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^{13}C-NMR STUDIES OF CURCUMENES

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ABSTRACT.—Unambiguous assignment of the ^{13}C-nmr signals of all ring carbons in a series of 32 curcumene derivatives, which include the naturally occurring parent hydrocarbon **1**, curcuphenol [**3**], and xanthorrhizol [**6**], as well as compounds closely related to perezone, 6-hydroxyperezone, and curcuquinone, was done with the aid of ^{13}C-^{1}H long-range spin-spin coupling constants, comparison with model compounds, and, in some cases, by heteronuclear double resonance experiments. The results reveal that while in general the chemical shifts can be reasonably predicted from Substituent Chemical Shift (SCS) values, those molecules having two ortho methoxyl groups show chemical shift variations of up to 11 ppm with respect to predicted values. These anomalies for hindered ortho dimethoxy-curcumenes that are absent in analogous compounds having hydroxyl or acetoxyl substituents are interpreted in terms of steric hindrance to resonance of the *O*-methoxyl group and partial double bond fixation in the benzene ring. Moreover, application of chemical shift variations derived from careful analysis of the ^{13}C-nmr spectra of the series allowed us to ascribe the position of the methoxyl group in 1,2-disubstituted curcumenes that were not prepared by unambiguous procedures.

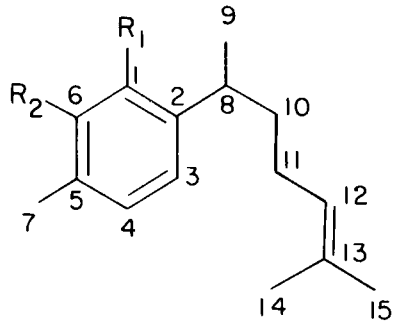
Curcumenes constitute an important class of monocyclic aromatic sesquiterpenoids that are widely distributed in nature. Some simple phenolic representatives of these molecules possessing the skeleton represented by α-curcumene [**1**] (1) are curcuphenol [**3**] (2,3) and curcuhydroquinone [**15**] (3,4), constituents of *Pseudopterogorgia rigida*; xanthorrhizol [**6**] (5–7) isolated from the rhizomes of *Curcuma xanthorrhiza*; and curcuhydroquinone-1-isovalerate [**22**] (8), found in the roots of *Perezia carpholepis* Gray (Compositae). In addition, curcumenes are closely related to sesquiterpenoid benzoquinones like naturally occurring perezone, 6-hydroxyperezone (9), and curcuquinone (3). The structural simplicity of these molecules provides the opportunity to study their ^{13}C-nmr spectra in detail, by making unambiguous assignments, especially for all ring carbons. This in turn allowed us to obtain accurate Substituent Chemical Shift (SCS) values for the methoxyl, acetoxyl, and hydroxyl groups, providing new insight into the successful application of these values to more complex molecules and giving significant improvement in agreement between experimental and predicted ^{13}C shifts.

RESULTS AND DISCUSSION

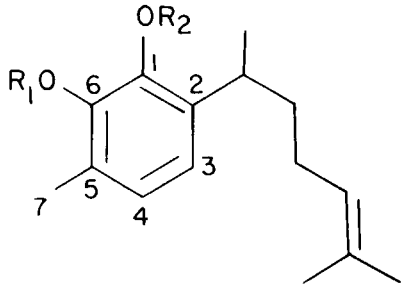
The ^{13}C-nmr spectral assignment of all curcumenes was achieved from ^{1}H-^{13}C long-range spin-spin coupling constants obtained from gated decoupled experiments, as well as chemical shift comparison with model compounds to assign the side chain carbons (C-8 to C-15) (10) (Table 1). Table 2 summarizes the long-range ^{1}H-^{13}C coupling constants for the aromatic ring of all compounds.

The assignment of the aromatic ring of the parent compound, α-curcumene [**1**], was done using the values reported for *p*-cymene (11) as the model and confirmed by long-range couplings that allow differentiation of the C-4/C-6 doublet of quintets (J = 115,5 Hz) and C-1/C-3 doublet of triplets (J = 155,5 Hz).

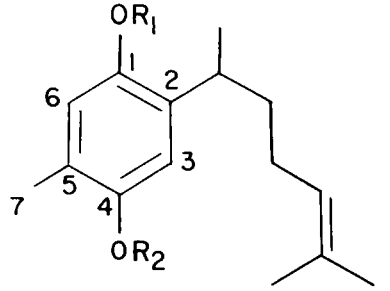
The methodology used for the assignment of the ^{13}C spectra of all compounds is illustrated using *p*-curcuhydroquinone-4-*O*-methyl ether [**20**]. The aromatic methoxyl- and hydroxyl-bearing carbons at 152.08 (C-4) and 146.54 (C-1) are differentiated by chemical shifts and confirmed by long range couplings, since the former is a double quartet. The carbon at position 2 (130.85) appears as a broad signal due to couplings to



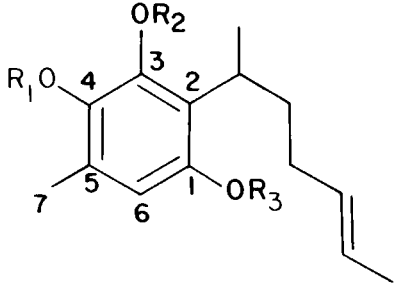
1 $R_1=R_2=H$
2 $R_1=OMe$, $R_2=H$
3 $R_1=OH$, $R_2=H$
4 $R_1=OAc$, $R_2=H$
5 $R_1=H$, $R_2=OMe$
6 $R_1=H$, $R_2=OH$
7 $R_1=H$, $R_2=OAc$



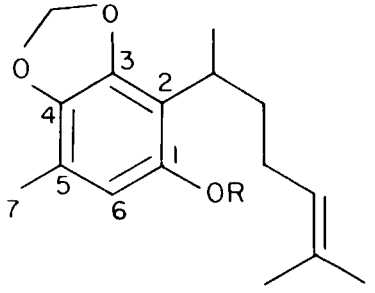
8 $R_1=R_2=Me$
9 $R_1=R_2=H$
10 $R_1=R_2=Ac$
11 $R_1=H$, $R_2=Me$
12 $R_1=Me$, $R_2=H$
13 $R_1=Ac$, $R_2=Me$
14 $R_1=Me$, $R_2=Ac$



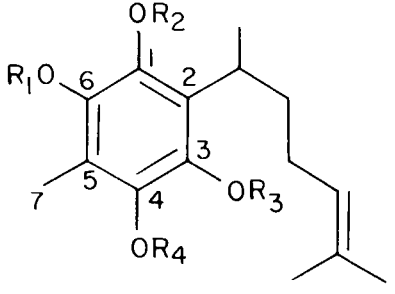
15 $R_1=R_2=H$
16 $R_1=R_2=Me$
17 $R_1=R_2=Ac$
18 $R_1=Me$, $R_2=H$
19 $R_1=Me$, $R_2=Ac$
20 $R_1=H$, $R_2=Me$
21 $R_1=Ac$, $R_2=Me$
22 $R_1=iVal$, $R_2=H$



23 $R_1=R_2=R_3=Me$
24 $R_1=R_2=R_3=Ac$
25 $R_1=R_3=Me$, $R_2=Ac$
26 $R_1=R_3=Ac$, $R_2=Me$



27 R=Ac
28 R=H
29 R=Me



30 $R_1=R_2=R_3=R_4=Me$
31 $R_1=R_2=R_3=R_4=Ac$
32 $R_1=R_3=Ac$, $R_2=R_4=Me$

TABLE 1. ^{13}C Chemical Shifts [a] of Curcumenes at 75.4 MHz.

Compound	Carbon														
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15
1	126.88	144.61	126.88	128.95	135.08	128.95	20.97	39.05	22.49	38.50	26.21	124.61	131.25	17.65	25.70
2	157.10	132.92	126.69	121.27	136.13	111.55	21.33	31.65	21.16	37.31	26.42	125.08	130.84	17.56	25.69
3[c]	152.95	130.16	126.93	121.73	136.48	116.28	20.86	31.56	21.09	37.34	26.16	124.71	131.85	17.65	25.70
4	148.34	136.02	127.02	127.11	136.46	122.81	20.79	32.00	21.12	37.60	26.12	124.44	131.49	17.61	25.70
5	109.07	146.75	118.79	130.41	123.94	157.73	15.77	39.60	22.50	38.54	26.27	124.67	131.32	17.68	25.68
6	113.67	147.25	119.50	130.80	120.99	153.65	15.30	39.09	22.34	38.45	26.21	124.61	131.37	17.67	25.68
7	120.42	146.93	124.68	130.85	127.19	149.44	15.76	38.95	22.18	38.42	26.13	124.48	131.41	17.64	25.68
8	151.38	139.36	121.51	125.63	129.32	150.92	15.64	31.87	21.97	37.86	26.48	124.77	131.22	17.63	25.68
9	141.19	131.25	117.94	122.25	121.26	142.00	15.30	31.83	21.15	37.44	26.11	124.83	132.28	17.69	25.67
10	140.57	138.68	124.05	128.19	129.14	141.30	15.92	32.34	21.00	37.55	26.08	124.31	131.64	17.62	25.67
11	144.62	137.89	117.27	126.48	122.01	146.97	15.30	31.48	22.16	38.08	26.38	124.57	131.40	17.59	25.65
12	146.50	131.79	122.31	121.65	127.33	145.25	15.63	32.39	20.87	37.07	26.32	124.88	131.09	17.59	25.68
13	149.64	139.50	124.04	125.85	128.94	142.85	15.82	31.72	21.92	37.92	26.38	124.58	131.36	17.61	25.65
14	142.13	138.53	121.71	128.43	129.33	150.09	15.67	32.37	21.15	37.58	26.16	124.48	131.45	17.63	25.68
15[b,d]	146.4	131.7	113.5	147.5	121.9	117.9	15.4	31.5	21.0	37.3	26.0	124.5	131.9	17.6	25.6
16[d]	151.01	134.06	109.93	152.02	124.27	114.43	16.04	32.04	21.30	37.41	26.42	124.95	131.02	17.60	25.69
17	145.77	137.90	120.48	147.30	128.42	124.51	15.81	32.11	20.93	37.42	25.97	124.24	131.57	17.58	25.68
18	151.08	135.03	113.99	147.81	121.52	114.62	15.84	31.46	21.18	37.36	26.29	124.92	131.08	17.60	25.68
19	154.71	134.61	120.13	142.80	127.40	112.75	16.17	31.48	20.90	37.04	26.19	124.74	131.08	17.56	25.71
20	146.54	130.85	109.51	152.08	124.89	118.20	15.71	31.91	21.21	37.38	26.14	124.67	131.97	17.69	25.72
21	141.23	136.89	108.07	155.79	125.07	124.09	15.86	32.34	21.21	37.61	26.09	124.34	131.58	17.67	25.75
22[b]	141.0	137.1	113.0	152.2	122.4	123.8	15.5	31.9	21.1	37.5	26.1	124.3	131.2	17.6	25.8
23[e]	154.46	126.91	152.11	145.66	128.89	108.52	15.93	30.36	19.67	35.56	27.19	125.30	130.74	17.56	25.70
24	146.51	129.94	141.66	139.38	129.64	122.49	16.05	31.07	19.02	35.30	26.37	124.17	131.71	17.62	25.74
25	150.44	126.94	136.69	156.34	128.54	108.46	16.16	30.49	19.24	35.24	26.99	124.98	130.86	17.48	25.60
26	146.67	130.68	151.06	140.89	129.58	120.17	15.90	30.82	19.62	35.75	26.74	124.51	131.39	17.60	25.69
27[b]	148.2	114.5	145.4	139.5	115.8	109.0	14.4	30.1	19.4	35.3	26.5	124.7	131.4	17.6	25.6
28	152.98	116.49	145.58	139.91	115.13	105.43	14.78	29.86	19.46	35.36	26.70	125.00	130.90	17.54	25.69
29[b,f]	142.6	119.6	145.2	143.6	116.2	116.3	14.3	30.8	19.0	35.1	26.4	124.3	131.2	17.6	25.6
30	147.70	130.89	147.70	147.41	122.87	147.41	8.61	30.61	20.15	35.92	26.95	124.84	130.30	17.13	25.28
31	139.34	130.98	139.34	139.80	123.99	139.80	10.62	31.46	18.94	35.29	26.36	124.08	131.81	17.60	25.72
32	146.60	131.35	140.74	146.60	123.50	141.12	9.79	30.95	19.61	35.72	26.73	124.41	131.46	17.62	25.72

[a]In ppm from TMS as internal reference. ^{13}C-nmr shifts for substituents are given in the Experimental section.
[b]Measured at 25 MHz.
[c]From McEnroe and Fenical (3).
[d]From Shirley *et al.* (20).
[e]From Pearce *et al.* (21).
[f]From Peutrill and Mirrington (23).

TABLE 2. ^{13}C-^{1}H Spin-Spin Coupling Constants (in Hz) of Curcumenes.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
1	dt 155,5	m	dt 155,5	dr[b] 156,5	m	dr[b] 156,5
2	m	m	dd 154,5	dr[b] 157,6	r[b] 7	dr[b] 154,5
3	d 9	m	dd 153,7	dr[b] 157,6	m	dr[b] 154,5
4	dt 10,5	m	dd 157,6	dr[b] 158,5	m	dr[b] 158,5
5	dt[a] 154,7	m	dt[a] 156,6	dq 155,5	o[d]	m
6	dt[a] 155,6	m	dt[a] 157,6	dq 157,5	r[b] 6	m
7	dt[a] 157,6	td 6,4	ddd 158,9,7	dq 158,4	m	m
8	dd 8,4	m	dd 157,6	dq 158,5	m	dq 7,4
9	dd 9,5	m	dd 157,5	dq 158,5	o[d]	m
10	dd 6,5	m	dd 160,5	dq 160,5	o[d]	dq 8,4
11	m	m	dd 158,5	dq 158,5	o[d]	m
12	dd 9,5	m	dd 157,5	dq 159,5	dq 9,6	m
13	m	d 4	dd 157,5	dq 159,5	r[a,b] 7	dq 8,4
14	dd 10,4	d 4	dd 158,5	dq 160,5	o[d]	dq 8,4
16	m	m	dd 155,5	m	r[b] 6	dq 155,5
17	dd 8,5	m	dd 159,5	dq 4,5	r[a,b] 6	dq 161,5
18	m	m	dd 153,5	m	r[a,b] 6	dq 155,4
19	m	m	dd 157,5	h[a,c] 5	dr[b] 6,2	dq 156,5
20	m	m	dd 153,5	dq 8,4	r[b] 6	dq 154,5
21	dt 10,5	m	dd 154,5	h[a,c] 4	o[d]	dq 158,5
23	m	m	m	dq 4	q 6	dq 155,5
24	dd 6,4	m	d 6	dq 10,5	q 6	dq 163,5
25	m	m	dq 10,5	m	q 6	dq 157,5
26	t[a] 5	m	t 4	dq 162,5	q 6	dq 9,5
28	m	d 7	m	m	q 6	dq 158,5
30	m	m	m	r[b] 4	q 6	r[b] 4
31	d 4	m	d 4	q 4	q 6	q 4
32	d 4	o[d]	d 5	q 4	q 6	q 4

[a]Apparent multiplicity
[b]r = quintet
[c]h = heptet
[d]o = overlapped

the side chain and aromatic proton, while C-5 is a quintet due to couplings to 7-Me and H-6.

In turn, C-6 and C-3 can be distinguished from their multiplicities since C-6 appears at 118.20 as a double (J = 154 Hz) quartet (J = 5 Hz) due to coupling to H-6 and 7-Me, while C-3 at 109.51 ppm is a double doublet (J = 153,5 Hz) due to coupling to H-3 and H-8.

In general, the broad signal due to C-2 is easily distinguished throughout the series, while C-5 is an apparent quintet in compounds **2**, **6**, **13**, and **16–20**, and a quartet in **23–32**. In all other samples C-5 was assigned by chemical shift comparisons. The methyl carbon at position 5 is a quartet of triplets in compounds **2** and **3**, a quartet in **30–32**, and a quartet of doublets in all the remaining compounds. Although in some cases 9-Me exhibits chemical shifts similar to 7-Me, assignment based on multiplicity is straightforward since 9-Me is generally observed as a quartet of quartets.

In some cases, single-frequency off-resonance decoupling experiments (SFORD) of the secondary methyl group in the ^{1}H-nmr region were of utility to assign specific resonances. This allows differentiation between C-6 and C-2 in xanthorrhizol acetate [**7**]; C-1 and C-4 in leucoperezone-1,4-dimethyl ether-3-acetate [**25**] and the C-1/C-3 doublet from the C-4/C-6 quartet in **30**. In the case of leucoperezone trimethyl ether [**23**], comparison with sample **29** containing a methylenedioxy group and further ir-

radiation at 3.78 ppm in the proton spectrum allowed ascription of the doublet at 154.46 to C-1 and the quartet at 145.66 to C-4.

Once the ^{13}C spectra of the series of compounds obtained from unequivocal syntheses had been analyzed in detail, it was possible to assign the 1,2-disubstituted curcumenes **11–14** prepared by monodemethylation of *o*-curcuhydroquinone dimethyl ether [**8**]. Characterization of samples **11–14** was done by comparison of the ^{13}C chemical shifts of C-7, C-8, and C-9 within the series and by long-range spin-spin coupling constants and was further confirmed by heteronuclear SFORD experiments on compound **11**.

The fact that in the 1,6-diacetylated **10**, dihydroxylated **9**, and dimethylated **8** samples C-1 is a double doublet (Table 2) and C-6 appears in **8** and **10** as a doublet of quartets allows assignment of these resonances. For compounds **5** and **6** containing a methoxy or hydroxy group at C-6, the C-9 methyl group absorbs around 22 ppm, while those having the same substituents at C-1 (compounds **2** and **3**) show chemical shifts around 21 ppm.

In turn, the carbon at position 8 shows chemical shifts below 32 ppm in samples containing a methoxyl or hydroxyl group adjacent to the side chain (compounds **2**, **3**, **8**, **9**, **15**, **18**, **20**), compared to compounds **4** and **21**, where C-8 shows chemical shifts above 32 ppm.

Moreover, in the case of *o*-curcuhydroquinone-1-*O*-methyl ether [**11**] irradiation of the methoxy signal in the ^1H-nmr spectrum showed the signal at 144.62 as a double doublet, thus confirming the location of the methoxyl group. Also, the C-8 and C-9 resonances appear at 31.48 and 22.16, in agreement with previous observations. Similar reasoning allows assignment of the double doublet at 146.50 ppm to C-1 in *o*-curcuhydroquinone-6-*O*-methyl ether [**12**] which shows the C-8 and C-9 signals at 32.39 and 20.87 ppm, respectively. On the other hand, *o*-curcuhydroquinone-6-*O*-methyl ether-1-acetate [**14**] shows the signal of the acetate-bearing carbon at 142.13 (C-1) as a double doublet and the C-8 and C-9 signals at 32.37 and 21.15 ppm, respectively. Isomeric *o*-curcuhydroquinone-1-*O*-methyl ether-6-acetate [**13**] shows the C-6 signal as a double quartet at 142.85 ppm and the C-8, C-9 signals at 31.72 and 21.92 ppm, respectively.

Although extensive tabulations of carbon chemical shifts for a large number of aromatic compounds have been published (12), it is known that these empirical parameters allow the prediction of ^{13}C-nmr shifts only in sterically unhindered aromatic systems (13), giving considerable divergence in the case of hindered systems such as ortho disubstituted methoxylated benzenes (14–17). Thus, the series of simple *O*-substituted curcumenes containing up to four oxygens provides a good opportunity for a systematic study of methoxyl, acetoxyl, and hydroxyl groups. The SCS values for all ring positions of the series of curcumenes studied are summarized in Table 3 and were calculated from the data in Table 1. All data are reported in $CDCl_3$, and downfield shifts from the parent compound are positive.

Although it is generally accepted that the induced shifts for the ipso, ortho, meta, and para positions in methoxyl substituted benzenes are 31.40, −14.42, 1.04, and −7.71, respectively (12), observation of Table 3 reveals that variations of up to 11 ppm can be found for the ipso carbon in OMe-disubstituted samples. Thus, *o*-dimethoxylated curcumene **8** gave SCS values of 39.3 and 42.3 ppm, respectively, for the ipso carbon, when compared to the corresponding 1-monomethylated **2** or 6-monomethylated **5** samples. Similar SCS data are obtained on comparison of leucoperezone trimethyl ether [**23**], with *p*-curcuhydroquinone dimethyl ether [**16**], as well as on comparison of 6-hydroxyleucoperezone tetramethyl ether [**30**] with **23** (ipso 42.18 and 38.89 ppm, respectively). As shown in Table 3, all other samples that contain methoxyl groups that

TABLE 3. Substituent Effects of Curcumenes.[a]

Group	Δ[b]	Compounds	*i*	*o* at alkyl	other *o*	*m* at alkyl	other *m*	*p*
		2-1	30.22	−11.69	−17.40	1.05	−0.19	−7.68
OMe	(1-0)	**5-1**	28.78	−11.14	−17.81	2.14	1.46	−8.09
		16-2	30.75	−11.86	−16.76	1.14	2.88	−6.09
		16-5	32.22	−12.69	−15.98	0.33	0.86	−5.71
		8-2	39.37	−6.81	−5.72	6.44	4.36	−5.18
		8-5	42.31	−7.39	−6.81	5.38	2.72	−4.78
OMe	(2-1)	**11-6**	30.95	−9.36	−6.68	1.02	−2.23	4.32
		12-3	26.97	−9.15	−6.45	1.63	−0.08	−4.62
		13-7	29.22	−7.43	−6.59	1.75	−0.64	−5.00
		14-4	27.28	−7.13	−6.21	2.51	1.32	−5.31
		20-3	30.35	−11.59	−17.42	0.69	1.92	−6.41
		21-4	28.68	−11.39	−18.95	0.87	1.28	−7.11
		23-16	42.18	−7.15	−6.36	4.62	3.45	−5.91
OMe	(3-2)	**23-8**	32.95	−12.45	−17.11	−0.43	0.73	−5.26
		25-14	28.73	−11.59	−19.97	−0.79	−5.44	6.25
OMe	(4-3)	**30-23**	38.89	−6.02	−6.76	3.98	1.75	−4.41
		32-26	26.43	−6.08	−5.93	0.67	0.23	−4.46
OAc	(1-0)	**4-1**	21.46	−8.59	−6.14	1.38	0.14	−1.84
		7-1	20.49	−7.89	−6.46	2.32	1.90	−2.20
		17-4	20.19	−8.04	−6.54	1.88	1.70	−2.57
		17-7	21.09	−9.03	−6.34	1.23	0.06	−2.14
		10-4	18.49	−7.32	−7.77	2.66	1.08	−2.97
OAc	(2-1)	**10-7**	20.15	−8.25	−8.14	1.95	0.63	−2.66
		19-2	21.53	−8.73	−6.56	1.69	1.20	−2.39
		13-2	31.30	−7.19	−7.46	6.58	4.58	−2.65
		14-5	33.06	−8.22	−7.64	5.39	2.92	−1.98
		24-17	21.18	−7.96	−7.92	1.22	0.74	−2.02
OAc	(3-2)	**24-10**	22.46	−8.74	−5.70	0.05	1.09	−1.92
		26-13	22.63	−8.82	−5.68	0.64	1.42	−1.96
OAc	(4-3)	**31-24**	17.31	−5.65	−7.17	1.04	0.42	−2.32
		32-26	26.43	−6.08	−5.93	0.67	0.23	−4.46
OH	(1-0)	**3-1**	26.07	−14.45	−12.67	1.40	0.05	−7.22
		6-1	24.70	−14.09	−13.21	2.64	1.85	−7.38
		9-3	25.72	−15.22	−11.76	1.09	0.52	−8.99
		9-6	27.52	−16.01	−11.65	0.27	1.56	−8.55
		15-3	25.77	−14.58	−13.43	1.54	1.62	−6.55
OH	(2-1)	**15-6**	26.90	−15.55	−12.90	0.91	−0.17	−6.15
		11-2	35.42	−14.12	−12.48	4.97	5.21	−9.42
		12-5	37.43	−14.96	−14.48	3.39	3.52	−8.76
		18-2	26.54	−14.61	−12.70	2.11	3.07	−6.02

[a]In ppm for $CDCl_3$ solutions. Downfield shifts are positive.
[b]Δ denotes *O*-substituents present in the compounds being subtracted.

do not occupy adjacent positions show C_{ipso} shifts in agreement with literature values (12). It should be mentioned, however, that similar differences of shifts are observed for samples containing a methoxyl group adjacent to either a hydroxyl or an acetate group, provided the route selected to obtain the SCS values considers introduction of the *O*-substituent into a methoxylated sample (compounds **11–14**).

Also, for methoxylated samples **2**, **5**, **16**, and **23** containing an alkyl group and a hydrogen at the ortho positions, one of the shifts lies at higher field (−17.81 to −17.11) than is calculated using the literature data (−14.4) (12). As has been

suggested in these cases, interference of the methoxyl group with the ortho substituent could favor a conformation in which the methoxyl carbon is turned away from the ortho group, thus shifting the resonance to higher fields (15). For these curcumenes, the ipso carbon exhibits only moderate departures from literature values.

An alternative plausible explanation, which has been suggested for indoles (18) but may also operate in substituted benzenes, involves fixation of double bonds. It has been described that substitution of a methoxyl group in the indole nucleus (18) induces fixation of the double bonds as evidenced by the two distinct values obtained for the ortho positions (−18 and −9.8 ppm). In turn, the mean value for these positions corresponds well to that observed in anisole for the same position (−14.4). Moreover, the ^{13}C-nmr spectra of *p*-substituted methoxybenzenes and phenols, in the solid state, have shown that there exists a nonequivalent distribution of electron densities, which has been attributed to a stereospecific electron delocalization through space interaction of the oxygen lone pair with the π electrons (19). This has been further supported by calculation of electron densities in these compounds. The differences in the SCS values for curcumenes suggest that, even in solution, introduction of a methoxyl group ortho to an alkyl substituent could induce a good degree of fixation of the double bond.

Introduction of two adjacent ortho methoxyl groups considerably alters the main canonical contribution as evidenced by the surprising increase in the positive SCS ipso value and the decrease in the negative ortho value.

The SCS values for the meta carbons seem to be of limited value because they do not show a definite trend, although in general, higher ipso SCS values give rise to higher positive meta values.

The para values vary from −4.4 to −8.1 giving a mean of −5.9, which is relatively far from the published value of −7.71 (12).

Regarding the hydroxyl and acetoxyl groups (Table 3), the data show good agreement with literature reports (12).

To conclude, it is suggested that predictions of ^{13}C shifts that result in agreement with the observed values are obtained if the following values are taken into consideration. First, introduction of a methoxyl, acetoxyl, or hydroxyl group at a position adjacent to a methoxyl group induces an additional C_{ipso} shift of +9 when compared to the popular values of 31.4 (OMe), 22.4 (OAc), and 26.9 (OH). That means that under such circumstances values of 40.4, 31.4, and 35.9, respectively, should be used. Second, for the introduction of a methoxyl group ortho to an alkyl group add 2.4 to the literature value of −14.5 to calculate the substituted C_{ortho} position and subtract 2.6 to obtain the unsubstituted one. This correction seems to apply well for substituents other than alkyl groups. Third, for the introduction of a methoxyl group between an alkyl substituent and either a methoxyl, acetoxyl, or hydroxyl, use a C_{ortho} value of −6.2 instead of −14.4. This value also seems to apply for the introduction of a methoxyl between any two *O*-substituents, as well as for two *t*-butyl substituents (15).

The synthetic pathway for the preparation of curcuphenol [**3**], xanthorrhizol [**6**], as well as the ortho-disubstituted **8–14** and para-disubstituted curcumenes **18–21**, involved metalation (20,21) of the corresponding anisole, followed by addition of commercially available 6-methyl-5-hepten-2-one. Removal of the benzylic tertiary hydroxyl group using Et_3SH/BF_3 (22) yielded the corresponding methyl ethers **2**, **5**, and **8**, which were treated with NaH/EtSH (23) to give **3**, **6**, and the mixture of **9**, **11**, and **12** or subjected to basic hydrolysis to afford **18** and **20**. The corresponding acetate derivatives **4**, **7**, **10**, **13**, **14**, **19**, and **21** were obtained using pyridine/Ac_2O.

The remaining compounds **15–17** and **23–32** were obtained from naturally occurring perezone, *O*-angeloylperezone, 6-hydroxyperezone, or synthetic curcuquinone

available from previous studies (24). The detailed procedure for the preparation of all samples and their spectroscopic characterizations are given in the Experimental section.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The nmr spectra were measured from $CDCl_3$ solutions containing TMS as the internal reference. ^{1}H-nmr measurements were determined on a Varian EM-390 spectrometer and ^{13}C-nmr measurements on either a Varian XL-100A-12FT-16K or an XL-300GS spectrometer. Ir spectra were obtained either on a Nicolet MX-1FT or a Pye Unicam SP3-200 spectrophotometer. Uv spectra were determined on a Pye Unicam SP800 spectrophotometer. Cc was performed on Si gel (70–230 mesh, Merck); tlc was done using Si gel plates (20 × 20 cm, 2 mm thickness, Merck). Mass spectra were recorded on a Hewlett-Packard 5985-A spectrometer at 70 eV.

3-Methylveratrole and 5-bromo-2-methylphenol are commercially available.

α-CURCUMENE [**1**].—Extraction of 7.6 kg of the air-dried roots of *P. carpholepis* with hexane as previously reported (8) gave 326 g of a dark red, oily residue, which was chromatographed on SiO_2 (3 kg). The fractions eluted with hexane were combined to yield 15.3 g of a pale yellow oil. Several successive rechromatographic separations using hexane as eluent provided from the more polar fractions 80 mg of α-curcumene [**1**] as a colorless oil: $[\alpha]_D$ −37.6. The spectroscopic data are in agreement with literature values (1).

CURCUPHENOL METHYL ETHER [**2**].—A solution of 1 g (8.18 mmol) of *m*-methylanisole in 20 ml THF at −10° under N_2 atmosphere was treated dropwise with 5.5 mol *n*-BuLi (1.5 M) and stirred 90 min (20). After cooling to −78°, it was treated with 1.03 g (8.16 mmol) of 6-methyl-5-hepten-2-one. The reaction mixture was warmed to room temperature and treated with 30 ml of a 10% NH_4Cl solution. The mixture was partitioned between H_2O and EtOAc and the organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed using petroleum ether-EtOAc (96:4) to yield 626 mg (31%) of 8-hydroxy-curcuphenol methyl ether: bp 50°/0.7 mm. The spectroscopic data are in agreement with literature values (25); ms *m/z* (rel. int.) $[M]^+$ 248 (2), $[M-H_2O]^+$ 230 (4), 165 (100), 147 (39), 43 (53), 41 (31).

A solution of 500 mg (2.01 mmol) of the above product and Et_3HSi (0.4 ml, 2.50 mmol) in 10 ml CH_2Cl_2 at −78° was treated with 0.4 ml (3.25 mmol) F_3B/Et_2O under N_2 atmosphere and stirred for 30 min (22). The solution was poured into saturated $NaHCO_3$ solution, and the organic layer was extracted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed with petroleum ether-EtOAc (99:1) to yield 421 mg (90%) of **2** (oil): bp 89°/0.3 mm. ^{1}H nmr ($CDCl_3$, 90 MHz) δ 7.08 (1H, d, J = 8 Hz, H-3), 6.76 (1H, broad d, J = 8 Hz, H-4), 6.70 (1H, broad s, H-6), 5.13 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 3.82 (3H, s, OMe), 2.32 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.17 (3H, d, J = 7 Hz, 9-Me); ir (film) 1670 (C=C), 1225 cm^{-1} (C-O); uv (EtOH) λ max 280 (log ε 2.20), 274 (2.20), 220 (2.59), 206 (2.65); ^{13}C nmr ($CDCl_3$) δ 55.20 (OMe).

CURCUPHENOL [**3**].—A solution containing 100 mg (0.430 mmol) of **2**, 100 mg (1.61 mmol) of C_2H_5SH, and 74 mg of NaH (50% in oil) in 7 ml DMS was refluxed for 90 min, followed by addition of a 10% HCl solution (23). The organic layer was extracted with Et_2O, washed with brine, dried (Na_2SO_4), and evaporated. The product was chromatographed using petroleum ether-EtOAc (98:2) to yield 75 mg (80%) of **3** (oil), showing spectroscopic data in agreement with the literature values (3): ms *m/z* (rel. int.) $[M]^+$ 218 (28), $[M+1]^+$ 219 (5), 148 (28), 136 (100), 135 (61), 121 (75), 41 (22).

CURCUPHENOL ACETATE [**4**].—A sample of **3** (50 mg, 0.23 mmol) was treated with Ac_2O (1 ml) and pyridine (1 ml) on a steam bath for 30 min. After workup, the product was chromatographed with petroleum ether-EtOAc (99:1) to yield 54 mg (90%) of **4** (oil), showing data in agreement with literature values (26); ^{13}C nmr ($CDCl_3$) δ 169.48 (C=O), 20.86 (Me).

XANTHORRHIZOL METHYL ETHER [**5**].—A solution of 5-bromo-2-methylphenol (300 mg, 1.60 mmol) (27) in 50 ml anhydrous Me_2CO was treated with 254 mg K_2CO_3 and 0.1 ml Me_2SO_4 and refluxed for 5 h. After addition of H_2O, the organic phase was extracted with EtOAc, washed with 10% NaOH and H_2O, dried (Na_2SO_4), and concentrated. The residue was chromatographed using hexane to yield 258 mg (80%) of 5-bromo-2-methylanisole [lit. (28) bp 108°/5 mm].

A mixture containing metallic lithium (26 mg, 3.73 mmol) and the above product (300 mg, 1.49 mmol) in 10 ml of THF was treated with 6-methyl-5-hepten-2-one (226 mg, 1.79 mmol) and stirred overnight at room temperature (21). After addition of 10% NH_4Cl solution, the organic phase was extracted with EtOAc, washed with H_2O, dried (Na_2SO_4), and evaporated. The oily residue was chromatographed with petroleum ether-EtOAc (96:4) to yield 189 mg (51%) of 8-hydroxy-xanthorrhizol methyl ether (oil). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 7.15 (1H, d, J = 8 Hz, H-4), 7.02 (1H, d, J = 2 Hz, H-1), 6.90 (1H, dd,

J = 8, 2 Hz, H-3), 5.13 (1H, t with further unresolved couplings, J = 6 Hz, H-12), 3.83 (3H, s, OMe), 2.20 (3H, s, 7-Me), 1.65 (3H, broad s, 15-Me), 1.53 (3H, s, 9-Me), 1.52 (3H, broad s, 14-Me); ir 3432 (OH) 1580, 1513 (C=C), 1253 cm^{-1} (C-O); uv (EtOH) λ max 280 (log ε 3.84), 273 (3.88), 223 (4.28) nm; ms *m/z* (rel. int.) $[M]^+$ 248 (6), $[M+1]^+$ 249 (2), $[M-H_2O]^+$ 230 (4), 166 (15), 155 (33), 43 (100).

Elimination of the tertiary hydroxyl group in the above compound (150 mg, 0.60 mmol) was done as in the preparation of **2** to yield 131 mg (94%) of **5** (oil) after chromatography with hexane-EtOAc (99:1). The compound has spectroscopic data in agreement with literature values (6). ^{13}C nmr ($CDCl_3$) δ 55.24; ms *m/z* (rel. int.) $[M]^+$ 232 (36), $[M+1]^+$ 233 (6), 150 (100), 135 (59), 91 (47), 41 (42).

XANTHORRHIZOL [**6**].—*Treatment of* **5** *(100 mg, 0.43 mmol) using the procedure described for* the preparation of **3** yielded 80 mg (85%) of **6** (oil) after chromatography with hexane-EtOAc (98:2). The spectroscopic data are in agreement with literature values (6).

XANTHORRHIZOL ACETATE [**7**].—Treatment of **6** (80 mg, 0.33 mmol) using the procedure described for the preparation of **4** yielded 80 mg (90%) of **7** (oil) after chromatography with hexane-EtOAc (98:2). ^1H nmr ($CDCl_3$, 90 MHz) δ 7.17 (1H, d, J = 8 Hz, H-4), 6.97 (1H, d, J = 8 Hz, H-3), 6.83 (1H, s, H-1), 5.09 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 2.30 (3H, s, OAc), 2.13 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.20 (3H, d, J = 6 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 168.99 (C=O), 20.71 (Me); ir (film) 1754 (C=O), 1224 cm^{-1} (C-O); uv (EtOH), λ max 273 (log ε 4.00), 264 (3.89), 259 (3.79), 222 (3.63) nm; ms *m/z* (rel. int.) $[M]^+$ 260 (11), $[M+1]^+$ 261 (3), 148 (54), 136 (100), 135 (57), 43 (97), 41 (52).

o-CURCUHYDROQUINONE DIMETHYL ETHER [**8**].—A solution of 1 *g* (6.57 mmol) of 3-methyl-1,2-dimethoxybenzene, 4.4 ml of *n*-BuLi (1.5 M), and 1 ml N,N,N′,N′-tetramethylethylene diamine (TMEDA) in 20 ml of cyclohexane was stirred 10 h, followed by addition of 0.8 ml of 6-methyl-5-hepten-2-one. After workup and chromatography with hexane-EtOAc (96:4), 731 mg (40%) of 8-hydroxy-*o*-curcuhydroquinone-dimethyl ether (oil) was obtained. ^1H nmr ($CDCl_3$, 90 MHz) δ 7.04 and 6.88 (1H each, J_{AB} = 9 Hz, H-3,4), 3.93 (3H, s, OMe), 3.77 (3H, s, OMe), 2.23 (3H, s, 7-Me), 1.63 (3H, s, 15-Me), 1.52 (3H, s, 9-Me), 1.50 (3H, s, 14-Me); ir (film) 3495 (OH), 1601 (C=C), 1273 cm^{-1} (C-O); uv (EtOH) λ max 272 (log ε 3.60), 220 (3.91), 212 (3.91) nm; ms *m/z* (rel. int.) $[M]^+$ 278 (6), $[M-H_2O]^+$ 260 (6), 195 (100), 91 (19), 43 (60), 41 (45).

Elimination of the tertiary hydroxyl group from the above compound (500 mg, 1.79 mmol) was done using the procedure described for the preparation of **2**. This yielded, after chromatography with hexane-EtOAc (99:1), 330 mg (70%) of **8** (oil). ^1H nmr ($CDCl_3$, 90 MHz) δ 6.97 and 6.83 (AB, J_{AB} = 6 Hz, H-3,4), 5.15 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 3.85 (6H, s, 2 × OMe), 2.23 (3H, s, 7-Me), 1.68 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.17 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 60.58 and 59.85 (OMe); ir (film) 1460 (C=C), 1067 and 1027 cm^{-1} (C-O); uv (EtOH) λ max 267 (log ε 2.7), 220 (4.0) nm; ms *m/z* (rel. int.) $[M]^+$ 262 (21), $[M+1]^+$ 263 (5), 179 (100), 149 (44), 91 (37), 43 (97), 41 (54).

DEMETHYLATION OF **8**.—The reaction was performed using 100 mg (0.38 mmol) of **8** and the procedure described for the preparation of **3**. This yielded 51 mg (54%) of the mixture of **11** and **12** after chromatography using hexane-EtOAc (98:2) followed by 9 mg (10%) of **9** (oil). Compounds **11** (oil) and **12** (oil) were separated by tlc developing three consecutive times with petroleum ether-EtOAc (90:10).

o-CURCUHYDROQUINONE [**9**].—^1H nmr ($CDCl_3$, 90 MHz) δ 6.80 and 6.67 (AB, J_{AB} = 9, H-3,4), 5.20 (1H, t with further unresolved coupling, J_t = 7 Hz), 2.23 (3H, s, 7-Me), 1.70 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.30 (3H, d, J = 7 Hz, 9-Me); ir (film) 3468 (OH), 1586 cm^{-1} (C-C); uv (EtOH) λ max 275 (log ε 2.94) nm; ms *m/z* (rel. int.) $[M]^+$ 234 (28), $[M+1]^+$ 235 (6), 152 (26), 151 (100), 137 (28), 41 (27).

o-CURCUHYDROQUINONE DIACETATE [**10**].—Compound **10** was prepared from 50 mg (0.21 mmol) of **9** using the procedure described for the preparation of **4**. This yielded 66 mg (98%) of **10** (oil) after chromatography with petroleum ether-EtOAc (98:2). ^1H nmr ($CDCl_3$, 90 MHz) δ 7.11 (2H, s, H-3,4), 5.10 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 2.32 (6H, s, 2 × OAc), 2.17 (3H, s, 7-Me), 1.68 (3H, broad s, 15-Me), 1.56 (3H, broad s, 14-Me), 1.18 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 168.24 and 167.84 (C=O), 21.00 and 20.28 (Me); ir (film) 1740 (C=O); uv (EtOH) λ max 267 (sh log ε 2.37), 257 (sh 2.50), 212 (3.89) nm.

o-CURCUHYDROQUINONE-1-*O*-METHYL ETHER [**11**].—^1H nmr ($CDCl_3$, 90 MHz) δ 6.90 and 6.67 (AB, J_{AB} = 9, H-3,4), 5.20 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 3.79 (3H, s, OMe), 2.20 (3H, s, 7-Me), 1.63 (3H, s, 15-Me), 1.52 (3H, s, 14-Me), 1.23 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 61.55 (OMe); ir (film) 3442 (OH), 1501 (C=C), 1276, 1205 cm^{-1} (C-O); uv (EtOH) λ max 278 (log ε 3.69), 274 (3.69) nm.

o-CURCUHYDROQUINONE-6-*O*-METHYL ETHER [**12**].—^{1}H nmr ($CDCl_3$, 90 MHz) δ 6.89 and 6.67 (AB, J_{AB} = 8 Hz, H-3,4), 5.17 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 3.82 (3H, s, OMe), 2.29 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.55 (3H, s, 14-Me), 1.22 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 60.49 (OMe); ir (film) 3500 (OH), 1056, 1018 cm^{-1} (C-O); uv (EtOH) λ max 222 (log ε 3.90), 275 (3.45) nm; ms *m/z* (rel. int.) $[M]^+$ 248 (30), $[M+1]^+$ 249 (4), 178 (35), 165 (100), 151 (35), 41 (79).

o-CURCUHYDROQUINONE-1-*O*-METHYL ETHER-6-ACETATE [**13**].—Compound **13** was prepared from 100 mg (0.40 mmol) of **11** using the procedure described for the preparation of **4**. This yielded 110 mg (95%) of **13** (oil) after chromatography with petroleum ether-EtOAc (99:1). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 7.02 (2H, s, H-3,4), 5.13 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 3.78 (3H, s, OMe), 2.37 (3H, s, OAc), 2.17 (3H, s, 7-Me), 1.68 (3H, s, 15-Me), 1.55 (3H, s, 14-Me), 1.20 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 168.56 (C=O), 20.50 (Me), 61.31 (OMe); ir (film) 1752 cm^{-1} (C=O); uv (EtOH) λ max 268 (log ε 2.19), 222 (3.79) nm.

o-CURCUHYDROQUINONE-6-*O*-METHYL ETHER-1-ACETATE [**14**].—Compound **14** was prepared from 100 mg of **12** using the procedure described for the preparation of **4**. This afforded 105 mg (90%) after chromatography using petroleum ether-EtOAc (99:1). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 7.04 and 6.90 (2H, J_{AB} = 8 Hz, H-3,4), 5.10 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 3.77 (3H, s, OMe), 2.33 (3H, s, OAc), 2.29 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.16 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 168.85 (C=O), 20.49 (Me), 60.34 (OMe); ir (film) 1757 cm^{-1} (C=O); uv (EtOH) λ max 267 (log ε 3.05), 221 (3.79) nm.

p-CURCUHYDROQUINONE [**15**].—This compound was available from previous studies (4).

p-CURCUHYDROQUINONE DIMETHYL ETHER [**16**].—Compound **16** was available from previous studies (4). ^{13}C nmr ($CDCl_3$) δ 56.35 and 56.13.

p-CURCUHYDROQUINONE DIACETATE [**17**].—A solution of 100 mg (0.43 mmol) of curcuquinone (4), Ac_2O (2 ml), NaOAc (105 mg, 1.29 mmol), and Zn (220 mg, 3.37) was refluxed 3 h, filtered, and evaporated. The mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with 10% $NaHCO_3$ solution and H_2O, dried (Na_2SO_4), filtered, and evaporated to yield 110 mg (80%) of **17**. ^{1}H nmr ($CDCl_3$, 90 MHz) δ 6.83 (2H, s, H-3,6), 5.04 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 2.24 (6H, s, 2 × OAc), 2.11 (3H, s, 7-Me), 1.65 (3H, s, 15-Me), 1.51 (3H, s, 14-Me), 1.16 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 169.32 and 168.88 (C=O), 20.74 and 20.65 (Me); ir (film) 1775 (C=O), 1210 and 1160 cm^{-1} (C-O); uv (EtOH) λ max 272 (log ε 2.86), 267 (2.85), 264 (sh, 2.83), 212 (2.79).

p-CURCUHYDROQUINONE-1-*O*-METHYL ETHER [**18**].—A solution of 1 g (4.60 mmol) of 5-bromo-4-methoxy-2-methylphenol (29) in 50 ml of Me_2CO, containing 1.3 g (9.2 mmol) of anhydrous K_2CO_3 and 740 mg (9.20 mmol) of $ClCH_2OCH_3$ was stirred for 12 h under N_2 atmosphere at room temperature. The solvent was evaporated, the residue partitioned between EtOAc and H_2O, and the organic layer washed with brine and H_2O, dried (Na_2SO_4) and evaporated to afford 1.1 g (90%) of 5-bromo-4-methoxy-2-methylphenol methoxymethyl ether after chromatography with petroleum ether-EtOAc (99:1). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 7.03 (2H, s, H-3,6), 5.20 (2H, s, O-CH_2-O), 3.83 (3H, s, OMe), 3.54 (3H, s, OMe), 2.17 (3H, s, 7-Me); ir (film) 1509 (C=C), 1221 (C-O) cm^{-1}; uv (EtOH) λ max 224 (log ε 4.0), 291 (3.65).

The above compound (200 mg, 0.77 mmol) was reacted with 6-methyl-5-hepten-2-one using the procedure described for the preparation of the corresponding curcuphenol derivative. The product was chromatographed with hexane-EtOAc (98:2) to afford 146 mg (62%) of 8-hydroxy-*p*-curcuhydroquinone-1-*O*-methyl ether methoxymethyl ether. ^{1}H nmr ($CDCl_3$, 90 MHz) δ 7.10 (1H, s, H-3), 6.77 (1H, s, H-6), 5.13 (2H, s, O-CH_2-O), 5.13 (1H, H-12), 3.80 (3H, s, OMe), 3.46 (3H, s, OMe), 2.22 (3H, s, 7-Me), 1.65 (3H, s, 15-Me), 1.50 (3H, s, 9-Me), 1.48 (3H, s, 14-Me); ir (film) 3461 (OH), 1501 (C=C), 1209 cm^{-1} (C-O); uv (EtOH) λ 286 (log ε 3.54), 226 (3.83) nm; ms *m/z* (rel. int.) $[M]^+$ 308 (14), $[M+1]^+$ 309 (3), 225 (100), 193 (62), 165 (23), 45 (71).

The tertiary alcohol in the above compound (200 mg, 0.65 mmol) was eliminated using the procedure described for the preparation of **2**. This yielded, after chromatography using hexane-EtOAc (99:1), 169 mg (89%) of *p*-curcuhydroquinone-1-*O*-methyl ether methoxymethyl ether. ^{1}H nmr ($CDCl_3$, 90 MHz) δ 6.93 (1H, s, H-3), 6.72 (1H, s, H-6), 5.13 (3H, OCH_2O, H-12), 3.80 (3H, s, OMe), 3.53 (3H, s, OMe), 2.26 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.16 (3H, d, J = 7 Hz, 9-Me); ir (film) 1503 (C=C), 1211 (C-O); uv (EtOH) λ max 287 (log ε 3.50), 222 (3.81), 213 (3.78) nm; ms *m/z* (rel. int.) $[M]^+$ 292 (39), $[M+1]^+$ 293 (8), 209 (25), 165 (30), 45 (100).

A solution of 300 mg (1.02 mmol) of the above compound in 15 ml HOAc (2 N) was heated during 40 h at 90°. The mixture was partitioned between EtOAc and H_2O, and the organic phase was washed

($NaHCO_3$ and H_2O), dried (Na_2SO_4), and evaporated. The residue was chromatographed with petroleum ether-EtOAc (98:2) to afford 105 mg of **18** (oil) (41%). ^1H nmr ($CDCl_3$, 90 MHz) δ 6.62 and 6.58 (1H each, s, H-3,6), 5.04 (1H, t with further unresolved couplings, $J_t = 6$ Hz, H-12), 3.76 (3H, s, OMe), 2.23 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.13 (3H, d, $J = 7$ Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 56.65 (OMe), ir (film) 3387 (OH), 1463 and 1408 (C=C), 1199 (C-O) cm^{-1}; uv (EtOH) λ max 292 (log ε 3.68), 221 (3.87), 211 (3.79) nm.

p-CURCUHYDROQUINONE-1-*O*-METHYL ETHER ACETATE [**19**].—Acetylation of **18** (100 mg) was performed using the procedure described for the preparation of **4**. It gave 104 mg (89%) of **19** (oil) after chromatography with hexane-EtOAc (99:1). ^1H nmr ($CDCl_3$, 90 MHz) δ 6.83 (1H, s, H-3), 6.72 (1H, s, H-6), 5.13 (1H, t with further unresolved couplings, $J_t = 6$ Hz, H-12), 3.83 (3H, s, OMe), 2.31 (3H, s, OAc), 2.16 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.55 (3H, s 14-Me), 1.17 (3H, d, $J = 7$ Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 169.50 (C=O), 20.67 (Me), 55.59 (OMe); ir (film) 1762 (C=O), 1215 and 1195 (C-O) cm^{-1}; uv (EtOH) λ max 285 (log ε 3.40), 278 (3.43), 219 (3.77) nm; ms *m/z* (rel. int.) $[M]^+$ 290 (18), $[M + 1]^+$ 291 (4), 248 (47), 165 (73), 43 (100), 41 (51).

p-CURCUHYDROQUINONE-4-*O*-METHYL ETHER [**20**].—Compound **20** was prepared from 2-bromo-4-methoxy-5-methylphenol (30) using the procedure described for the preparation of the corresponding derivative in the synthesis of **18**. This afforded 1 g (85%) of 2-bromo-4-methoxyl-5-methyl phenol methoxymethyl ether. ^1H nmr ($CDCl_3$, 90 MHz) δ 7.33 (1H, s, H-6), 6.80 (1H, s, H-3), 5.12 (2H, s, O-CH_2-O), 3.83 (3H, s, OMe), 3.48 (3H, s, OMe), 2.22 (3H, s, 7-Me); ir (film) 1250 cm^{-1} (C-O); uv (EtOH) λ max 291 (log ε 3.56), 225 (3.87) nm.

The above product (200 mg, 0.77 mmol) was treated as described for the preparation of the corresponding analogue of **18**. The alcohol was chromatographed using hexane-EtOAc (98:2) to yield 115 mg (49%) of 8-hydroxy-*p*-curcuhydroquinone-4-*O*-methyl ether methoxymethyl ether. ^1H nmr ($CDCl_3$, 90 MHz) δ 6.83 (2H, s, H-3,6), 5.08 (2H, s, OCH_2O), 5.03 (1H, t with further unresolved couplings, $J_t = 6$ Hz, H-12), 3.75 (3H, s, OMe), 3.45 (3H, s, OMe), 2.15 (3H, s, 7-Me), 1.63 (3H, s, 15-Me), 1.50 (3H, s, 9-Me), 1.50 (3H, s, 14-Me); ir (film) 3500 (OH); uv (EtOH) λ max 286 (log ε 3.60), 227 (3.90) nm; ms *m/z* (rel. int.) $[M]^+$ 308 (13), $[M + 1]^+$ 309 (3), 178 (33), 151 (77), 45 (100), 41 (22).

Elimination of the tertiary alcohol in the above compound (200 mg, 0.65 mmol) was performed using the procedure described for the preparation of **2**. This yielded 142 mg (75%) of *p*-curcuhydroquinone-4-*O*-methyl ether methoxymethyl ether after chromatography with hexane-EtOAc (99:1). ^1H nmr ($CDCl_3$, 90 MHz) δ 6.90 (1H, s, H-6), 6.67 (1H, s, H-3), 5.03 (3H, OCH_2O, H-12), 3.72 (3H, s, OMe), 3.42 (3H, s, OMe), 2.10 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.55 (3H, s, 14-Me), 1.20 (3H, d, $J = 7$ Hz, 9-Me); ir (film) 1503 (C=C), 1200 (C-O) cm^{-1}; uv (EtOH) λ max 287 (log ε 3.55), 223 (3.84) nm; ms *m/z* (rel. int.) $[M]^+$ 292 (18), $[M + 1]^+$ 293 (5), 165 (100), 45 (27).

Removal of the protecting group in the above compound (300 mg) was achieved using the procedure described for the preparation of **18**. This yielded, after chromatography with petroleum ether-EtOAc (98:2), 100 mg (39%) of **20** (oil). ^1H nmr ($CDCl_3$, 90 MHz) δ 6.64 (1H, s, H-6), 6.58 (1H, s, H-3), 5.16 (1H, t with further unresolved couplings, $J_t = 6$ Hz, H-12), 3.83 (3H, s, OMe), 2.20 (3H, s, 7-Me), 1.72 (3H, s, 15-Me), 1.53 (3H, s, 14-Me), 1.22 (3H, d, $J = 7$ Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 56.19 (OMe): ir (film) 3417 (OH), 1199 and 1173 (C-O) cm^{-1}; uv (EtOH) λ max 2.92 (log ε 3.65), 222 (3.82) nm.

p-CURCUHYDROQUINONE-4-*O*-METHYL ETHER ACETATE [**21**].—Compound **21** was prepared from **20** (103 mg) using the procedure described for the preparation of **4**. This yielded 103 mg (88%) of **21** (oil) after chromatography using hexane-EtOAc (99:1). ^1H nmr ($CDCl_3$, 90 MHz) δ 6.82 (1H, s, H-6), 6.72 (1H, s, H-3), 5.12 (1H, t with further unresolved couplings, $J_t = 7$ Hz, H-12), 3.85 (3H, s, OMe), 2.32 (3H, s, OAc), 2.20 (3H, s, 7-Me), 1.69 (3H, s, 15-Me), 1.57 (3H, s, 14-Me), 1.18 (3H, d, $J = 6$ Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 170.11 (C=O), 2.84 (Me), 55.54 (OMe); ir (film) 1760 (C=O), 1195 and 1170 (C-O) cm^{-1}; uv (EtOH) λ max 284 (log ε 3.42), 177 (3.52), 223 (3.88) nm.

p-CURCUHYDROQUINONE-1-ISOVALERATE [**22**].—Compound **22** was available from previous studies (8).

LEUCOPEREZONE TRIMETHYL ETHER [**23**].—A solution of 250 mg (0.83 mmol) of *O*-methylperezone (10) in 10 ml of $CHCl_3$ was treated with 1.74 g of Zn and 3 ml HCl (80%) until the solution decolorized. The solution was filtered, and the $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), filtered, and evaporated. The residue (139 mg) was dissolved in Me_2CO, treated with 250 mg (1.88 mmol) of K_2CO_3 and 0.5 ml (5.28 mmol) of Me_2SO_4, and refluxed 1 h. The solution was filtered and the solvent evaporated. The residue was partitioned between EtOAc and H_2O and the organic layer washed with 10% NaOH and H_2O, dried (Na_2SO_4), and evaporated. The product was chromatographed using hexane to yield 260 mg (95%) of **23** (oil) showing spectroscopic data in agreement with previous reports (31).

LEUCOPEREZONE TRIACETATE [**24**].—Compound **24** was available from previous studies (32); ms *m/z* (rel. int.) $[M]^+$ 376 (9), $[M+1]^+$ 377 (2), 292 (32), 250 (100), 167 (70), 166 (35), 43 (77).

LEUCOPEREZONE-1,4-DIMETHYL ETHER-3-ACETATE [**25**].—A solution of 250 mg (0.76 mmol) of *O*-angeloylperezone (24) in 20 ml of EtOAc was stirred with Pd/C (25 mg) at room temperature and normal pressure until the solution decolorized (5 min). The catalyst was filtered, the solvent was evaporated, and the residue was treated with 0.2 ml (2.1 mmol) of Me_2SO_4 and 210 mg (1.51 mmol) of K_2CO_3 at reflux for 30 min. After workup, 190 mg of the ester was obtained which was hydrolyzed using KOH (190 mg) in 2 ml H_2O at reflux for 30 min. The mixture was partitioned between EtOAc and H_2O, the organic layer washed (H_2O), dried (Na_2SO_4), and evaporated. The residue was chromatographed on a Si gel plate developing with C_6H_6 to yield 95 mg (65%) of the product, which was acetylated with pyridine (1 ml) and HOAc (1 ml), heating on a steam bath for 3 h. Extraction with EtOAc/H_2O yielded, after workup and chromatography with hexane-$CHCl_3$ (8:2), 65 mg (60%) of **25** (oil). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 6.47 (1H, s, H-6), 5.10 (1H, t with additional unresolved couplings, J_t = 7 Hz, H-12), 3.77 and 3.73 (3H each, 2 s, 2 OMe), 2.32 (3H, s, OAc), 2.12 (3H, s, 7-Me), 1.63 (3H, broad s, 15-Me), 1.53 (3H, broad s, 14-Me), 1.23 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 168.98 (C=O), 20.42 (Me), 61.24 and 55.43 (OMe); ir (film) 1780 (C=O), 1230 (C-O) cm^{-1}; uv (EtOH) λ max 279 (log ε 4.02), 274 (sh, 4.00), 220 (sh, 4.07), 209 (4.28) nm.

LEUCOPEREZONE-3-METHYL ETHER-1,4-DIACETATE [**26**].—*O*-Methylperezone (10) (250 mg, 0.95 mmol) was treated with Ac_2O (4 ml) and NaOAc (250 mg) in the presence of Zn (0.5 g, 7.65 mmol). Workup as in **17** gave a residue which was chromatographed with hexane-$CHCl_3$ (7:3) to yield 636 mg (57%) of **26** (oil). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 6.73 (1H, s, H-6), 5.13 (1H, t with additional unresolved couplings, J_t = 7 Hz, H-12), 3.78 (3H, s, OMe), 2.33 and 2.27 (3H each, 2 s, 2 × OAc), 2.11 (3H, s, 7-Me), 1.67 (3H, broad s, 15-Me), 1.55 (3H, broad s, 14-Me), 1.25 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 169.24 and 168.27 (C=O), 21.02 and 20.40 (Me), 61.27 (OMe); ir (film) 1770 (C=O) and 1195 (C-O) cm^{-1}; uv (EtOH) λ max 265 (log ε 2.51), 219 (sh, 4.01), and 212 (4.08) nm.

METHYLENEDIOXYLEUCOPEREZONE ACETATE [**27**].—Compound **24** (1 g, 2.66 mmol) (33) in 25 ml DMSO was treated with NaOH (0.64 g), CH_2Cl_2 (1 ml), and $NaHCO_3$ (0.276 g) under N_2 atmosphere and heated for 90 min under reflux, adding 1 ml of CH_2Cl_2 at intervals of 20 min (33). The solvent was evaporated, the mixture was partitioned between EtOAc and H_2O, and the organic layer was washed (H_2O), dried (Na_2SO_4), and evaporated to yield 40 mg (5%) of **27** (oil) after chromatography using petroleum ether-EtOAc (98:2). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 6.21 (1H, s, H-6), 5.89 (2H, s, OCH_2O), 5.03 (1H, t with further unresolved couplings, J_t = 7 Hz, H-12), 2.21 (3H, s, OAc), 2.16 (3H, s, 7-Me), 1.64 (3H, s, 15-Me), 1.52 (3H, s, 14-Me), 1.18 (3H, d, J = 6 Hz, 9-Me).

METHYLENEDIOXYLEUCOPEREZONE [**28**].—A solution of 200 mg (0.66 mmol) of **27** in 10 ml of THF was treated with 50 mg (1.32 mmol) of $LiAlH_4$ at 0° stirring for 30 min. After addition of H_2O, the residue was filtered, dried (Na_2SO_4), and evaporated to yield 155 mg (90%) of **28** (oil). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 5.94 (1H, s, H-6), 5.80 (2H, s, OCH_2O), 5.03 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 4.26 (1H, broad s, OH), 2.08 (1H, s, 7-Me), 1.64 (3H, s, 15-Me), 1.49 (3H, s, 14-Me), 1.23 (3H, d, J = 6 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 56.51 (OMe), 100.30 (O-CH_2-O).

METHYLENEDIOXYLEUCOPEREZONE METHYL ETHER [**29**].—A solution of 200 mg (0.76 mmol) of **28** in 25 ml of Me_2CO containing 0.15 ml (1.52 mmol) of Me_2SO_4 and 157.5 mg (0.14 mmol) of K_2CO_3 was refluxed for 5 h. After workup as in **23**, the residue was chromatographed using hexane-EtOAc (19:1) to yield 160 mg (80%) of **29** (oil). Uv λ max (EtOH) 290 (log ε 3.57), 239 (3.41), 222 (3.92) nm; remaining spectroscopic data have been described (34); ms *m/z* (rel. int.) $[M]^+$ 276 (46), $[M+1]^+$ 277 (11), 193 (100), 166 (86), 41 (27).

6-HYDROXYLEUCOPEREZONE TETRAMETHYL ETHER [**30**].—A solution containing 250 mg (0.95 mmol) of 6-hydroxyperezone was hydrogenated (20 min) as described for **25**. The residue was methylated using the procedure described for the preparation of **23**. The product was chromatographed with hexane giving 213 mg (70%) of **30**. ^{1}H nmr ($CDCl_3$, 90 MHz) δ 5.15 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 3.82 and 3.78 (3H each, s, 2 × OMe each), 2.16 (3H, s, 7-Me), 1.67 (3H, broad s, 15-Me), 1.53 (3H, broad s, 14-Me), 1.28 (3H, d, J = 6 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 59.87 and 59.24 (OMe); ir ($CHCl_3$) 1315 and 1373 cm^{-1} (C-O); uv (EtOH) λ max 223 (log ε 3.77), 277 (2.99) nm.

6-HYDROXYLEUCOPEREZONE TETRAACETATE [**31**].—Compound **31** was prepared from 250 mg (0.95 mmol) of 6-hydroxyperezone as described previously (35). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 5.03 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 2.30 (12H, s, 4 × OAc), 1.97 (3H, s, 7-Me), 1.67 (3H, s, 15-Me), 1.55 (3H, s, 14-Me), 1.20 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 167.68 and

167.21 (C=O), 20.31 and 20.11 (Me); ms *m/z* (rel. int.) $[M]^+$ 434 (10), $[M+1]^+$ 435 (2), 308 (46), 350 (33), 266 (100), 43 (89).

6-HYDROXYLEUCOPEREZONE-1,4-DIMETHYL ETHER DIACETATE [**32**].—A solution of hydroxyperezone dimethyl ether (10) (250 mg, 0.85 mmol) was treated with NaOAc (250 mg) and Zn (0.5 g) and refluxed 3 h. Workup as in **17** gave a residue which was chromatographed using hexane-C_6H_6 (1:1) to yield 87 mg (27%) of **32** (oil). ^{1}H nmr ($CDCl_3$, 90 MHz) δ 5.08 (1H, t with further unresolved couplings, J_t = 6 Hz, H-12), 3.75 and 3.71 (3H each, s, 2 × OMe), 2.36 and 2.32 (3H each, s, 2 × OAc), 2.08 (3H, s, 7-Me), 1.66 (3H, broad s, 15-Me), 1.55 (3H, broad s, 14-Me), 1.22 (3H, d, J = 7 Hz, 9-Me); ^{13}C nmr ($CDCl_3$) δ 168.27 (C=O), 20.71 and 20.50 (Me), 61.41 and 60.78 (OMe); ir ($CHCl_3$) 1765 (C=O), 1195 (C-O) cm^{-1}; uv (MeOH) λ max 225 (log ε 3.33), 272 (2.86), 292 (2.16) nm; ms *m/z* (rel. int.) $[M]^+$ 378 (22), $[M+1]^+$ 379 (6), 335 (20), 295 (30), 294 (100), 184 (37), 43 (63).

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