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^{13}C NMR SPECTRAL ANALYSIS OF GRINDELANE DITERPENOID ACIDS

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Key Word Index—^{13}C NMR spectra; grindelane diterpenoid acids; methyl grindelate; methyl grindelate epoxide; 6α-hydroxygrindelic acid; 6α-hydroperoxygrindelic acid; solidagenone; 6α-solidagenol; 6β-solidagenol.

Abstract—The ^{13}C NMR spectra of methyl grindelate and some of its derivatives were recorded and the signals assigned. Based on these assignments and on a comparison with previously reported data, information regarding the structures and stereochemistry of the products under study was obtained.

INTRODUCTION

In the last few years considerable interest has been focused on the isolation and structure elucidation of grindelane diterpenoid acids, mainly due to the feeding deterrent properties exhibited by some members of this group [1, 2]. In view of the fact that in the structural studies ^{13}C NMR was extensively used and in our opinion some of the data were not analysed correctly, we decided to carry out an exhaustive analysis of methyl grindelate (**1**), and some related products, in order to assign their signals unambiguously. This information together with the previously reported data has enabled us to elucidate features of their structures and stereochemistry.

RESULTS AND DISCUSSION

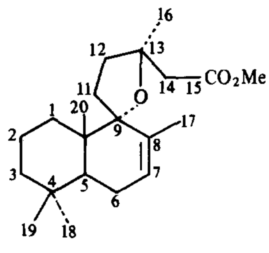
The carbon shifts assignment of methyl grindelate (**1**) was made by standard chemical shift theory, specific proton decoupling, analysis of the SFORD spectrum, generated CH/CH$_3$ and CH$_2$/q subspectra by spin-echo sequences utilizing the proton-flip method (APT) [3] and comparison with diterpenes previously studied.

The resonances due to C-2, C-3, C-4, C-6 and those of the methyls C-18 and C-19 were in good agreement with the reported values for the analogous carbon atoms of methyl eperua-7,13-dien-15-oate (**2**) [4]. C-1 and C-5 were shielded by 7.5 and 6.4 ppm, respectively, due to the γ effect induced by the axial oxygen atom of the tetrahydrofuran ring. On the other hand, as a consequence of the β effect produced by the same oxygen atom, C-10 and C-11 appeared deshielded by 3.8 and 6.4 ppm, respectively. The methylene signals of C-12 and C-14 and those of the methyl groups of C-16, C-17 and C-20 were assigned by specific irradiations at the frequences of absorption of the C-14, C-16 and C-17 protons. Although the assignment of both trigonal carbon signals is obvious, it is interesting to mention that the $\Delta\delta$ observed for C-7 and C-8, in comparison with the analogous carbon atoms of **2**, are of the magnitudes expected for those produced on the β and γ sp^2 carbons by an allylic hydroxyl group at an anticlinal position, with respect to the double bond [5]. Finally, the lower field signal of the oxygenated quaternary carbons was assigned to the neopentilic C-9.

A comparison, of the fully analysed ^{13}C NMR spectrum of **1**, with the reported data for methyl 18-hydroxygrindelate (**3a**) and methyl 4α-carbomethoxygrindelate (**3b**) [1], indicated that the C-1, C-11 and C-12 resonances were misassigned and must be corrected.

Literature precedents indicated conflicting reports regarding the configuration (α [6, 7] or β [8, 9]) of epoxide **4**. Since ^{13}C NMR spectroscopy is the method of choice for this type of determination [10–12], we decided to study it carefully. Epoxidation of **1** produced an isomerically pure epoxide which was shown to be identical to the methyl ester of the natural product [6, 7]. The signal of C-5, at 5.4 ppm higher field than the corresponding one of **1**, indicated clearly an α configuration for **4**. In agreement with published data [6], lithium aluminium hydride treatment of **4** afforded the diol **5**. The ^{13}C NMR spectrum of **5** showed that the methyl group at C-8 was axial [4, 13] and that **4** had not undergone the usual *trans* diaxial opening. The remarkable stereoselectivity toward the exclusive formation of an α-epoxide can be attributed to the directing effect of the 9α,13-oxide moiety by hydrogen bonding [14]. It is worthwhile mentioning that the ^{13}C NMR data reported for the epoxide of dimethyl 18-succinyl oxygrindelate indicate a β configuration [1]. This result suggests that the succinyl residue induced a steric hindrance for the attack of the peracid from the α-face of the molecule. The ^{13}C NMR data for **1**, **4** and **5** are listed in Table 1.

Recently, two new grindelic acid derivatives were isolated from *G. humilis* and shown to be the 6α-hydroxy and 6β-hydroxygrindelic acids. Because of the similarity found for the H-6 $J_{5,6}$ values such stereochemistry was established exclusively by applying the Mills' rule [2]. However, the effects of the orientation of the allylic hydroxyl group on the β- and γ-olefinic carbon shifts of those compounds, in comparison with the corresponding ones of **1**, were exactly opposite to those expected [5]. These conflicting results prompted us to look for more related model compounds. The diterpene solidagenone (**6**) appeared as the choice starting material for the preparation of such models. In fact, reduction of **6** with diisobutyl aluminium hydride, gave two allylic alcohols that were chromatographically isolated in pure form. An axial hydroxyl group in the major isomer (**7**), expected by



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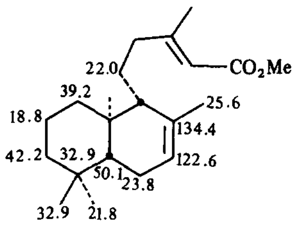

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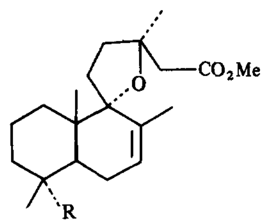
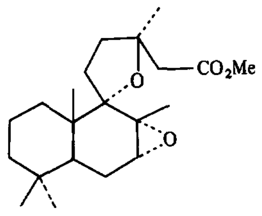


R

3a CH_2OH
3b CO_2Me



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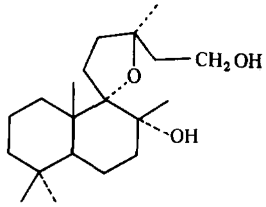

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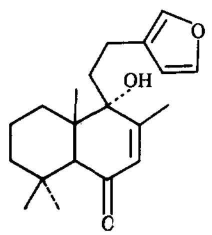

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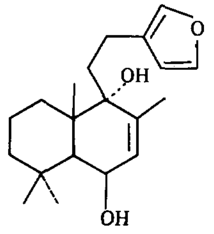

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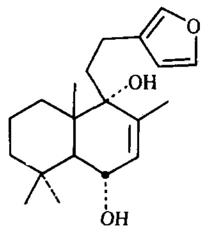

8

attack of the reducing agent from the α-face of **6**, was in agreement with the $J_{5,6}$ value (5 Hz) for the (δ4.36) H-6 NMR signal, whereas the epimer **8** (H-6, δ4.18) showed a larger value ($J_{5,6}$ = 9.2 Hz). The ^{13}C NMR data for compounds **6**, **7** and **8** are listed in Table 1.

Comparison of ^{13}C NMR shifts of C-5, C-6, C-7 and C-8 for the reported epimeric 6-hydroxygrindelic acids and their methyl esters (Table 2) with the model compounds **7** and **8** were in excellent agreement with the values for the 6β-hydroxy derivatives and compound **8**, even with regard to the effects of the allylic hydroxyl group orientation on the shifts of the olefinic carbons. These results strongly suggest the same stereochemistry at C-6 for both compounds. Since it is clear to us that **8** has an α configuration, the assignment indicated in ref. [2] must be reversed.

Bohlmann *et al.* [9] recently isolated a 6-hydroxygrindelic acid from *G. stricta* to which the 6α-hydroxyl configuration was suggested on the basis of its ^{1}H NMR spectrum. From the preceding analysis arose also a striking difference concerning the signal assigned to C-6 in the spectrum of the assumed 6α-hydroxygrindelic acid compared with those of the other isolated and synthetic compounds. Our recent experience with hydroperoxides [15], led us to consider the possibility that such a rather low field signal was due to the presence of an allylic hydroperoxyl group, since these type of compounds have been found in nature [16–18]. This alternative structure was supported by the observed effects of the hydroperoxyl group on the α, β and γ carbons compared with the allylic alcohols, as shown in Table 3. In addition, there is a trend in the variation of the optical rotation values going from the hydroperoxides to the allylic alcohols as the one observed for epimeric allylic alcohols (Mills' rule) (Table 4). In view of these findings, we propose that the reported 6α-hydroxygrindelic acid is in fact the corresponding 6α-hydroperoxide.

EXPERIMENTAL

Compounds **4** and **5** were obtained from **1** by previously

Table 1. Carbon shifts of compounds studied (20.15 MHz (Fourier transform mode), $CDCl_3$)*

C	1	4	5	6	7	8
1	32.8	31.8	34.5	31.8†	32.5	32.5
2	18.7	18.3	18.4	17.6	18.5	18.5
3	42.0	41.7	41.4	42.2	41.7	42.9
4	33.1	33.1	33.1	33.1	33.2	32.8
5	42.6	37.2	46.4	55.4	46.3	50.0
6	24.1	22.9	20.0	200.7	65.4	68.5
7	126.5	61.5	39.9	128.5	128.3	130.9
8	134.8	59.0	73.4	156.3	139.0	137.6
9	90.5	88.3	97.9	76.0	76.4	76.4
10	40.5	39.8	42.7	46.2	44.1	43.9
11	28.4	29.1	26.4	31.2†	34.0	33.2
12	38.2	37.5	40.6	20.9	21.2	21.3
13	81.5	81.4	85.2	124.8	125.6	125.6
14	47.9	47.1	41.8	110.4	110.7	110.7
15	171.4	171.9	59.6	138.1	138.3	138.3
16	27.3	26.7	25.4†	142.5	142.7	142.6
17	21.2	23.1	25.0†	21.4	24.7	22.4
18	32.8	32.5	33.1	33.5	32.9	36.4
19	22.3	22.5	21.5	18.0	20.3	17.4
20	16.6	16.5	18.4	19.8	19.4	19.7
OMe	51.2	51.2				

*The ^{13}C resonance of $CDCl_3$ was used as internal reference and converted to the TMS scale by use of the following correction: $\delta(TMS) = \delta(CDCl_3) + 76.9$.

†The assignments for these signals may be reversed.

Table 2. ^{13}C NMR shifts, reported in ref. [2], for the 6α-hydroxy and 6β-hydroxygrindelic acid derivatives

	6α-hydroxy		6β-hydroxy	
C	Acid	Me ester	Acid	Me ester
5	44.7	44.9	51.2	51.0
6	80.7	81.6	68.0	68.0
7	128.4	126.1	131.4	130.7
8	139.2	139.8	136.2	136.5

reported procedures [6] and the model compounds 7 and 8 were prepared by $(i\text{-}Bu)_2AlH$ reduction of solidagenone (6) according to ref. [19].

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Table 3. Effects of the hydroperoxyl group on the α, β and γ carbons of several natural and synthetic allylic alcohols (δ units)

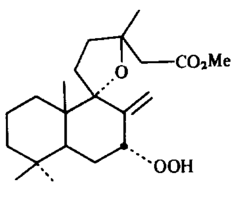
Compound		α-C			β-C (sp^2)			γ-C (sp^2)			
OOH	OH	OOH	OH	Δ	−OOH	−OH	Δ	OOH	OH	Δ	Reference
4*‡	8*‡	80.7	68.0	+12.7	128.4	131.4	−3.0	139.2	136.2	+3.0	[2]
23*‡	18*‡	82.1	69.3	+12.8	126.7	131.2	−4.5	144.5	142.0	+2.5	[15]
I*	II*	85.0	75.0	+10.0	145.0	147.7	−2.7	116.0	111.0	+5.0	§
2†‡	4†‡	91.4	78.2	+13.2	146.5	151.1	−4.6	112.6	110.0	+1.8	[16]
9†‡	11†‡	91.2	78.1	+13.1	145.0	150.2	−5.2	117.7	114.0	+3.7	[16]
1†‡	10*‡	90.2	78.2	+12.0	142.9	146.2	−3.3	120.0	117.0	+3.0	[18]

*$CDCl_3$.

†Pyridine-d_5.

‡The structure of this compound is described with this number in the reference.

§Colombo, M. I., Zudenigo, M. E., González Sierra, M. and Rúveda, E. A. (unpublished results).



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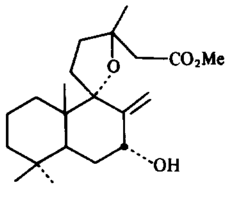

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Table 4. Optical rotation values of hydroperoxides and the corresponding allylic alcohols.

Hydroperoxide			Allylic alcohol			
Compound	$[\alpha]_D$	Solvent	Compound	$[\alpha]_D$	Solvent	Reference
1*	+30	MeOH	**10***	+17	MeOH	[18]
2*	+171	Me_2CO	**4***	+89	$CHCl_3$	[16]
9*	+27	Me_2CO	**11***	−11	Me_2CO	[16]
4*	+19.3	$CHCl_3$	**8***	−42.9	$CHCl_3$	[2]

*Number used in the reference.

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