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HIGH-FIELD ^{1}H-NMR SPECTRAL ANALYSIS OF SOME CUCURBITACINS

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ABSTRACT.—^{1}H-nmr spectra of the natural products cucurbitacins A, B, C, D, E, F, I, L, 23,24-dihydrocucurbitacin F, and hexanorcucurbitacin F, as well as three acetylated derivatives, were measured at 360 MHz in pyridine-d_5. Chemical shifts and coupling constants were tabulated. In addition to all of the ring and side-chain protons, it was possible to assign several of the hydroxy group signals of these compounds. These compiled data should be useful for the structure determination of new compounds in this series.

The cucurbitacins are a group of triterpenoids having a 19-(10→9β)-*abeo*-10α-lanost-5-ene (cucurbitane) skeleton (1). Most of the naturally occurring cucurbitacins are tetracyclic and have a double bond between C-5 and C-6, but some representatives of this compound class are known in which formal cyclization between C-16 and C-24 provides an extra ring (e.g., cucurbitacin S); certain cucurbitacin glycosides have also been discovered that are based on the 5β-cucurbitane skeleton (e.g., momordicoside G) (1-3). Biologically, the cucurbitacins exhibit a wide range of activities and are known, for example, to produce increased rat capillary permeability (1), antifertility effects in female mice (4), and preventative action on experimental hepatitis and cirrhosis induced in rats (5). These compounds possess a characteristically bitter taste (1, 6, 7) and have been found to exert a gibberellin-antagonistic activity in rice seedlings (8), and both feeding stimulant (9, 10) and antifeedant (11) effects for insects. In addition, the cucurbitacins have received a great deal of attention because of their cytotoxic (1, 12-17) and anticancer (1, 12-14) effects.

In response to both the widespread occurrence in the plant kingdom of the curcubitacins (1, 16) and their biological activities, there has appeared in the literature a number of papers specifically dealing with analytical observations on these compounds, such as their mass spectrometric (18, 19), low-field ^{1}H-nmr spectroscopic (20), and ^{13}C-nmr spectroscopic (21, 22) parameters. The present communication is intended to contribute to the understanding of the high-field ^{1}H-nmr spectral attributes of the cucurbitacins. We have assigned chemical shifts and coupling constants obtained at 360 MHz for a total of thirteen such compounds, on the basis of both double irradiation experiments and by comparison of our experimental results with appropriate ^{1}H-nmr high-field data obtained previously (2, 15, 17, 22-24).

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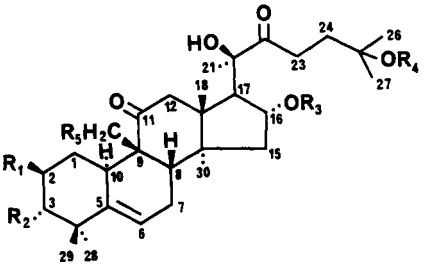
RESULTS AND DISCUSSION

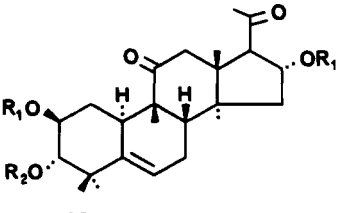
^{1}H-nmr chemical shifts and coupling constants are reported in Tables 1-3 for the following 13 cucurbitacins: cucurbitacin A (**1**); cucurbitacin B (**2**); cucurbitacin C (**3**); cucurbitacin D (**4**); cucurbitacin E (**5**); cucurbitacin F (**6**); cucurbitacin F 2,3,16-triacetate (**7**); 23,24-dihydrocucurbitacin F (**8**); 23,24-dihydrocucurbitacin F 2,3,16-triacetate (**9**); hexanorcucurbitacin F (**10**); hexanorcucurbitacin F 2,3,16-triacetate (**11**); cucurbitacin I (**12**); and cucurbitacin L (**13**). The ^{1}H-nmr observations made here for protons situated in rings A through D and in the side-chain, and for the methyl protons and the hydroxy groups, will be discussed in turn.



	R_1	R_2	R_3	R_4	R_5	Other
1	OH	=O	H	$COCH_3$	OH	$\Delta^{23,24}$
2	OH	=O	H	$COCH_3$	H	$\Delta^{23,24}$
3	H	OH	H	$COCH_3$	OH	$\Delta^{23,24}$
4	OH	=O	H	H	H	$\Delta^{23,24}$
5	OH	=O	H	$COCH_3$	H	$\Delta^{1,2}$; $\Delta^{23,24}$
6	OH	OH	H	H	H	$\Delta^{23,24}$
7	$OCOCH_3$	$OCOCH_3$	$COCH_3$	H	H	$\Delta^{23,24}$
8	OH	OH	H	H	H	—
9	$OCOCH_3$	$OCOCH_3$	$COCH_3$	H	H	—
12	OH	=O	H	H	H	$\Delta^{1,2}$; $\Delta^{23,24}$
13	OH	=O	H	H	H	$\Delta^{1,2}$

The ring-A protons H-1α, H-1β, H-2, H-3, and H-10 in compounds **1-13** could be assigned (Tables 1 and 2) quite readily as a result of comparison of the observed resonances with published high-field ^{1}H-nmr data (15, 17, 22). The H-1α and H-2 protons in compounds **1, 2,** and **4** were somewhat deshielded by the α-hydroxyketone unit present in each case, as compared with the corresponding signals in **6-11**, which all have a 2,3-diol group in ring A. When a diosphenol group was present, as in **5, 12,** and **13**, the H-10 proton appeared about 0.7 ppm further downfield than in the other compounds investigated. Acetylation of the hydroxy groups affixed to C-2 and/or C-3 resulted in a downfield shift of ca. 1.5 ppm for each methine proton.

Chemical shift and coupling constant measurements for the H-6, H-7α, H-7β, H-8, H-12α, H-12β, H-15α, H-15β, H-16, H-17, H-23, and H-24 protons (ring-B, -C, -D, and side-chain protons) of compounds **1-3** (Tables 1 and 2) were in general



10 R_1, R_2=H
11 R_1, R_2=$COCH_3$

TABLE 1. Chemical Shifts Obtained at 360 MHz of Relevant Protons of Cucurbitacins **1-13**[a-c]

Atom	Compound												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
H-1α	2.83, ddd	2.65, ddd	n.o.	2.67, ddd	6.31, d	2.45, ddd	2.30, ddd	2.45, ddd	2.30, ddd	2.40, ddd	2.30, ddd	6.34,d	6.34, d
H-1β	1.59[d]	1.62[d]	n.o.	1.37[d]		1.54[d]	1.50[d]	n.o.	n.o.	1.53, m	1.40, ddd		
H-2	4.86, dm	4.87, dd	n.o.	5.00[d]	—	4.14, m	5.49, ddd	4.14, m	5.47, ddd	4.09, m	5.43, ddd	—	—
H-3	—	—	3.46, dt	—	—	3.43, dd	5.05, d	3.43, dd	5.05, d	3.41, dd	5.03, d	—	—
H-6	5.77, br d	5.67, d	5.80, d	5.04, br d	5.68, br d	5.72, d	5.70, d	5.72, br d	5.70, br d	5.72, br d	5.69, br d	5.67, br s	5.67, br s
H-7α	2.58, dm	2.25, dm	2.62, m	2.27, dm	2.23, dm	2.33, dm	2.28, m	2.34, m	2.24, m	2.24, br dd	2.27, m	2.25, dm	2.22, m
H-7β	2.03, dd	1.95, m	2.0[d]	1.99, dd	n.o.	1.90, m	1.78, dd	1.90, m	1.77, dd	1.97, m	1.79, br d	n.o.	n.o.
H-8	3.29, d	1.95, d	3.27, d	1.92, d	2.01, d	1.93. d	1.88, d	1.93, d	1.88, d	1.88, d	1.84, d	2.00, d	2.01, d
H-10	3.20, br d	3.08, br d	n.o.	3.00, br d	3.76, br s	2.71, br d	2.70, br d	2.72, br d	2.70, br d	2.74, br d	2.73, br d	3.75, br s	3.77, br s
H-12α	3.38, d	3.37, d	3.34, d	3.16, d	3.37, d	3.16, d	2.93. d	3.23, d	2.99, d	3.34, d	3.15, d	3.24, d	3,20, d
H-12β	2.97, d	2.98, d	2.93, d	2.81, d	2.94, d	2.78, d	2.64, d	2.78, d	2.66, d	2.50, d	2.49, d	2.89, d	2.88, d
H-15α	2.10, dd	1.95, m	2.0[d]	n.o.	1.95, dd	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	1.92, dd	1.91, dd
H-15β	1.81, d	1.73, d	1.83, d	1.68, d	1.76, d	1.71, d	1.44, d	1.69, d	1.50, d	1.80, d	1.56,d	1.73, d	1.72, d
H-16	5.12, m	5.10, dd	5.12, m	5.00, m	5.11, dd	4.99, m	5.81, dd	4.90, m	5.88, dd	5.34, m	5.99, m	5.03, dd	4.9[d]
H-17	3.05, d	3.01, d	3.07, d	2.97, d	3.01, d	2.99, d	2.96, d	2.97, d	3.01, d	3.48, d	3.48, d	2.99, d	2.96, d
H-19a	3.45, d	—	3.54, dd	—	—	—	—	—	—	—	—	—	—
H-19b	4.77, d	—	4.84, dd	—	—	—	—	—	—	—	—	—	—
H-23a	7.36, d	7.34, d	7.36, d	7.48, d	7.35, d	7.48, d	7.42, d	3.29, m	3.22, m	—	—	7.48, d	3.32, m
H-23b	—	—	—	—	—	—	—	3.50, m	3.32, m	—	—	—	3.50, m
H-24a	7.41, d	7.40, d	7.40, d	7.55, d	7.40, d	7.56, d	7.54, d	2.23, m	n.o.	—	—	7.58, d	2.21, m
H-24b	—	—	—	—	—	—	—	2.23, m	n.o.	—	—	—	2.21, m
2-OH	6.26, d	6.28, d	—	6.30, br s	n.o.	6.18, d	—	6.18, d	—	6.16, d	—	n.o.	n.o.
3-OH	—	—	6.07, d	—	—	6.37, d	—	6.38, d	—	6.40, d	—	—	—
16-OH	6.13, d	6.18, d	6.08, d	6.32, d	6.22, d	6.26, d	—	6.46, d	—	6.78, d	—	6.40, br s	6.55, d
19-OH	6.58, br s	—	6.43, t	—	—	—	—	—	—	—	—	—	—
20-OH and 25-OH	6.34, s	6.38, s	6.24, s	5.95, s	6.37, s	5.90, s	6.14, s	5.65, s	6.33, s	—	—	5.98, br s	5.83, s
	—	—	—	6.75, s	—	6.73, s	6.76, s	5.76, s	5.75, s	—	—	6.72, br s	5.62, s

[a]Spectra were measured in pyridine-d_5; chemical shifts are expressed in parts per million (ppm), and are referenced to the pyridine peak appearing at δ7.19 ppm.

[b]Multiplicity is designated as follows: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; ddd, doublet of doublet of doublets; m, multiplets, br, broad.

[c]Signal totally obscured by other signals: n.o.

[d]Signal partially obscured by other signals.

TABLE 2. ^{1}H-nmr Coupling Constants Obtained for Compounds **1-13**[a,b]

	Compound												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
$J_{1\alpha,1\beta}$	12.1	12.2	[c]	12.4	—	12.1	12.2	12.4	11.8	12.4	12.0	—	—
$J_{1\alpha,2}$	5.5	5.5	[c]	5.6	—	3.8	4.1	3.5	4.0	4.0	4.2	—	—
$J_{1\alpha,10}$	3.2	3.6	[c]	3.6	2.7	3.9	4.0	3.5	4.0	4.0	4.2	2.6	2.7
$J_{1\beta,2}$	12.5	12.1	[c]	[c]	—	10.0	10.9	[c]	10.4	10.6	12.0	—	—
$J_{1\beta,10}$	13.0	12.3	[c]	13.0	—	12.5	12.6	11.2	10.0	11.5	12.0	—	—
$J_{2,3}$	—	—	6.4	—	—	9.1	10.5	9.3	10.4	9.1	10.1	—	—
$J_{2,OH}$	4.1	5.0	—	[c]	—	5.0	—	3.9	—	3.8	—	[c]	[c]
$J_{3,OH}$	—	—	4.9	—	—	4.7	—	4.4	—	4.2	—	—	—
$J_{6,7\beta}$	5.7	5.4	5.6	7.4	[c]	5.4	5.5	5.5	4.8	5.7	5.8	[c]	[c]
$J_{7\alpha,7\beta}$	20.2	[c]	[c]	18.8	[c]	[c]	19.4	19.0	19.3	19.1	[c]	[c]	[c]
$J_{7\alpha,8}$	8.1	7.6	7.6	7.5	8.5	8.2	8.2	7.7	7.9	7.6	8.3	8.1	8.4
$J_{12,12}$	14.8	14.6	14.8	14.6	14.6	14.6	14.8	14.7	14.6	14.2	14.5	14.5	14.7
$J_{15\alpha,15\beta}$	13.3	12.8	12.8	12.8	12.4	12.8	12.0	14.4	14.6	13.1	14.2	13.0	12.7
$J_{15\alpha,16}$	10.2	11.8	[c]	7.1	10.7	7.0	7.8	8.0	7.8	7.0	7.3	8.0	8.6
$J_{16,17}$	6.8	7.3	7.3	7.0	7.2	7.0	7.8	7.1	7.4	6.5	6.7	7.3	7.1
$J_{16,OH}$	4.3	4.7	5.3	4.6	4.7	4.8	—	4.7	—	4.2	—	[c]	4.3
$J_{19,19}$	9.8	—	10.3	—	—	—	—	—	—	—	—	—	—
$J_{19,OH}$	[c]	—	4.9	—	—	—	—	—	—	—	—	—	—
$J_{23,24}$	16.0	15.8	14.1	15.2	15.8	15.3	15.2	—	—	—	—	15.2	—

[a]Coupling constants were measured in pyridine-d_5; J values are expressed in Hz. These values represent the average of two or more measurements, made directly from coupled spectra or after selective decoupling.

[b]All geminal coupling constants are assumed to be negative (25).

[c]J value not estimated.

agreement with literature values (15, 17, 22). However, it was also seen here that the H-7α and H-8 protons were deshielded by some 0.3 ppm and 1.4 ppm, respectively, in compounds **1** and **3**, where a C-9 hydroxymethyl substituent was present. For the hexanor-compounds **10** and **11**, the H-12β proton was shielded by approximately 0.2 ppm by the C-20 keto group, while the H-17 proton was deshielded by nearly 0.5 ppm. Acetylation of the C-16 hydroxy group in **7, 9,** and **11** resulted in a downfield shift of the H-16 proton by about 1 ppm.

Although all methyl group signals have been typically clearly resolved in previous high-field ^{1}H-nmr investigations on cucurbitacins (2, 15, 17, 22-24), the individual signals have been assigned to date in only one study by Vande Velde and Lavie (22). Their data, however, were obtained at 270 MHz in $CDCl_3$ and so are not totally comparable with our present results determined at 360 MHz in pyridine-d_5. Thus, while Vande Velde and Lavie reported CH_3-18 and CH_3-30 as the two most shielded methyl group signals in all nine cucurbitacins they studied (22), no two upfield methyl group resonances were clearly delineated from the other five or six methyl groups of compounds **1-13** in the present study. For the majority of the cucurbitacins studied here, it can be reasonably expected that the CH_3-18, CH_3-30, and CH_3-19 (where present) groups will resonate upfield of the remaining methyls. However, it is uncertain as to whether the relative order of occurrence of these signals is constant. In the absence of additional ^{1}H-nmr studies, such as those involving nOe measurements or appropriate lanthanide shift-reagents (26, 27), which were precluded because of compound quantity limitations, we therefore have not provided specific cucurbitacin methyl group chemical shift assignments in Table 3.

Where present, the hydroxy groups of compounds **1-13** at C-2, C-3, and C-16 could be readily distinguished, as a result of double resonance experiments (Table 1).

All of these signals appeared as sharp doublets. In compounds with a diosphenol function in ring A (**5, 12,** and **13**), the hydroxy group affixed to C-2 was not observed, possibly due to tautomeric transformation into the diketone form, or deprotonation in pyridine. No differentiation was made between the C-20 and C-25 OH groups (Table 1) or between the various acetate groups in compounds **7, 9,** and **11** (Table 3).

TABLE 3. Chemical Shifts of Methyl and Acetate Protons of Cucurbitacins **1-13**[a,b]

Compound												
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
1.30	1.11	1.26	1.10	1.12	1.21	1.12	1.21	1.12	0.79	0.70	1.12	1.13
1.42	1.19	1.44	1.19	1.21	1.23	1.14	1.24	1.12	1.22	1.12	1.21	1.22
1.50	1.27	1.50	1.30	1.30	1.29	1.16	1.31	1.16	1.31	1.16	1.32	1.35
1.53	1.42	1.53	1.43	1.45	1.43	1.21	1.37	1.22	1.47	1.21	1.43	1.38
1.54	1.50	1.56	1.43	1.51	1.45	1.22	1.37	1.23	1.54	1.22	1.45	1.38
1.67	1.54	1.66	1.46	1.54	1.46	1.50	1.47	1.41	2.14	1.98[c]	1.46	1.46
1.69	1.57	1.71	1.51	1.60	1.50	1.51	1.52	1.41		2.07[c]	1.54	1.56
1.88[c]	1.69	1.87[c]	1.58	1.71	1.60	1.54	1.58	1.53		2.12[d]	1.62	1.60
	1.89[c]			1.89[c]		1.98[c]		1.97[c]		2.13[d]		
						2.08[c]		2.13[c]				
						2.13[c]		2.15[c]				

[a]Experimental conditions were the same as in Table 1.
[b]All signals were observed as singlets and are methyl group resonances unless otherwise indicated.
[c]Acetate signal.
[d]Acetate or methyl signal.

In this study, the effects on the ^{1}H-nmr spectrum of the introduction of various structural elements into the cucurbitacin molecule have been tabulated, such as ring-A α-hydroxyketone, diol, and diosphenol units, and the occurrence of hydrogenation, hydroxylation, and acetylation in rings B through D and in the side-chain. It is therefore hoped that the data presented in Tables 1-3 will prove useful to other investigators in the elucidation of cucurbitacin structures where these types of functionalities occur in novel arrangements.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Tlc was performed with Analtech silica gel GHLF precoated plates (250 μm thick layers). Chromatograms were visualized with 60% H_2SO_4, by heating at 100° for 10 min. Melting points were determined using a Kofler hot-stage microscope. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Uv spectra were obtained with a Beckman model DB-G grating spectrophotometer with MeOH as the solvent, and ir spectra were obtained on a Nicolet model MX-1 Fourier Transform spectrophotometer. ^{1}H-nmr spectra were recorded on a Nicolet NT-360 spectrometer. Low-resolution mass spectra were run on a Varian MAT-112S mass spectrometer, operating at 70 eV, or on a Finnigan model 4500 mass spectrometer, operating at 20 eV.

STANDARD CUCURBITACINS.—Cucurbitacins A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), I (**12**), and L (**13**) were generously donated by other workers in the area. Cucurbitacin F (**6**), 23,24-dihydrocucurbitacin F (**8**), and hexanorcucurbitacin F (**10**) were isolated from the stembark of *Elaeocarpus dolichostylus* Schltr. (Elaeocarpaceae) (17). Cucurbitacin F 2,3,16-triacetate (**7**) and hexanorcucurbitacin F 2,3,16-triacetate (**11**) were obtained from **6** and **10**, respectively, by acetylation, as described previously (17). 23,24-Dihydrocucurbitacin F 2,3,16-triacetate (**9**) was prepared from the parent cucurbitacin **8** using pyridine-Ac_2O. Workup in the usual manner afforded a gum, $[\alpha]^{21}D+3.4°$ (c 0.3, EtOH); uv λ max 210 nm (log ε 4.12); ν max (KBr) 3445, 2970, 1745, 1702, 1370, 1249, 1049, and 1026 cm^{-1}; ^{1}H nmr (360 MHz, pyridine-d_5) see Tables 1-3; ms *m/z* (rel. int.) M^+ missing, 531 (M^+-115, 9), 411 (6), 369 (6), 351 (17), 219 (11), 179 (5), 177 (11), 171 (12), 149 (22), 133 (18), 129 (21), 113 (18), 97 (11), and 43 (100).

The purity of each cucurbitacin used in this study was tested by mp and ms determinations and by analytical tlc in several solvent systems.

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