

Grindelic and Oxygrindelic Acids

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Some observations are recorded on the mass spectra, the nuclear magnetic resonance spectra and the chemistry of grindelic and oxygrindelic acids and certain of their derivatives. The results of these studies confirm the structures (I, R = COOH), and (II, R = COOH) proposed by Panizzi, Mangoni and Belardini¹ for the two acids, respectively.

In the course of an investigation of *Compositae*, which has been pursued for some years in Trondheim, several *Grindelia* species were grown and investigated for their content of acetylenic compounds; cf. Ref.² During an examination of *Grindelia squarrosa* (Pursh.) it was observed that the flower heads were very sticky, and after steam distillation, extraction of the wet material with ether afforded two acidic substances which could be isolated as their crystalline methyl esters. The one occurring in the higher proportion was crystallised from petroleum to constant melting point, 71–72°, and rotation $[\alpha]_D - 132^\circ$; it is identical with methyl grindelate¹; cf. Table 1. The minor component similarly gave methyl oxygrindelate, m.p. 114–114.5°, $[\alpha]_D - 106^\circ$, and is identical with the ester prepared by Woodward oxidation of methyl grindelate, Table 1.

On the basis of degradative experiments, Panizzi, Mangoni, and Belardini¹ have recently assigned structures (I; R = COOH) and (II; R = COOH) to grindelic and oxygrindelic acids, respectively. We have independently investigated these two acids, and by examination of their infrared, ultraviolet,

nuclear magnetic resonance, and mass spectra, and those of some of their transformation products, we have confirmed the correctness of the structures (I) and (II).

A number of the compounds investigated have also been prepared by the Italian workers. A comparison of physical constants is made in Table 1. The experimental section includes only those compounds which have not been described by Panizzi and his co-workers.

Grindelic acid, $C_{20}H_{32}O_3$, readily yields methyl and ethyl esters, the infrared spectra of which indicate the absence of hydroxyl groups. Both methyl grindelate and methyl oxygrindelate are readily saponified, indicating the presence of a primary ester grouping. This is confirmed by pK^*_{MCS} values^{3,4}, very kindly determined by Dr. V. P. Arya, who found the values 7.06 for grindelic acid and 7.04 for oxygrindelic acid. Reduction of the methyl ester with lithium aluminium hydride gives a primary alcohol, grindelenol (I, $R = CH_2OH$), $C_{20}H_{34}O_2$, which does not possess a carbonyl stretching band in its infrared spectrum. These observations show that the three oxygen atoms in grindelic acid are present as a carboxyl group and an ether. That this ether is not an epoxide, follows from its inertness to lithium aluminium hydride, and from the fact that grindelic acid was recovered unchanged from an attempted reduction with sodium in propanol.

The n.m.r. spectra of methyl grindelate and methyl oxygrindelate (Table 2) indicate that both compounds contain four methyl groups attached to fully substituted carbon atoms, one of which also carries an oxygen atom (bands near 8.70). Methyl grindelate also gives rise to a broad band at 8.23 assignable to an olefinic methyl group since this methyl group absorbs as a doublet at 9.20 in methyl dihydrogrindelate. The 8.23 band is replaced in the spectrum of methyl oxygrindelate by one equivalent to two protons at 5.93, suggesting

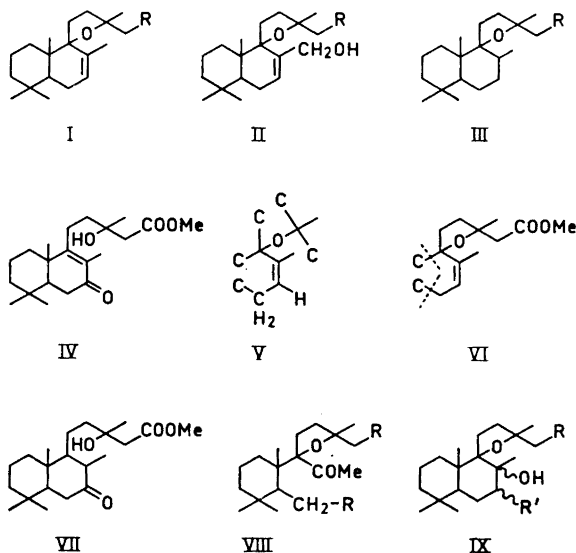


Table 1.

		M.p.	[α] _D	<i>c</i>	λ_{\max}	ϵ
Grindelic acid (I, R = COOH)	<i>a</i>	98 - 99	-102	0.71		
Methyl grindelate (I, R = COOMe)	<i>a,c,d</i>	70 - 70.5	-134	1.46		
	<i>b</i>	71 - 72	-132	2.67		
Methyl oxygrindelate (II, R = COOMe)	<i>a,d</i>	115 - 116	-105	0.95		
	<i>b</i>	114 - 114.5	-106	2.69		
Methyl dihydroxygrindelate (IX, R = COOMe, R' = OH)	<i>a,d</i>	122 - 123	+ 19	0.84		
	<i>b</i>	118.5 - 119	+ 15	2.00		
Isomeric dihydroxygrindelate (IX, R = COOMe, R' = OH)	<i>b</i>	152 - 154	+ 24	0.84		
Benzoate of methyl dihydroxygrindelate (IX, R = COOMe, R' = OBz)	<i>b</i>	193 - 194	+ 53	2.00		
Dihydroxygrindelic acid (IX, R = COOH, R' = OH)	<i>b</i>	197 - 198	+ 25	2.20		
Keto diacid (VIII, R = COOH)	<i>b</i>	197 - 198	+ 22	2.29		
Keto diester (VIII, R = COOMe)	<i>a</i>	102 - 103				
	<i>b</i>	98 - 99	- 21	2.20		
13,15-Dihydroxylabdene-8	<i>a</i>	104 - 105	+ 87	1.0		
13,15-Dihydroxylabdane	<i>a,d</i>	121 - 122	+ 29	1.3		
	<i>b</i>	119 - 120	+ 30	1.05		
Ketol (IV)	<i>b</i>	78 - 78.5	+ 65	2.86	2500	17 000
2,4-DNP	<i>b</i>	115 - 116			3950	28 000
2,4-DNP of dihydro-ketol (VII)	<i>b</i>	128 - 129			3685	27 000

a: See Ref.¹

b: This work.

c: Sample for comparison provided by Professor L. Panizzi.

d: IR spectrum for comparison provided by Professor L. Panizzi.

that this compound differs from methyl grindelate by having a hydroxy-methyl group in place of the olefinic methyl group. We confirmed this conclusion by oxidising methyl grindelate with selenium dioxide to the oxy ester.

The proton spectrum of methyl grindelate also contains a band at 4.50 which is absent in the spectrum of methyl dihydrogrindelate (III, R = COOMe) prepared from the former ester by catalytic hydrogenation. Thus, methyl grindelate contains a trisubstituted double bond. The fine structure of the olefinic proton indicates the presence of a methylene group α to the olefinic proton so that grindelic acid possesses the grouping $-\text{CH}_2\cdot\text{CH}:\text{C}(\text{CH}_3)-$. The absence of further absorption (apart from the ester methoxyl group) below 7.0 shows that the ether oxygen atom is attached at fully substituted carbon atoms. Oxidation of methyl grindelate with sodium dichromate yielded a neutral compound (IV). The U.V. spectrum (λ_{\max} 2500 Å, ϵ 17 000) and infrared spectrum (3480, 1730, 1655, 1610 cm^{-1}) revealed this compound to be an α,β -unsaturated ketol ester. The absence of olefinic absorption and the presence of one methyl absorption at 8.18 in its n.m.r. spectrum requires the double

bond to be of the type $\begin{matrix} \text{R}' \\ \diagdown \\ \text{C}=\text{C}(\text{CH}_3)\cdot\text{CO}- \\ \diagup \\ \text{R} \end{matrix}$; R \neq H or Me. Clearly, this com-

ound is formed by oxidation of the trisubstituted double bond to a ketone, followed by β -elimination of the ether oxygen atom which accordingly must be allylic in grindelic acid. We may now write the part structures (V) in

Table 2. Chemical shifts (τ -values) of protons of grindelic acid derivatives.

Compound	Methyl groups at						
	C(4) and C(10) ^a		8-Me	13-Me	7-H	-CH ₂ CO ₂ Me	
Methyl grindelate (I, R = CO ₂ Me)	9.20	9.14	9.12	8.23	8.68	4.50	7.40, 7.27 ^d
Methyl oxygrindelate (II, R = CO ₂ Me)	9.21	9.5	9.12	5.93 ^b	8.69	4.53	7.31 ^e
Methyl dihydrogrindelate (III, R = CO ₂ Me)	9.23	9.17	9.15	9.20 ^c	8.68	—	7.33 ^e
α,β -Unsaturated ketol ester (IV)	9.14	9.11	8.92	8.18	8.705	—	—
Grindelanol (I, R = CH ₂ OH)	9.21	9.16	9.13	8.20	8.74	4.55	7.46 ^e
Keto diester (VIII) ¹	9.22	9.09	8.97	7.76	8.75	—	—
Diol (IX) ¹ m.p. 118–119°	9.19	9.12	8.97	8.62	8.71	—	7.32

^a The bands are not assigned to specific methyl groups. ^b Hydroxy-methyl group.

^c Doublet, $J \sim 7$ c/s. ^d AB spectrum, $\delta_{AB} = 7.8$ c/s, $J_{BA} = 14.0$ c/s. ^e Singlet equivalent to two protons.

which the ether oxygen atom is part of a heterocyclic ring since the β -elimination did not result in fragmentation.

The immediate environment of the carboxyl group of grindelic acid is suggested by the n.m.r. spectrum of grindelenol (I, R = CH₂OH) in which the two protons adjacent to the hydroxyl group give rise to a complex multiplet at 6.25. The fine structure of this band is compatible with the grouping —CH₂CH₂—. This conclusion is confirmed by the observation that the n.m.r. spectra of a number of compounds (Table 2) in which the carboxyl group is present, exhibits a singlet or an AB multiplet equivalent to two protons near

7.4, which therefore arise from the methylene group —C— $\overset{|}{\text{CH}_2}$ COOMe.

Consideration of the mass spectra of compounds in this series allows an extension of the part structure (V). Methyl grindelate, methyl oxygrindelate, and ethyl grindelate give rise to abundant fragment ions at 210, 226 (210 + O), and 224 (210 + CH₂), respectively, all of which correspond to ion radicals. It is clear that the 210 fragment from methyl grindelate contains the olefinic methyl group and the three oxygen atoms. Similarly, grindelene (I, R = Me), prepared by lithium aluminium hydride reduction of grindelenyl *p*-toluene-

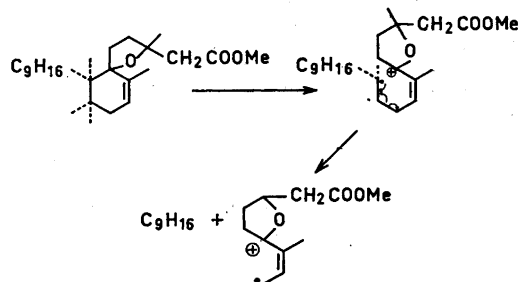
Table 3. Infrared absorption in the region 1030–970 cm⁻¹ of grindelic acid derivatives.

Methyl grindelate (I, R = CO ₂ Me)	1000 ^b	985 s
Methyl oxygrindelate (II, R = CO ₂ Me)	1003	983 s
Grindelene (I, R = Me)	1027 w	997 s ^c
Methyl dihydrogrindelate (III, R = CO ₂ Me)	1017	1007 ^b
Grindelane (III, R = Me)	1015	993 s
Diol (IX), m.p. 118–119° ^a	1015	987
Diol (IX), m.p. 152–154° ^a	1006 s	992 s
Diol		996 vw
Unsaturated keto/ester (IV)	1003 ^b	978 vw
Saturated keto ester (VIII)	1002	970 ^c

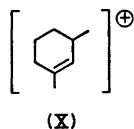
^a These diols were obtained from the osmium tetroxide oxidation of methyl grindelate. That with m.p. 118–119° is identical with the diol described by Panizzi *et al.*¹

^b Shoulder. ^c Broad.

sulphonate, gives an abundant ion at 166 ($210-\text{CO}_2$). However grindelene (III, $\text{R} = \text{Me}$) (obtained by catalytic hydrogenation of grindelene) does not give a strong peak at 168. Evidently, the ion radical (210) is formed from methyl



grindelate by cleavage at allylic positions so that the part structure (V) can be extended to (VI). This type of fragmentation is readily explicable if the double bond is part of a six-membered ring (see annexed mechanism). The accompanying molecule, C_9H_{16} , contains three methyl groups which in grindelic acid are attached to fully substituted carbon atoms. Thus grindelic acid must have a structure such as (I, $\text{R} = \text{COOH}$) based on decalin with one angular methyl group and one geminal dimethyl group in ring A. Biogenetic considerations favour the 4-position for the geminal methyl groupings. The mass spectra of manoyl oxide and methyl labdanoate, which are known to possess *gem*-dimethyl groups at position 4, show a high peak at m/e 109,



presumably due to the ion (X). The high peak at m/e 109 found in the mass spectra of methyl grindelate, ethyl grindelate and grindelene thus does not contradict the biogenetic considerations.

The structure (I, $\text{R} = \text{COOH}$) is firmly established by the elegant degradation of grindelic acid to 14,15,16-trisnorlabdanoic acid reported by the Italian workers.

The infrared spectra of methyl grindelate and methyl oxygrindelate contain a prominent band in the region of 1000 cm^{-1} , see Table 3. It is broad and complex with the highest peak at about 985 cm^{-1} . Its presence appears to have some bearing on the allylic relationship between the double bond and the ether ring in methyl grindelate and methyl oxygrindelate, and also between the double bond and hydroxyl group in methyl oxygrindelate, since on hydrogenation it is split into two distinct bands, and it disappears when the ether ring is opened. The band is strong with an intensity comparable with that of the carbonyl band, and it is stronger in methyl oxygrindelate than in methyl grindelate.

EXPERIMENTAL

All melting points are uncorrected. Mixed melting points were determined simultaneously with the melting points of the pure components. Unless otherwise stated, rotations were measured with chloroform solutions in 1 dm tubes unless specified, ultraviolet spectra were measured with a Perkin-Elmer Model 13 spectrophotometer using ethanol solutions, and infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer using chloroform solutions. Nuclear magnetic resonance spectra were obtained with a Varian 4300 spectrometer operating at 56.4 Mc/sec. Deuteriochloroform solutions were used, and the spectra were calibrated against tetramethyl silane as an internal reference by the side band method employing a Muirhead-Wigan-D-695-A decade oscillator. Mass spectra were measured with a Dempster type mass spectrometer, *cf.* Ref.⁵

Ethyl grindelate. Pure methyl grindelate (0.2 g) was saponified and the acid converted directly to its silver salt. The dried and powdered salt was refluxed for 8 h in ethyl bromide. Removal of the silver bromide and solvent, and distillation of the residue afforded ethyl grindelate, b.p. 110°/10⁻³ mm, n_D^{22} 1.5037, $[\alpha]_D -123^\circ$ (c, 2.22). The ester was subjected to gas-liquid chromatography prior to the determination of its mass spectrum.

Partial synthesis of methyl oxygrindelate. Methyl grindelate (2 g) was refluxed with selenium dioxide (2 g) in 1-butanol (50 ml) for 5 h. After removal of the solvent, ether was added, and the deposited selenium (0.3 g) removed by filtration. Evaporation of the ether, and recrystallisation of the residue from light petroleum containing a little ether yielded methyl oxygrindelate, m.p. 113–114° (undepressed by admixture with the natural ester) $[\alpha]_D -105^\circ$ (c, 2.09).

Attempted reduction of grindelic acid with sodium and n-propanol. Methyl grindelate (2 g) was saponified and the resulting acid was dissolved in propanol (25 ml). Sodium was added in small pieces to the boiling solution until saturation. The product was poured into water, acidified and extracted with ether. Treatment of the ethereal solution with diazomethane and evaporation of the solvent gave an oil which slowly crystallised to crude methyl grindelate, m.p. 65–72°. A mixture with the starting material melted at 70–72°.

Isomeric methyl dihydroxygrindelates. Osmium tetra-oxide (1.17 g) and methyl grindelate (1.548 g) in ether (35 ml) with pyridine (1 ml) were left in the dark for 5 days. The osmic ester was reduced with hydrogen sulphide⁶, and the crude product subjected to a rough chromatographic separation on alumina. With benzene 75 mg of starting material were obtained whilst ether eluted 395 mg and the remainder, 1042 mg, came off with methanol. The material eluted with ether on crystallisation from petroleum furnished methyl dihydroxygrindelate, m.p. 118–119°, *cf.* Ref.¹ Subsequent concentrations of the mother liquors (repeated three times) finally afforded crystals melting at 137–145° (22 mg), $[\alpha]_D + 20^\circ$ (c, 2.00). Recrystallisation of this material from petroleum gave an isomeric methyl dihydroxygrindelate, melting at 152–154°, $[\alpha]_D + 24^\circ$ (c, 0.84).

Similar treatment of the fraction eluted with methanol furnished only methyl dihydroxygrindelate of the same m.p. (118–119°) and rotation, $[\alpha]_D + 15^\circ$ (c, 0.72 for the last crop).

Benzoylation of methyl dihydroxygrindelate with excess benzoyl chloride in pyridine gave the monobenzoate, which was crystallised from petroleum with a trace of chloroform and from carbon tetrachloride until constant m.p., 193–194°, and rotation, $[\alpha]_D + 53^\circ$ (c, 2.00).

α,β -Unsaturated ketol ester (IV). A solution of sodium dichromate (3.20 g) in water (2 ml) and acetic acid (25 ml) was added to a solution of methyl grindelate (1.02 g) in acetic acid (5 ml). The mixture was left at room temperature for 72 h and then poured into water. The mixture was extracted with ether. Removal of ether from the dried (Na₂SO₄) extract, and chromatography of the residue afforded a crude product (0.69 g) which on recrystallisation from petroleum gave the α,β -unsaturated ketol ester (IV) (0.33 g), m.p. 78–78.5°, $[\alpha]_D + 66^\circ$ (c, 2.07), $+ 65^\circ$ (c, 2.86), λ_{\max} 2500 Å, ϵ 17 000, (Found: C 72.3; H 9.5. C₂₁H₃₄O₄ requires C 71.9; H 9.8). This compound yields a 2,4-dinitrophenylhydrazone as fine, red needles from petroleum, m.p. 115–116°, λ_{\max} 3950 Å, ϵ 23 000 in chloroform (Zeiss spectrophotometer, Model PMQ2). (Found: C 61.4; H 7.1; N 10.5. C₂₇H₃₈N₄O₇ requires C 61.1; H 7.2; N 10.55).

Hydrogenation of the above ketol ester (IV) over 2 % palladium on barium sulphate in acetic acid afforded a *saturated ketol ester* (VII), b.p. 125°/10⁻³ mm (bath), n_D^{25} 1.4966, $[\alpha]_D -17^\circ$ (c, 4.05). (Found: C 71.4; H 9.9. C₂₁H₃₈O₄ requires C 71.6; H 10.3). The saturated ketol ester furnished a yellow *2,4-dinitrophenylhydrazone*, m.p. 128–129°, from methanol, λ_{\max} 3685 Å, ϵ 27 000. (Found: C 61.1; H 7.4; N 10.6. C₂₇H₄₀N₄O₇ requires C 60.9; H 7.55; N 10.5).

Grindelene (I, R = Me). Methyl grindelate (0.5 g) was treated with a large excess of lithium aluminium hydride in ether. The product was isolated in the usual way and treated with *p*-toluenesulphonyl chloride (1 g) in pyridine (5 ml). After standing for 24 h at room temperature the solution was poured into water and the oily ester was extracted with ether. The ethereal extract was dried (Na₂SO₄) and added to a solution of lithium aluminium hydride in large excess in ether. The reaction mixture was treated with dilute sulphuric acid, and the ethereal layer was removed and washed successively with aqueous sodium hydroxide and water. Removal of the solvent from the dried (Na₂SO₄) extract and distillation of the residue gave *grindelene*, b.p. 70–75°/10⁻³ mm, n_D^{21} 1.5069, $[\alpha]_D -138^\circ$ (c, 3.03). (Found: C 82.5; H 11.55. C₂₀H₃₄O requires C 82.7; H 11.8). The infrared spectrum showed the absence of OH and C=O and the compound was homogeneous by gas-liquid chromatography.

Grindelane (III, R = Me). Hydrogenation of grindelene over 2 % palladium on barium sulphate in acetic acid afforded *grindelane*, b.p. 70°/10⁻³ mm, n_D^{22} 1.4961, $[\alpha]_D -9^\circ$ (c, 1.93). (Found: C 81.7; H 12.2. C₂₀H₃₆O requires C 82.1; H 12.4). Gas-liquid chromatography indicated the presence of a trace of an impurity, possibly an epimer.

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