^{13}C NMR Spectra of Natural Products

1—Guaianolides

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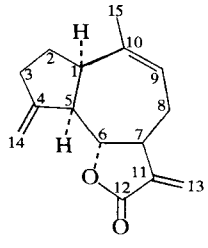
The ^{13}C NMR spectra of 18 guaianolides have been measured and the chemical shifts assigned. The compounds investigated include the naturally occurring eremanthin (1), dehydrocostus lactone, eregoyazin, eregoyazidin and other semisynthetic lactones derived from 1. Qualitative analysis of the data suggests that the predominant conformation in almost all compounds so far studied is a distorted chair-like form.

In spite of the large number of studies dealing with the isolation and structure elucidation of sesquiterpene lactones,[1] the literature concerning the ^{13}C NMR spectra of this important group of compounds is scarce and fragmentary in nature. The limited studies available include correlations of eudesmanolides, germacranolides and pseudoguaianolides.[2]

As part of our programme on sesquiterpene lactones[3] we have recorded the ^{13}C NMR spectra of a number of naturally occurring and modified guaianolides. It was soon recognized that the presence of the 7-membered ring provides the molecules with a certain degree of conformational mobility which could impose some difficulties in the interpretation of the spectra. It was hoped, therefore, that detection of the well-investigated effects of functional groups in more rigid systems would help in elucidating the preferred conformation of the compounds under investigation. The present report is an account of our preliminary findings in this field.

RESULTS

Chemical shift data for the guaianolides studied are given in Table 1. The carbon chemical shifts were assigned on the basis of their multiplicity in the off-resonance decoupled spectra and by consideration of



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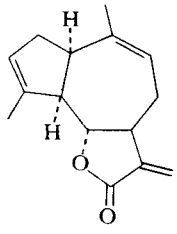

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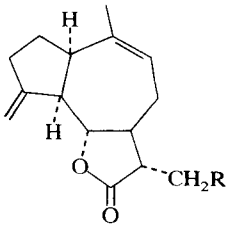

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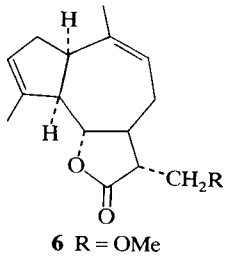
5 R = NMe_2



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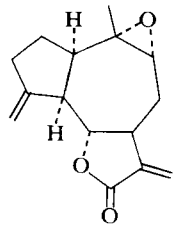

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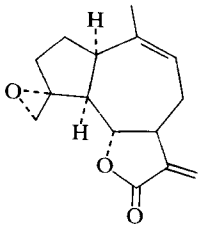

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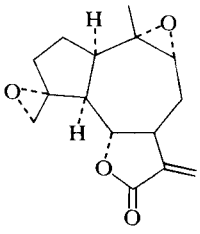

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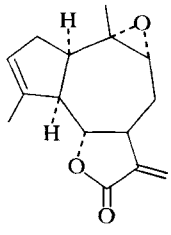

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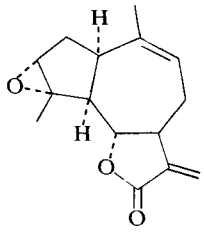

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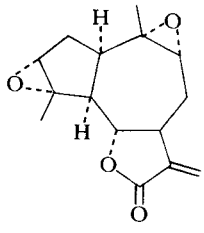

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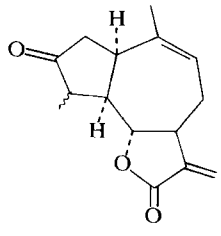

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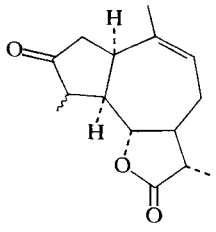

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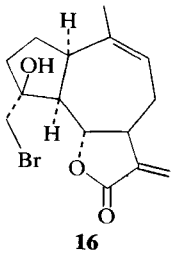

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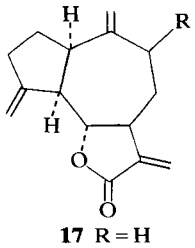

17 R = H
18 R = Cl

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Table 1. ^{13}C Chemical shifts of guaianolides[a]

Compound	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	OMe	NMe_2
1	47.1	29.2[b]	30.5[b]	150.4	52.7	83.2	45.3	29.7	121.2	138.2	140.7	170.1	119.4	110.9	27.2		
2	47.9	38.1	125.5	143.3	54.9	86.1	45.0	30.0	119.5	137.3	139.3	170.0	119.3	17.8	28.0		
3	47.3	29.3	30.3	150.2	52.7	83.2	48.9	29.8	121.3	137.9	42.2	177.8	12.9	110.3	27.8		
4	47.1	29.4	30.2	150.2	51.9	83.2	47.9	30.1	121.5	137.6	43.7	175.5	68.9	110.2	27.8	59.1	
5	47.1	29.5	30.3	150.3	52.2	83.1	46.6	30.4	121.8	137.5	45.9	177.0	58.8	110.4	27.8		45.6
6	48.0	37.8	125.3	144.4	54.2	86.6	47.4	31.1	120.0	137.1	43.6	176.1	69.2	17.8	27.8	59.1	
7	48.1	37.9	125.5	144.4	54.6	86.4	46.3	31.3	120.5	136.7	44.9	177.2	58.7	17.9	27.9		45.7
8	46.6	27.6	28.3	148.4	52.0	81.5	40.9	28.2	61.5	63.3	139.5	169.4	118.9	110.9	26.2		
9	45.6	28.7	28.7	66.1	53.2	82.3	45.4	29.5	120.3	138.4	139.6	169.4	119.6	49.9	28.0		
10	45.0	26.4	28.1	65.6	52.2	81.3	40.8	28.3	61.3	63.2	138.6	169.2	119.3	49.8	25.8		
11	47.5	34.8	125.1	144.8	53.3	85.4	39.9	29.0	62.0	63.0	138.8	169.7	119.4	18.0	26.4		
12	40.2	34.0	61.0	65.4	48.8	83.5	46.3	29.2	121.4	137.3	139.0	170.1	120.2	19.1	28.4		
13	40.2	31.3	59.4	64.8	48.0	82.3	38.7	28.4	60.9	62.6	138.2	169.2	119.4	19.3	26.8		
14	38.5	42.4	218.4	47.6	52.5	84.2	44.0	29.9	122.2	135.4	139.9	169.6	120.3	15.5	27.1		
15	39.2	42.4	218.6	47.8	51.7	84.1	48.3	30.3	122.6	135.8	42.7	176.6	13.1	15.7	27.4		
16	43.2	30.6	38.9	81.5	54.2	82.1	45.7	29.9	120.5	135.6	138.9	169.3	120.2	43.6	27.2		
17	47.5	32.5	30.2	150.9	51.9	85.1	45.0	30.9	36.2	148.9	139.5	170.0	119.9	109.4	112.4		
18	45.4	32.9	30.7	150.5	51.4	85.1	43.2	41.9	62.5	148.5	137.6	169.3	120.8	109.3	113.1		

[a] The spectra were recorded in 0.5–1 M solutions in $CDCl_3$.
[b] Assignments may be interchanged.

the known substituent effects of the groups concerned.[4] Some of the assignments were also confirmed by deuterium labelling, specific proton decoupling and by evaluation of lanthanide induced shifts.[4]

Assignment of most carbons in eremanthin (**1**)[5] was simplified by analysis of their chemical shifts and multiplicities. In addition to the contact shifts induced for C-6 and the olefinic carbons close to C-12, the addition of $Eu(fod)_3$ also induced pseudocontact shifts for other carbons as shown in Table 2. The relative values of these latter shifts allowed the unambiguous assignment of C-1, C-5, C-7, C-8 and the identification of C-2 together with C-3.

Although the spectrum of isoeremanthin (**2**),[6] could, in general, be easily correlated with that of **1**, some doubts remained about the assignment of C-10 and C-11. These carbons were distinguished by specific stepwise irradiation of the magnetically non-equivalent C-13 protons according to the technique of Bhacca *et al.*[7]

Table 2. $Eu(fod)_3$ induced shift (LIS) for eremanthin (1)

Carbon	Chemical shift ($CDCl_3$)	LIS[a]
1	47.1	1.00
2	29.2	0.71[b]
3	30.5	0.73[b]
4	151.9	0.97
5	52.7	1.56
6	83.2	3.97
7	45.3	2.58
8	29.7	1.04
9	121.2	0.77
10	138.2	0.88
11	140.7	2.86
12	170.1	[c]
13	119.4	6.09
14	110.9	1.04
15	27.2	0.46

[a] Obtained at a ratio $|Eu(fod)_3|/|eremanthin| = 0.77$.
[b] Values may be interchanged.
[c] The induced shift on this carbon is large and its signal is so broadened that its detection becomes difficult.

Compounds **3**[5] to **7**, obtained from **1** or **2** by selective addition to the conjugated double bond, gave ^{13}C NMR spectra which were easily elucidated by comparison with their parent compounds, and by consideration of the specific shifts due to the heteroatoms involved.

Epoxides **8–13**[5,6,8] are of interest, not only because of the widespread distribution of this function in nature, but also because the specific changes observed for the signals of the β and γ carbons helped to define the conformations of these derivatives (*vide infra*).

With the exception of those signals directly affected by saturation of the conjugated double bond, the spectra of eregoyazin (**14**) and eregoyazidin (**15**) are remarkably similar. This result is not consistent with the hypothesis that these two substances are C-4 epimers.[8]

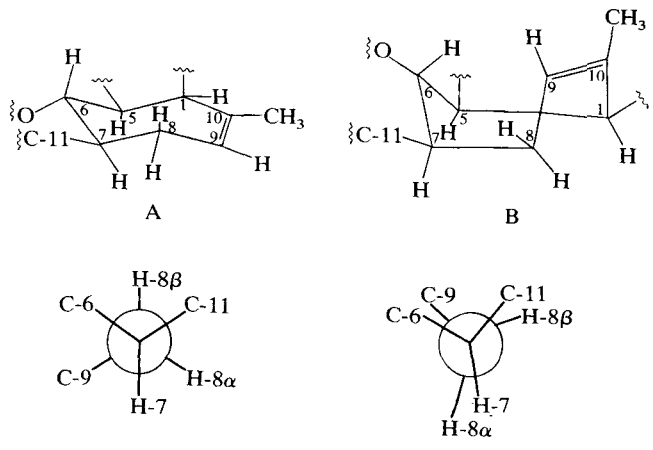
Known substituent effects were useful in the interpretation of the spectrum of the bromohydrin **16**. Thus, the most deshielded methylene signal (C-14, 43.6 ppm) was attributed to the carbon bonded to the bromine atom. The quaternary carbinol carbon resonated at 81.5 ppm, as indicated clearly in the SFORD spectrum, and was in this manner differentiated from C-6. C-3 and C-5 are less shielded than C-1 and C-2 because of the effects exerted by the β hydroxyl group.

Spectral assignment for dehydrocostus lactone (**17**) was facilitated by comparison with the spectrum of **18**[6] and its 9-deuterated derivative.

DISCUSSION

Inspection of Dreiding models of **1** and **2** shows that these guaianolides can exist in two main conformations; a distorted chair-like form and a boat conformation, as shown in partial structures A and B, respec-

tively, together with the corresponding Newman representations of the 7,8-segment. The lack of appropriate models makes the automatic association of a



given conformer with its spectral characteristics difficult. Indirect evidence, however, indicates that the chair conformation predominates. [Unfortunately, the 100 MHz ^{1}H NMR spectra of these compounds are not sufficiently resolved to allow a direct measurement $J(7, 8\beta)$. Indirect evidence indicating the possible predominance of the chair form in **1** include: (a) the relatively low chemical shift of H-6 (3.98 ppm), which compares favourably well with 4.06 ppm observed for 9,10,4,14-tetrahydrocostus lactone.[9a] In the boat form H-6 lies almost at the centre of the π system of the 9,10-double bond, which would probably cause an upfield shift for H-6; (b) in experiments in which the ^{13}C NMR spectra were obtained in the presence of Eu(fod)$_3$, a better correlation between induced shifts and distances was obtained for the chair form and (c) the large T_1 value (2.5 s) for C-15 suggests that its relaxation is dominated by a spin-rotation mechanism.[9b] In the boat form the free rotation suggested by the T_1 value would probably be diminished by interaction with one of the protons at C-2.] Furthermore, if an equilibrium is considered, this must be rapid compared with the NMR time scale, as indicated by the narrow line widths in the ^{1}H and ^{13}C spectra at room temperature.

The following discussion tends to give support to the idea of a rapid equilibrium between the two conformers with the prevalence (in all compounds studied) of the chair form.

Thus, the well-known effects of epoxides[10] make it easy to interpret the spectrum of compounds **8–13**. For example, in **8**, C-7 appears at 40.9 ppm, 4.4 ppm upfield from the corresponding value in **1**. This effect is only consistent with the chair conformation in which the 9,10-α-epoxide is *cis* to the axial hydrogen at C-7. It is important to note that C-2, C-4, and C-6 also experience considerable upfield shifts. Because of the similar geometrical constraints imposed by 1,2 epoxides and olefins, we believe that the latter shifts are possibly due to a greater displacement of the equilibrium towards the chair form. A similar situation is found in **11** where C-7 also experiences a pronounced upfield shift (5.1 ppm), only consistent with the predominance of the chair conformation. Furthermore, comparison of the Dreiding models of **8** and **11** allows the observation of the greater steric crowding (**8** has one additional sp^3 carbon in the 5-membered ring) induced in the former upon driving the molecule towards the chair form. We believe that this additional steric compression is the main factor responsible for the greater upfield shift (1.7 ppm) experienced by C-6 in **8** (relative to **1**) compared with that of C-6 (0.7 ppm) in **11** (relative to **2**).

The predominance of the chair conformation in **12** is also clearly established by observing the strong shielding effect on C-1 (7.7 ppm) following the introduction of the 3,4-α-epoxide. The same line of reasoning applies to the other epoxides.

Compounds **3–7** show ^{13}C NMR spectra in complete agreement with the α-orientation of the substituent at C-11, as shown by the constant values observed for C-6 and C-8 when compared with their parent compounds. If it were β-oriented, the substituent at C-11 would induce an upfield shift at C-6 and C-8 due to γ effects.[11]

The importance of the chair form is also stressed by the intense effect experienced by C-1 (−3.9 ppm) in the bromohydrin **16**. As expected, C-6 experiences a relatively small effect (−1.1 ppm) from the equatorially oriented C-4—OH group.

Other changes were also noted in **16**, as well as in some of the previously discussed compounds. For example, C-10 of **16** resonated 2.6 ppm upfield from the corresponding value in **1**, in good agreement with δ-shielding effects already reported.[12]

It has been suggested that the 3-oxoguaianolides **14** and **15** could be C-4 epimers.[8] The observation that their spectra are very similar does not lend support to this idea. Assuming that the conformation of these two compounds is the same, it seems reasonable to argue that the specific upfield shift effect of the C-3 carbonyl group on C-1 would be the same for both compounds. Thus, significant differences of chemical shifts of C-1 could be attributed to specific γ effects caused by the methyl group at C-4. Since the observed values are very similar, we can conclude that **14** and **15** have an identical configuration at C-4. Furthermore, the fact that C-1 in **14** and **15** absorbs at higher field than C-1 in **16** (which has an α substituent at C-4) suggests that the methyl group at C-4 in **14** and **15** is α-oriented. The recent X-ray analysis[13] of **14** fully confirms our conclusions. In addition, the proposed α orientation of the methyl group at C-11 in **15** seems to be well supported by the virtually unchanged chemical shifts of C-6 and C-8 when compared with those of **14**.[11]

Finally, analysis of the spectrum of **18** shows that, apart from the specific deshielding effect of the Cl atom on C-9 and C-8 and its small γ effect on C-1 and C-7 (~−2 ppm), the remainder of the spectrum is almost identical with that of **17**, suggesting the same conformation for both compounds. Unfortunately, we do not have, at the moment, sufficient data to decide on the conformation of guaianolides having an exocyclic methylene group at C-10.

Further work is now in progress to gain a more detailed picture of the contributing factors which determine the ^{13}C NMR spectra of guaianolides.

EXPERIMENTAL

The natural abundance ^{13}C NMR spectra were obtained in the PFT mode on a Varian XL-100-12 spectrometer operating at 25.2 MHz using 10% $CDCl_3$ solutions. An rf tilt angle of 39 μs (90°) and an acquisition time of 0.8 s for a 5 KHz spectral width were generally used for obtaining the spectra. Off-resonance decoupled spectra (SFORD) were obtained by irradiation 200 Hz upfield from TMS in the proton spectrum. The chemical shifts (relative to internal TMS) in the fully decoupled spectra are estimated to be accurate to ±0.1 ppm.

Lactones **1**, **2**, **3**, **8**, **12**, **14**, **15**, **17** and **18** were obtained as previously reported.[5,6,8] The others were prepared from known substances by standard simple procedures. Thus, compounds **4–7** were prepared by reaction of **1** or **2** with $MeOH/Na_2CO_3$ or $Me_2NH/EtOAc$. After purification, the adducts were characterized by the absence of the characteristic pair of doublets at ~δ5.40 and δ6.10 (C-11 CH_2) and the presence of signals at ~δ3.3 and ~δ2.2 for the —OMe and —$N(Me)_2$ groups, respectively, in the ^{1}H NMR spectrum. The reaction of **1** with *m*-chloroperbenzoic acid in $CHCl_3$ at room temperature yields **8**[5] (~60%) together with **9** (~4%) and **10**(~9%). Epoxide **9**, m.p. 123–5°, ^{1}H NMR (100 MHz, $CDCl_3$) δ1.89 (bs, 3, C-10—CH_3), 2.94 and 3.29 (2d, J = 4 Hz, C-4—CH_2), 4.09 (dd, J = 9 and 11 Hz, 1, H-6) 5.51 and 6.23 (2d, J = 3 Hz, C-11—CH_2), 5.58 (m, 1, H-9); *m/e* (rel. intensity): 246 (M, 33), 150 (56), 149 (100), 91 (51). Diepoxide **10**: m.p. 151–3°; ^{1}H NMR (100 MHz, $CDCl_3$) δ1.45 (s, 3, C-10—CH_3), 2.95 and 3.21 (2d, J = 4 Hz, C-4—CH_3), 3.12 (d, J = 4.5 Hz, 1, H-9); 3.78 (dd, J = 9.5 and 10 Hz, 1, H-6), 5.54 and 6.22 (2d, J = 3.5 Hz, C-11—CH_2); *m/e* (rel. intensity) 262 (M, 12), 43 (100). Compounds **11** and **13** were obtained by reaction of **2** with *m*-chloroperbenzoic acid in $CHCl_3$ at −50° in ~62% and ~21% yield, respectively. Epoxide **11**, m.p. 106–9°, ^{1}H NMR (100 MHz, $CDCl_3$) δ1.36 (s, 3, C-10—CH_3), 1.93 (bs, 3, C-4—CH_3), 3.1 (d, J = 4.5 Hz, 1, H-9), 3.73 (dd, J = 9 and 10.5 Hz, 1, H-6), 5.54 (m, 1, H-3), 5.49 and 6.19 (2d, J = 3.5 Hz, C-11—CH_2); *m/e* (rel. intensity) 246 (M, 12), 188 (20), 143 (21), 107 (52), 93 (36), 91 (38), 43 (100), 41 (39). Diepoxide **13**: m.p. 140–5°; ^{1}H NMR (100 MHz, $CDCl_3$) δ1.35 (s, 3, C-10—CH_3), 1.64 (s, 3, C-4—CH_3), 3.05 (d, $J \simeq 5$ Hz, 1, H-9), 3.31 (bs, 1, H-3), 3.64 (dd, J = 9 and 11 Hz, 1, H-6), 5.51 and 6.20 (2d, J = 3.5 Hz, C-11—CH_2); *m/e* (rel. intensity) 262 (M, 1), 247 (10), 111 (96), 97 (22), 95 (24), 55 (27), 53 (32), 43 (100), 41 (31), 39 (31), 27 (26). The bromohydrin **16** was prepared in ~90% yield by reaction of 9,14-dibromoeremanthin-4, 10-ether[5b] with Zn in refluxing MeOH: m.p. 89–91°; ^{1}H NMR (100 MHz, $CDCl_3$) δ1.82 (bs, 3, C-10—CH_3), 2.58 (bs, 1, eliminated by addition of D_2O, C-4—OH), 3.49 and 3.77 (2d, J = 10 Hz, C-4—CH_2), 4.42 (dd, J = 9 and 9 Hz, 1, H-6), 5.44 (m, 1, H-9), 5.50 and 6.20 (2d, J = 3.5 Hz, C-11—CH_2); *m/e* (rel. intensity) 328 (M, 25), 326 (M, 23), 310 (5), 308 (5), 247 (58), 229 (85), 150 (100).

A more detailed account of the experimental procedures used to obtain the above compounds will be published elsewhere.

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