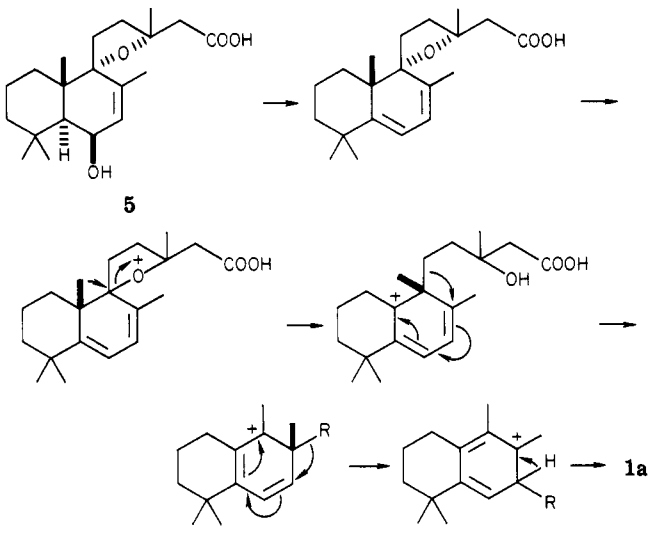
Scheme I. Proposed Biosynthetic Pathway of 1a from 6β-Hydroxygrindelic Acid (5)



one methyl meta to the aryl hydrogen (J = 0.36 Hz) and one methyl either ortho (J = −0.75 Hz) or para (J = −0.62 Hz) to the aryl hydrogen.

Of structures **1a–4a**, the former is by far the most biogenetically reasonable; it may arise from 6β-hydroxygrindelic acid (**5**), which also occurs in *C. paniculatus*, as shown in Scheme I.

The EI mass spectrum of methyl chrysolate (**1b**) exhibited a strong $M^{+\cdot}$ peak (m/z 332) followed by fragment ion peaks that were readily interpretable as shown in Scheme II. The elemental composition of these fragment ions were verified by high-resolution exact-mass measurement and, where indicated by m, the transitions shown were substantiated by metastable peaks.

Experimental Section

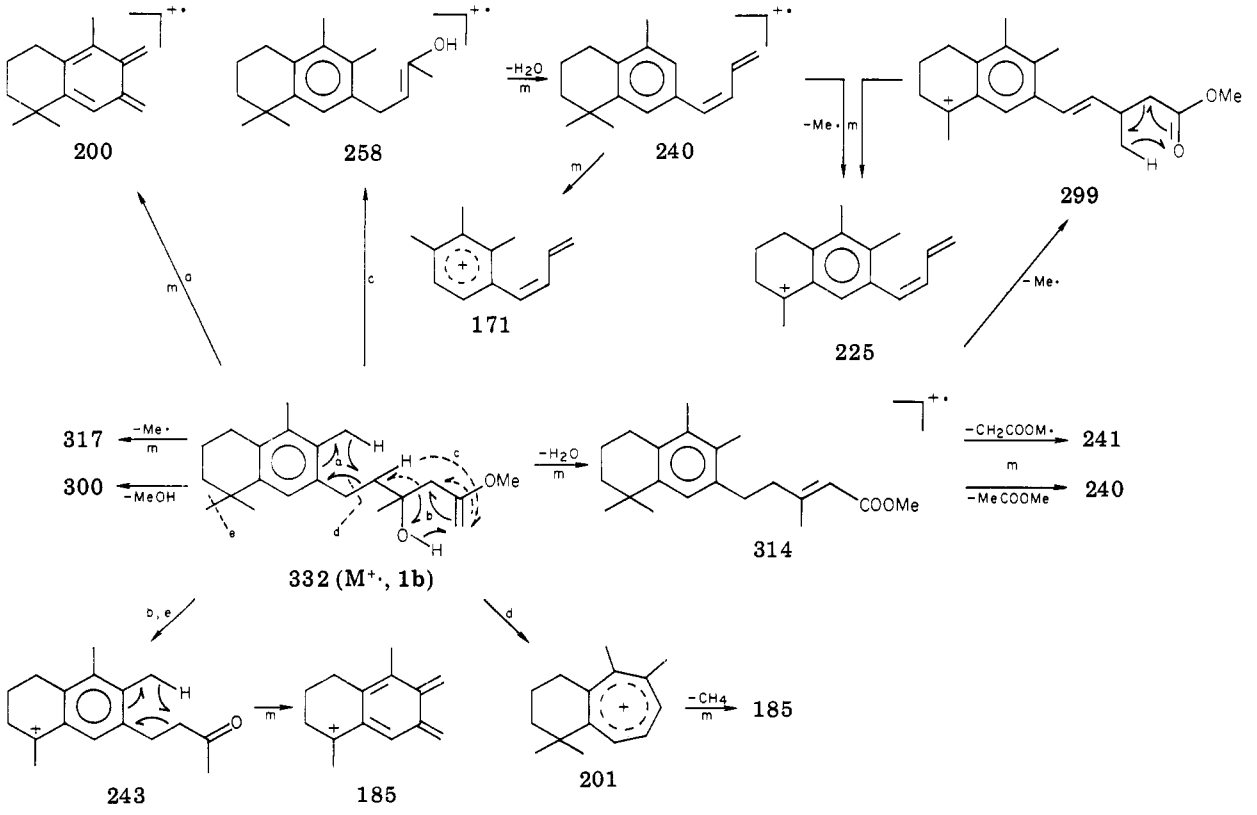
See ref 3 for description of analytical procedures used.

Isolation of Acid Constituents. Dried *C. paniculatus* was ground in a Wiley mill and stored at −10 °C prior to extraction. The ground material (1900 g) was extracted exhaustively in a Soxhlet extractor with EtOAc. The concentrated EtOAc extract after drying under vacuum (240 g) was stirred magnetically (2 h) with ether and then filtered. The ether-soluble filtrate was extracted with 5% aqueous Na_2CO_3 and the separated alkali phase after acidification (pH 6) with 10% aqueous HCl was extracted with ether followed by the usual workup. The resulting foamy residue (136 g) was redissolved in a minimum of ether, precipitated with a large excess of petroleum ether, and left in a freezer overnight, the supernatent layer was filtered by decantation, decolorized (Norit), and filtered, and the filtrate after removal of the solvent under vacuum yielded a yellow thick syrup. After repetition of the above precipitation step, the resulting light-yellow thick syrup (63 g) was subjected to methylation.

Methylation of Acid Constituents. Into a 1000-mL two-necked round-bottom flask fitted with a condenser topped by a drying tube was placed a solution of the above acid mixture (45 g) in dry acetone (450 mL) followed by anhydrous K_2CO_3 (45 g) and methyl iodide (45 mL). The mixture was gently refluxed at 56–60 °C for 6 h, cooled, and filtered, and the residue obtained after removal of the solvent under vacuum was distributed between ether and water. The organic layer after the usual workup followed by decolorization and evaporation of the solvent under vacuum gave a nearly colorless thick syrup (45 g), the IR spectrum of which showed no characteristic carboxylic acid absorption bands.

Isolation of Methyl Chrysolate (1b). A solution of the above methyl ester mixture (35.2 g) in 4% EtOAc in *n*-hexane (54 mL) was subjected to preparative HPLC (Waters PrepLC/SYSTEM 500A equipped with a refractive index detector) by using a Waters prepPAK-500/SILICA cartridge column in three equal batches. With the initial flow rate set at 0.2 L/min for 23 min (increased to 0.35 L/min for the remainder of each run), elution was conducted via a step-gradient consisting of increasing concentrations (v/v) of EtOAc [4% (for fractions A and B) 15% (for fraction C) and 30% (for fraction D)] in *n*-hexane.

Scheme II. Major Fragment Ions (m/z Ratios) in the Mass Spectrum of 1b[a]



[a] m = metastable ion.

Fraction C (15.6 g from four batches), which showed the presence of methyl chrysolate (**1b**) as judged from TLC, was subjected to EM SiO_2-60 (500 g) column chromatography, eluting the column with CH_2Cl_2 followed by gradually increasing concentrations of EtOAc. After an initial 400-mL fraction, 20-mL fractions were collected. Fractions 110–130 (CH_2Cl_2 eluent) containing **1b** as the major spot as judged from TLC were combined, and after evaporation of the solvent under vacuum the oily residue (1.18 g) was subjected to preparative TLC (SiO_2-60 PF254), using CH_2Cl_2/EtOAc (99:1) as the developing solvent system. Repetition of the preparative TLC procedure gave **1b** as a colorless oil, homogenous by TLC, $[\alpha]^{25}_D$ −12.3° (*c* 2.39, $CHCl_3$). The IR (CCl_4, described in the text), ^1H and ^{13}C NMR (Table I), and mass (Scheme II) spectra were in accord with structure **1b**.

Anal. Calcd for $C_{21}H_{32}O_3$: mol wt, 332.2351. Found: mol wt, 332.2348 (high-resolution MS).

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Registry No. 1a, 82731-92-8; **1b**, 82731-93-9.

α-Methyl Functionalization of Electron-Poor Heterocycles:[1] Chloromethyl Derivatives of 2,2′-Bipyridines

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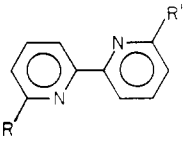
The syntheses of 6-(chloromethyl)- (**3**), 6-(chloromethyl)-6′-methyl- (**2**), and 6,6′-bis(chloromethyl)-2,2′-bipyridine (**1**) are reported. Complete spectral analyses including ^1H and ^{13}C NMR data are given for each compound. Experimental results and appropriate comparisons justify the reassignments of the ^{13}C NMR spectral data for the bipyridine derivatives. Descriptions of the synthetic techniques with the new, critical modifications utilized to prepare these key starting materials are presented. Bipyridine *N*-oxides have been shown to undergo intra-ring rearrangements; no *N*-oxide migration occurs under thermolysis at 200 °C.

Over the past few years, the numerous syntheses of macrocycles which possess one or more subheterocyclic unit(s) have been reported.[5] In view of our interest in site-specific bi- and polynuclear complexes, inclusion of the 2,2′-bipyridine subunit into macrocycles[6] and organometallics[7] has been accomplished from the appropriate α-halomethyl precursors. Although numerous routes to the simple α-(halomethyl)pyridines have been reported,[8] the literature procedures are either lengthy and/or thwarted with sporatic yields, when applied to the functionalization of polypyridines. We herein report improved routes to these pivotal bipyridine starting materials: 6-(chloromethyl)- (**3**), 6-(chloromethyl)-6′-methyl-(**2**), and 6,6′-bis(chloromethyl)-2,2′-bipyridine (**1**).

Results and Discussion

6,6′-Bis(chloromethyl)-2,2′-bipyridine (1). 6,6′-Difunctionalized bipyridines have been generally derived from 6,6′-dibromo-2,2′-bipyridine (**4**) via a lithium–bromide



1, R = R′ = CH_2Cl
2, R = CH_2Cl; R′ = CH_3
3, R = CH_2Cl; R′ = H
4, R = R′ = Br
5, R = R′ = CHO
6, R = R′ = CH_2OH
7, R = R′ = CH_3
8, 2 N→O; R = R′ = CH_3
9, R = R′ = CH_2OAc
10, R = R′ = $CHCl_2$
11, N→O; R = R′ = CH_3
12, R = CH_2OAc; R′ = CH_3
13, R = CH_2OH; R′ = CH_3
14, R = R′ = H
15, R = CH_3; R′ = H
16, R = $CHCl_2$; R′ = H
17, N→O; R = CH_3; R′ = H
18, N′→O; R = CH_3; R′ = H
19, R = CH_2OAc; R′ = H
20, R = CH_3; R′ = OAc
21, R = CH_2OH; R′ = H

exchange, followed by addition of suitable electrophiles, e.g., *N*,*N*-dimethylformamide, to give dialdehyde **5**.[9] Quantitative reduction ($NaBH_4$) of **5** gave the bis carbinol **6**, which upon treatment with purified[10] $SOCl_2$ afforded (73%) the bis(chloromethyl) derivative **1**. *Care must be exercised in handling all of these halomethyl derivatives*

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(2) On leave from the University of Delhi, Delhi, India, 1980–1982.
(3) On leave from Lanchow Institute of Chemical Physics, Academia Sinica, Lanchow, China, 1981–1982.
(4) Undergraduate Researcher.
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