Phytochemistry, 1977, Vol. 16, pp. 1811–1816. Pergamon Press. Printed in England

CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY OF FLAVONOID AND ISOFLAVONOID COMPOUNDS*

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(*Revised received* 2 *June* 1977)

Key Word Index—^{13}C NMR spectroscopy; flavonoids; isoflavonoids; flavone; 7-hydroxyflavone; 5-methyl-7-hydroxy-4′-methoxyflavone; rubraflavone-A; mulberrin; mulberrochromene; quercetin; tri-*O*-methylgalangin; artemetin; rutin; robinin: flavanone; naringenin; dihydromorin; catechin; isoformononetin; cabreuvin; di-*O*-methyltexasin; caviunin; 7,4′-dimethoxyisoflavanone; 3′-hydroxy-7,4′-dimethoxyisoflavanone; di-*O*-methylmucronulatol; duartin; 1,1-dimethylallylcyclobin.

Absract—The ^{13}C NMR spectra of 15 flavonoid and 9 isoflavonoid substances of various ring C oxidiation states were analyzed and their carbon shifts assigned. In the case of 3 terpenic flavones and two glycoflavones linewidths were related qualitatively to molecular segmental motion.

Flavonoid compounds represent a large class of natural products, whose generalized ^{13}C NMR analysis has not been previously described. Whereas spectroscopic data have been reported on flavone (**1a**) [2] and its methoxy derivatives [3], the present communication portrays the application of ^{13}C NMR spectroscopy to various types of natural flavonoid and isoflavonoid substances.‡

FLAVONOID COMPOUNDS

In order to assist with the spectral interpretation of natural flavonoid products, the synthetic flavones **1b** and **1c** were studied. Their carbon shift assignment is based on the use of flavone (**1a**) as a model and additive substituent parameters [6]. Distinction of close resonances in these and other flavones was made on the basis of qualitative coupling and relaxation data. As an example of the application of these analytical tools the analysis of the 4 oxygenated, non-protonated carbons of model **1c**, resonating within a 3 ppm range, is described. If the decoupler is set at low power in the aromatic H range, only the C(4′) signal is broadened due to unresolved coupling to the OMe hydrogens [7]. Under these conditions the C(5) signal is split into a quartet, when the aliphatic hydrogens are decoupled, carbons 1′ and 4′ appear as triplets, whereas C(7) and C(8a) remain as singlets. This is a consequence of *meta*-coupling [$^3J_{CH}$] by each of the two pairs of carbons to two and zero hydrogens, respectively [7]. The C(7) and C(8a) signals can be recognized by the different relaxation rates of the two carbons, C(7) possessing the most intense (due to 3 hydrogens two bonds away) and C(8a) the least intense signal (due to one β hydrogen) among the 4 carbons under consideration [8]. The deshielding of C(5) on Me substitution (**1b** → **1c**) is larger than usual [6] due to a loss of the γ-effect from the carbonyl oxygen. The chemical shifts of flavones **1a–1c** are presented in Table 1.

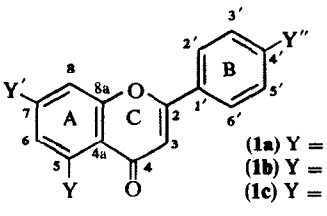
Table 1. Carbon shifts of flavones*

Carbons	1a	1b	1c†	2‡	3	4
2	162.1	162.6	160.0	160.3	159.0	158.5
3	106.7	106.5	106.1	121.2	119.4	120.1
4	176.7	176.1	178.1	176.2	181.7	181.7
4a	123.1	116.0	114.2	115.5	103.6	104.4
5	125.1	126.3	141.2	126.6	161.1	161.1
6	124.5	114.9	116.5	114.4	105.5	100.5
7	133.8	161.7	160.9	162.1	161.6	161.7
8	118.2	102.4	100.7	101.9	98.0	98.9
8a	155.3	157.3	158.5	157.6	155.0	151.8
1′	130.8	131.1	123.0	111.9	111.3	110.9
2′	126.0	126.0	127.5	160.0	160.3	160.6
3′	128.7	128.9	114.2	102.9	102.8	103.0
4′	131.4	131.3	161.5	156.1	156.5	156.6
5′	128.7	128.9	114.2	106.5	106.7	107.0
6′	126.0	126.0	127.5	130.8	130.9	131.1

* The δ values are in ppm downfield from TMS; δ(TMS) = δ(d_6-DMSO) + 39.5 ppm.

† The shifts of the 5-Me and OMe groups are 22.3 and 22.3 and 55.3 ppm, respectively.

‡ Spectrum run at 50°.



(**1a**) Y = Y′ = Y″ = H
(**1b**) Y = Y″ = H, Y′ = OH
(**1c**) Y = Me, Y′ = OH, Y″ = OMe

* Part 49 in the series 'Carbon-13 Nuclear Magnetic Resonance spectroscopy of naturally occurring substances'. For part 48 see ref. [1].

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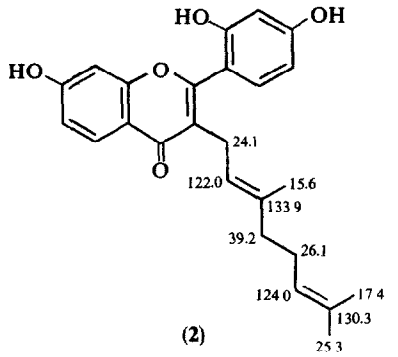
‡ A major portion of this work is covered in ref. [4]. Since its completion ^{13}C NMR data on some flavonoid compounds have appeared [5]. In the absence of any confirmatory long-range carbon-hydrogen coupling information (*vide infra*) the shift data [5b, c] harbor discrepancies with the results of the present work.

The spectra of the prenylated flavones rubraflavone-A (**2**) [9], mulberrin (**3**) [10] and mulberrochromene (**4**) [10] can be analyzed by the methods described and by comparisons within the group. Farnesol [11] serves as a model for the isoprenyl side chains. The olefinic methines can be recognized in the single-frequency off-resonance decoupled (sford) spectra by the smaller residual coupling [12] due to the higher field position of the olefinic hydrogens (decoupling frequency at the high-field end of the hydrogen spectrum) [11, 12]. The shifts of the aromatic units are shown in Table 1, whereas those of the side-chains are decpicted on the formulae.



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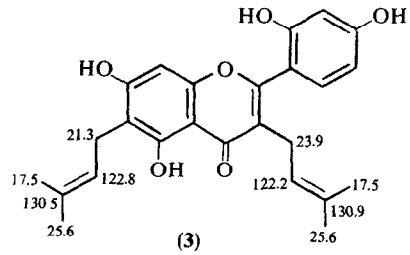

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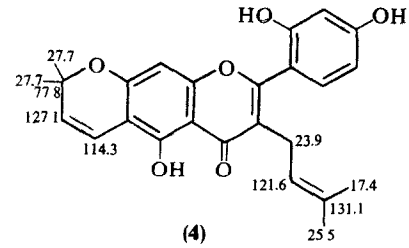


(4)

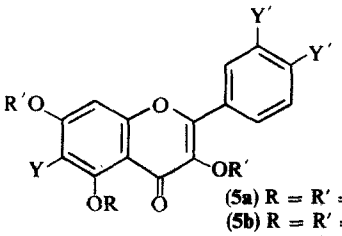
The introduction of a 5-OH group deshields the carbonyl resonance by *ca* 5 ppm (**2** → **3** or **4**), as observed in previous cases [13], and introduces coupling between the H-bonded phenolic H and ring carbons [5a, 14]. An interesting feature of the spectra of the 3 prenylated flavonoids **2–4** is the linewidths of the signals. The widths at half signal height ($\nu_{1/2}$) appear in 3 forms: (a) non-protonated carbons—$\nu_{1/2}$ = 2 to 3 Hz, (b) ring methines and the benzylic methylenes—$\nu_{1/2}$ = 10 ± 2 Hz, and (c) other side-chain carbons—$\nu_{1/2}$ = 4 to 5 Hz. Apparently the molecular tumbling of the flavones in solution is relatively slow and the relaxation times fast enough to make differences in segmental motion observable as differences in linewidth. The relaxation times of the protonated carbons are shorter in the hydroxylated aromatic rings than in the nonpolar, freely rotating side-chains, except for the carbons directly attached to the cycles. An increase in temperature increases the overall rate of molecular motion and sharpens all protonated carbon signals.

The spectrum of the flavonol quercetin (**5a**) was assigned by the use of the decoupling methods presented above and by comparison with morin [15], a substance possessing the same substitution pattern of rings A and B. The C(5′) and C(6′) signals can be differentiated from those of other methines by the presence of extra second-order couplings in the sford spectrum [7, 12]. The carbonyl carbon is shielded by the neighboring 3-OH group relative to flavone (**1a**), even though the 5-OH group tends to deshield it (*vide supra*). This is analogous to the relationship of 2-cyclohexenone with 2-hydroxy-2-cyclohexenone [16]. However, the effects of hydroxylation on 2-cyclohexenone are 17.2 ppm on C(2) and −32.1 ppm on C(3), whereas on the flavones (**1a** → **5a**) they are 29.2 and −16.8 ppm for the corresponding carbons. This contrast is strongly reminiscent of aromatic substituent parameters [6] and may be due to the partial aromaticity of the pyrone nucleus, a postulate used previously [3] to explain the asymmetry of the effect of ring A oxygenation on the carbon shifts of flavone (**1a**). Etherification of the 3-OH group, cf. the natural ethers tri-*O*-methylgalangin (**5b**) [17] and artemetin (**5c**) [18], introduces steric inhibition of its resonance interaction with the aromatic ring and therefore C(2) and C(4) deshielding (**5a** → **5c**). The chemical shifts of compounds **5** are presented in Table 2.

Table 2. Carbon shifts of 3-oxygenated flavones*

Carbons	5a†	5b‡§	5c‡‖	6†	7†
2	147.1	152.0	151.4	156.6	156.0
3	136.0	141.4	138.0	133.5	133.6
4	176.0	173.6	180.0	177.4	177.6
4a	103.4	109.1	105.7	104.2	105.7
5	160.9	160.5	151.9	161.3	161.6
6	98.7	95.5	131.5	99.0	99.5
7	164.2	163.5	158.0	164.1	160.8
8	93.9	92.1	89.8	93.9	94.8
8a	160.9	158.4	155.0	156.8	157.1
1′	122.4	130.5	122.1	121.4	120.7
2′	115.5	127.7	110.7	115.4	131.1
3′	145.3	128.0	148.0	144.8	115.2
4′	147.9	129.0	150.8	148.5	160.1
5′	116.0	128.0	110.3	116.5	115.2
6′	120.5	127.7	121.5	121.5	131.1

* The δ values are in ppm downfield from TMS.
† In d_6-DMSO; δ(TMS) = δ(d_6-DMSO) + 39.5 ppm.
‡ In $CDCl_3$; δ(TMS) = δ($CDCl_3$) + 76.9 ppm.
§ δ(3-OMe) = 59.7 ppm; δ(5-OMe, 7-OMe) = 55.4 and 56.0 ppm.
‖ δ(3-OMe) = 59.4 ppm; δ(6-OMe) = 60.1 ppm; δ(7-OMe, 3′-OMe, 4′-OMe) = 55.4, 55.5 and 55.7 ppm.



(**5a**) R = R′ = Y = H, Y′ = OH
(**5b**) R = R′ = Me, Y = Y′ = H
(**5c**) R = H, R′ = Me, Y = Y′ = OMe

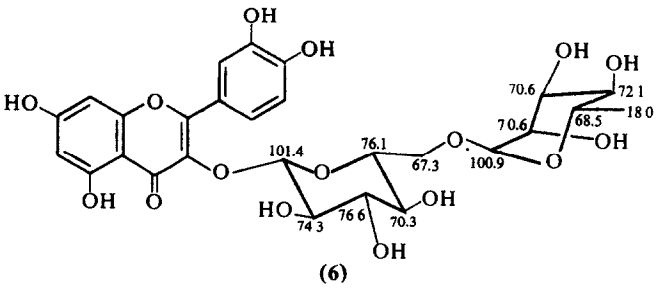
The aromatic carbon shifts of the flavonoid glycosides rutin (**6**) and robinin (**7**) can be assigned by the use of quercetin (**5a**) and **1c** as models and the δ values of the sugar carbons by analogy with monosaccharide and Me glycoside data [6]. The effect of 6-*O*-substitution on glucose [cf. rutin (**6**)] and, by extension, on the related galactose residue of robinin (**7**) could be evaluated from the shift data of a polymeric glucan possessing such substitution pattern [19]. Finally, the fact of anomeric carbons of aryl glycosides being *ca* 2 ppm more shielded than the corresponding Me glycosides [20] and comparison with the rutin (**6**) shifts yield the distinction of the two rhamnose units in robinin (**7**).

Signal linewidths serve again to resolve close chemical shift differences and to provide insight into segmental motion of the compounds (*vide supra*). The rutin (**6**) signals can be divided into 4 groups: (a) non-protonated carbons ($\nu_{1/2}$ = 1 Hz), (b) methines of ring B and the rhamnose moiety and the latter's Me group ($\nu_{1/2}$ = 3 Hz), (c) methines of ring A and the glucose moiety ($\nu_{1/2}$ = 5 Hz), and (d) the glucose methylene ($\nu_{1/2}$ = 8 Hz). This indicates that rings A, C and the glucose moiety constitute a central, less-mobile portion of the substance, while ring B and the rhamnose moiety can rotate more freely. Robinin (**7**) behaves similarly. The two rhamnose units show signals of like linewidths, indicating that linkage of a sugar unit to the uncrowded C(7) position allows relatively free rotation of the former. The chemical shifts of the flavone nuclei of **6** and **7** are shown in Table 2, those of the sugar units being indicated on the formulae.

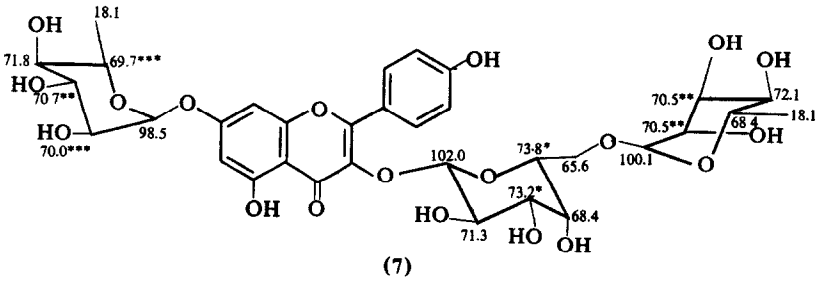
Table 3. Carbon shifts of 2,3-dihydroflavones*

Carbons	8a†	8b†	8c†	9‡
2	78.7	78.8	78.3	81.2
3	43.5	42.4	70.9	66.6
4	191.1	196.4	198.4	28.1
4a	120.5	102.1	100.9	99.4
5	128.3	163.7	163.7	156.3§
6	121.2	96.3	96.5	95.5
7	136.0	166.9	167.1	156.6§
8	117.8	95.4	95.5	94.3
8a	160.8	163.1	163.3	155.5
1′	138.7	129.1	114.2	130.8
2′	126.3	128.5	159.0	114.7
3′	128.3	115.6	103.0	145.0
4′	126.1	157.9	157.5	145.0
5′	128.3	115.6	107.1	115.4
6′	126.3	128.5	130.3	118.8

* The δ values are in ppm downfield from TMS.
† In d_6-DMSO; δ(TMS) = δ(d_6-DMSO) + 39.5 ppm.
‡ In $CDCl_3$; δ(TMS) = δ($CDCl_3$) + 76.9 ppm.
§ Signals may be interchanged.



(6)

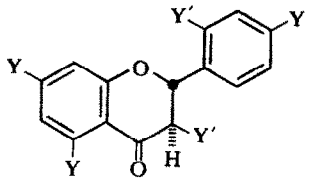


(7)

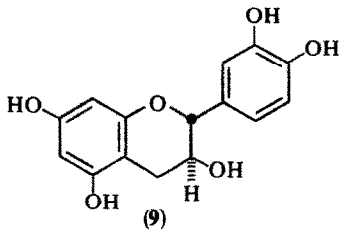
The carbon shifts of flavanone (**8a**), the substituted flavanones naringenin (**8b**) and dihydromorin (**8c**) and the flavan catechin (**9**) are presented in Table 3. The assignment of the ring A carbons of flavanone (**8a**) is based on the model 2-methoxyacetophenone [21], that of naringenin and dihydromorin on a thorough analysis of the coupling pattern of the former compound [15] and that of catechin on the data for xanthene [22]). Hydroxylation of C(5) causes a 5.3 ppm deshielding of the carbonyl carbon (**8a** → **8b**), as it does in the flavone series. Introduction of a 3-OH group (cf. **8c**) has an added deshielding (β) effect. Reduction of the carbonyl functionality (**8c** → **9**) causes strong (8–11 ppm) shielding of the carbons *ortho* and *para* to the modified site. Comparison of ring B of compounds **8** and **9** with that of the 2-dehydro compounds shows consistently strong deshielding of C(1′) (6 ± 2 ppm) and weaker shielding of C(4′) (−3 ± 2 ppm), the remaining ring B carbons staying almost invariant.

ISOFLAVONOID COMPOUNDS

Isoflavones differ from the flavones by ring B being linked to C(3) instead of C(2). Comparison of the chemical shifts of isoformononetin (**10a**) [23] with those of flavone **1b** shows that the site of attachment of ring B has a negligible effect on the ring A and carbonyl carbons.

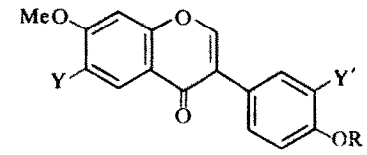


(8a) Y = Y′ = H
(8b) Y = OH, Y′ = H
(8c) Y = Y′ = OH

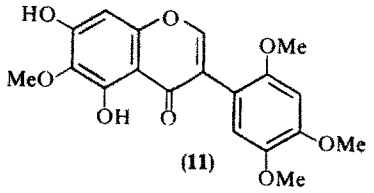


(9)

Carbon-2 is now a characteristic low-field methine. The sford spectrum of cabreuvin (**10b**) [24] lacks strangely any second-order coupling of C(5) and C(6) [12]. On analysis of the residual couplings it could be shown that H(5) resonates at *ca* as low a field as H(2), i.e., at *ca* 7.7–7.8 ppm. As a consequence the coupling between H(5) and higher field H(6) is not strong enough for the appearance of significant second-order transitions. The chemical shifts of isoformononetin (**10a**) and cabreuvin (**10b**) as well as those of texasin diMe ether (**10c**), the natural product being a 6,7-dihydroxyisoflavone [25], and those of the hexaoxygenated isoflavone caviunin (**11**) [26] are presented in Table 4. The last compound is hydroxylated at C(5) and carbons 4a, 5 and 6 couple with the phenolic H [14], even in the presence of methanol as a co-solvent. Deuterium exchange removes this added feature. It is of diagnostic importance that H(2) couples with its '*meta*' carbons, i.e. the carbonyl group and C(8a), as if in an aromatic ring. As in the case of the flavones (*vide supra*) the carbonyl group is shielded by *ca* 4.5 ppm on introduction of a *peri*-OH group (**10** → **11**). This effect is extended into polarization of the ring C double bond, thereby deshielding C(3) and shielding C(4).



(10a) R = Y = Y′ = H
(10b) R = Me, Y = H, Y′ = OMe
(10c) R = Me, Y = OMe, Y′ = H



(11)

The spectra of isoflavanone Me ethers **12a** and **12b**, the natural products being 7-hydroxylated and 7,3′-dihydroxylated [27], respectively, can be assigned by their comparison with those of isoflavones **10**. Relative to the latter the ring A shifts are modified in the same way as those of flavanone (**8a**) vs flavone (**1a**), i.e. shielding of carbons 4a, 6 and 8 and deshielding of carbons 5, 7 and 8a as well as of the carbonyl carbon. The chemical shifts of isoflavanones **12** are shown in Table 5.

The diMe ether of mucfonulatol (**13a**), the natural product being 7,3′-dihydroxylated [28], and duartin (**13b**) [28] are isoflavans. Their chemical shifts can be interpreted using xanthene [22] as a model for ring A and 1,2,3-trimethoxybenzene [29] for ring B. Introduc-

Table 4. Carbon shifts of isoflavones*

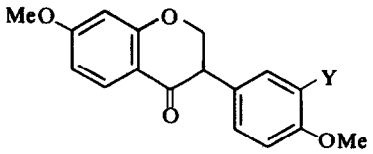
Carbons	10a†	10b	10c	11†‡
2	152.2	151.8	151.5	154.5
3	123.9	124.3§	124.2§	119.3
4	176.3	175.3	175.2	180.6
4a	116.9	118.0	117.6	105.5
5	127.2	127.2	104.7	152.6
6	115.0	114.2	147.4	130.9
7	162.4	163.5	154.1	156.3
8	102.1	99.8	99.3	93.6
8a	157.8	157.4	151.9	153.0
1′	123.9	124.4§	124.1§	110.4
2′	129.8	112.3	129.8	151.6
3′	113.5	148.4‖	113.7	97.8
4′	159.1	148.7‖	159.2	149.6
5′	113.5	110.9	113.7	142.4
6′	129.8	120.6	129.8	115.0
OMe	55.0	55.5	55.2	55.7
		55.7	56.2	56.2
		55.7	56.3	56.2

* The δ values are in ppm relative to TMS; δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm.
† MeOH was adeed to improve solubility.
‡ δ(6-OMe) = 60.1 ppm.
§‖ Signals with the same superscript within any vertical column may be interchanged.

Table 5. Carbon shifts of isoflavanones and isoflavans*

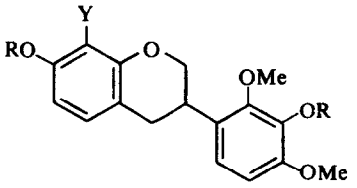
Carbons	12a	12b	13a	13b†	14†
2	71.7	71.5	70.4	70.3	69.6
3	50.9	51.5	31.8	31.4	32.5
4	190.6	190.4	31.2	31.5	30.1
4a	114.6	114.4	114.3	115.1	114.1
5	129.1	129.0	130.0	123.9	130.1
6	109.8	109.7	107.1‡	106.3‡	108.1
7	165.6	165.6	158.9	147.2	154.9
8	100.4	100.3	101.3	134.6	103.0
8a	163.1	163.0	154.9	146.8§	154.5
1′	127.1	127.5	127.2	127.0	122.0
2′	129.3	111.6	151.8	145.1	145.8
3′	114.0	148.7‡	142.2	138.5	137.1
4′	158.7	148.2‡	152.5	146.4§	142.2
5′	114.0	111.2	107.3‡	106.9‡	132.4
6′	129.3	120.2	121.2	116.7	116.3
7-OMe	55.4	55.3	55.3		
2′-OMe			60.7	60.8	60.4
3′-OMe		55.6	61.2		
4′-OMe	55.0	55.6	55.9	56.0	

* The δ values are in ppm relative to TMS; δ(TMS = $\delta(CDCl_3)$ + 76.9 ppm.
† MeOH was added to improve solubility.
‡§ Signals with the same superscript within any vertical column may be interchanged.



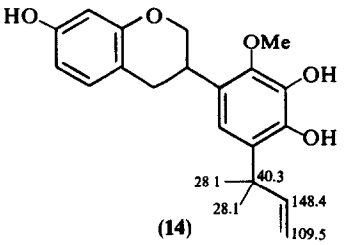
(12a) Y = H
(12b) Y = OMe

tion of a 4-allyl substituent in the latter model, as in **13a**, causes steric inhibition to resonance by the OMe group next to it and the isoflavone carbons *ortho* and *para* to the OMe function to resonate at lower field than expected [30]. Demethylation of the 3'-OMe unit (**13a** → **13b**) has the opposite effect, i.e. removal of steric inhibition to resonance and therefore shielding of carbons 2', 4' and 6 [29]. The signal for C(2') of both compounds is characteristically weak due to its very long relaxation time. The chemical shifts of the isoflavans **13** are presented in Table 5.



(13a) R = Me, Y = H
(13b) R = H, Y = OMe

The ring A chemical shifts of 1,1-dimethylallylcyclobin (**14**) [31] are analogous to those of **13a**, the ring B shifts being comparable to those of **13b**. The negligible effect of the dimethylallyl group on C(6') is surprising in view of the −3.3 ppm *ortho* effect of the *t*-butyl group in *t*-butylbenzene [32]. Other anomalies are noted also around the C(3)–C(1') bond. Thus the ring C carbons and, most remarkably, C(1') itself are shielded by 5 ppm. These variations point to a change in the preferred rotamer population around the C(3)–C(1') bond, C(6') pointing away from the axial C(2) and C(4) hydrogens and thus feeling no γ effect. The change in the C(1') shift may be due to a concommitant reorientation of the 2'-OMe group causing its Me part to exert an increased γ effect on C(1'). The chemical shifts of the *O*-Me and ring carbons of **14** are in Table 5 and those of the prenyl sidechain on the formula.



(14)

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.02 MHz in the Fourier transform mode. The stars on formula **7** indicate permissible signal reversals.

Acknowledgements—The authors are indebted to Drs A. B. de Oliveira (Universidade Federal de Minas Gerais, Belo Horizonte, Brasil), O. R. Gottlieb (Universidade de São Paulo, São Paulo, Brasil), H. H. Mathur (Indian Institute of Technolgy, Bombay, India) and K. Venktataraman (National Chemical Laboratory, Poona, India) for generous gifts of samples.

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