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^{13}C NMR SPECTROSCOPY OF NEOLIGNANS*

ERNEST WENKERT,†‡ HUGO E. GOTTLIEB,† OTTO R. GOTTLIEB,§
MARILIA O. DA S. PEREIRA¶ and MARIZA D. FORMIGA¶

† Department of Chemistry, Indiana University, Bloomington, IN 47401, U.S.A.,
§ Instituto de Química, Universidade de São Paulo, São Paulo, Brasil,
¶ Instituto de Ciências Exatas, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

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Key Word Index—^{13}C NMR spectra; neolignans; aurein; licarin A; licarin B; 5-allyl-2-aryl-5-methoxy-3-methyl-6-oxo-2,3,5,6-tetrahydrobenzofurans; eusiderin; mirandin A; mirandin B; burchellin; 3a-allyl-2-aryl-5-methoxy-3-methyl-6-oxo-2,3,3a,6-tetrahydrobenzofurans; porosin; pluviatolide; hinokinin; pyrogallol ethers; aryl ethyl carbinols; 1-ethoxy-1-arylpropanes; 5,6-dimethoxy-1-(3,4-dimethoxyphenyl)-3-ethyl-2-methylindane.

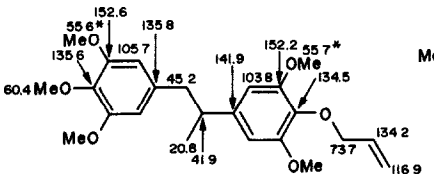
Abstract—The ^{13}C NMR spectra of 15 neolignans of several structural types and two lignans were analyzed and their carbon shifts assigned. The shifts of pyrogallol ether and ethyl phenyl carbinyl ether models were used in this connection. The stereochemistry of a dimeric sideproduct in the preparation of the latter models was determined by ^{13}C NMR analysis.

INTRODUCTION

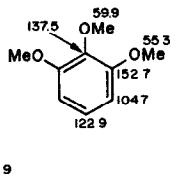
Recent years have witnessed the isolation of a large number of C_6–C_3 oxidation dimers of the neolignan type [2]. In order to facilitate their structure analysis, several representatives of this proliferating class of natural substances were submitted to inspection by the new, powerful ^{13}C NMR analytical method. The present communication describes the first ^{13}C NMR analysis of neolignans and pinpoints carbon shifts characteristic of specific structural types.

RESULTS AND DISCUSSION

The chemical shift assignment for the structurally unusual neolignan aurein (**1**) [3] is based on that of 1,2,3-trimethoxybenzene (**2**) and standard chemical shift theory [4,5].



(1)



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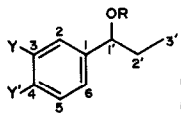
For the evaluation of the 2-aryl carbons of the neolignans of the benzofuran type and of their cyclohexadienone equivalents (*vide infra*) the ^{13}C NMR analysis of ethylphenylcarbinol (**3a**) [6], its acetate (**3b**) [7], methyl (**3c**) [8] and ethyl (**3d**) [9] ethers and the ethyl ethers of 3,4-dimethoxyphenylethylcarbinol (**3e**) [10] and 3,4-methylenedioxyphenylethylcarbinol (**3f**) [11], **3g** and **3h**, respectively, were undertaken. The synthesis of ethers **3g** and **3h** is described in the Experimental and the carbon shifts are shown in Table 1. As previously observed [12], the change of a vicinal dimethoxyphenyl unit to a methylenedioxy moiety causes shielding of the aromatic oxycarbons and their neighbors by 1–1.5 and 3–4 ppm respectively, and deshielding of the remaining carbons by 1–2 ppm.

Table 1. Carbon shifts of models **3***

Carbons	3a	3b†	3c‡	3d§	3g§¶	3h§‖
1	144.3	140.3	142.0	142.8	135.3	136.9
2	125.7	126.3	126.5	126.4	109.0	106.5
3	128.0	128.0	128.0	127.9	148.7	147.6
4	127.1	127.5	127.2	127.0	147.9	146.5
5	128.0	128.0	128.0	127.9	110.4	107.6
6	125.7	126.3	126.5	126.4	118.8	120.0
1′	75.6	77.1	85.4	83.4	83.1	83.2
2′	31.7	29.1	30.8	31.1	30.9	31.0
3′	10.0	9.7	10.1	10.2	10.1	10.2

* The δ values are in ppm downfield from TMS; $\delta(TMS) = \delta(CDCl_3) + 76.9$ ppm. † The acetyl C=O and Me shifts are 169.9 and 21.0 ppm, respectively. ‡ The OMe shift is 56.5 ppm. § The ethoxy CH_2 and Me shifts are 63.7 and 15.2 ppm, respectively. ¶ The OMe shift is 55.5 ppm. ‖ The dioxymethylene shift is 100.7 ppm.



(**3a**) R = Y = Y′ = H
(**3b**) R = Ac, Y = Y′ = H
(**3c**) R = Me, Y = Y′ = H
(**3d**) R = Et, Y = Y′ = H
(**3e**) R = H, Y = Y′ = OMe
(**3f**) R = H, Y + Y′ = O_2CH_2
(**3g**) R = Et, Y = Y′ = OMe
(**3h**) R = Et, Y = Y′ = O_2CH_2

The ^{13}C NMR data of the models **3** aid in the shift assignment of the aromatic carbons of licarin A (**4a**) and B (**4b**) [13]. Comparison of the aromatic carbon shifts of **4a**, **4b** and **3f** differentiates the 2-aryl sidechain from the dihydrobenzofuran nucleus in the two neolignans and permits the complete shift designation of the 2-aryl sidechain of licarin B(**4b**). The aromatic carbons of the

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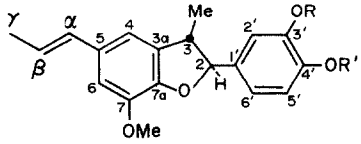
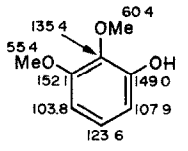
‡ Present address: Department of Chemistry, Rice University, Houston, TX 77001, U.S.A.

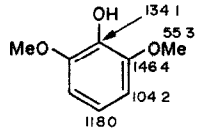
fused bicyclics are distinguished on the basis of the following arguments. The oxycarbons are expected to be downfield of the other non-protonated centers and the methine *ortho* to the OMe group upfield of the methine *para* to the OMe function, a condition mitigated by a countering γ-effect of the 3-Me group on the latter methine. Aliphatic proton decoupling differentiates the oxycarbons by the methoxylated center being reduced to a singlet and the other site retaining three-bond coupling characteristics by interaction with the *meta* hydrogens [12]. The remaining non-protonated centers are distinguished from each other similarly in view of C(3a) degenerating into a singlet but C(5) still exhibiting coupling with the neighboring olefinic hydrogens. The multiplicity of the latter, i.e. a triplet, shows this coupling to be of similar magnitude with both hydrogens. Finally, the assignment of the 2-aryl shifts of licarin A (**4a**) is based on the δ values of model **3e** as well as the difference of the shifts of 1,2,3-trimethoxybenzene (**2**) and the monodemethylated compounds 2,3-dimethoxyphenol (**5**) and 2,6-dimethoxyphenol (**6**).



(**4a**) R = Me, R' = H
(**4b**) R+R' = CH_2



(**5**)



(**6**)

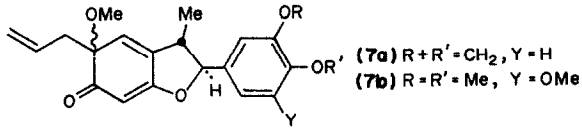
While the non-aromatic carbons of licarin A (**4a**) and B (**4b**) are identified readily, differentiation of the Me groups depends on the larger residual coupling of the allylic Me function [12]. All chemical shifts of **4a** and **4b** are listed in Table 2.

The carbon shift data for aurein (**1**), the licarins (**4a** and **4b**) and model **3f** permit the signal assignment of the ^{13}C NMR spectra of the naturally occurring cyclohexadienones **7a** [14] and **7b** [15]. The ring carbon shifts of the cyclohexadienone units are derived from 3-alkoxy-2-cyclohexenone models [16], while the other non-aromatic carbons are assigned by standard chemical shift theory [4]. The similarity of the C(2), C(3) and 3-Me shifts of the cyclohexadienones (**7a** and **7b**) and licarins (**4a** and **4b**) show the four substances to possess the same furanoid stereochemistry. The shift non-identity of these centers as well as of C(1') of licarin B (**4b**) and cyclohexadienone **7a** reflects most probably the different electronic environment of the aromatic and cyclohexadienone nuclei. Carbon-1' of compounds **4** and **7** is at a surprisingly high field position on comparison with the like centers in aurein (**1**) and **3h**. The δ values of **7a** and **7b** are listed in Table 2.

Table 2. Carbon shifts of the licarins, mirandins and the cyclohexadienones **7***

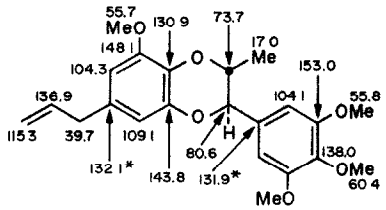
Carbons	4a†	4b‡	7a‡	7b§	9a§	9b§
2	93.3	93.0	93.7	93.7	94.3	91.2
3	45.2	45.5	42.6	42.6	46.9	49.8
3a	132.8	132.7	140.2	140.0	80.9	77.6
4	112.9	113.0	134.1	134.1	131.6	130.9
5	131.7¶	131.8	80.8	80.6	142.5	142.8
6	109.0	109.2	199.3	199.2	186.8	186.8
7	143.6	143.7	99.5	99.6	104.6	102.7
7a	146.3	146.2	172.0	171.9	172.6	174.3
3-Me	17.2	17.6	16.1	16.3	16.1	6.9
OMe	55.5	55.7	53.5	53.4	50.3	51.1
1'	131.6¶	134.0	131.4	133.2	135.5	132.7
2'	108.6	106.3	106.1	103.0	102.6	103.5
3'	146.1	147.5	148.1	153.4	152.8	153.3
4'	145.3	147.2	148.1	138.5	137.2	138.4
5'	113.8	107.7	108.2	153.4	152.8	153.3
6'	119.3	119.7	120.0	103.0	102.6	103.5
α	130.5	130.6	45.0	44.8	33.2	33.5
β	122.8	122.9	130.7	130.8	134.8	134.8
γ	18.0	18.1	119.0	118.8	116.9	117.1

*The δ values are in ppm downfield from TMS; δ(TMS) = δ($CDCl_3$) + 76.9 ppm. † δ(3'–OMe) = 55.5 ppm. ‡ δ(3',4'–O_2CH_2) of **4b** and **7a** is 100.7 and 101.3 ppm, respectively. § δ(3'–OMe) = 56.1 ± 0.1 ppm and δ(4'–OMe) = 60.7 ± 0.1 ppm. ¶ Signals may be interchanged.



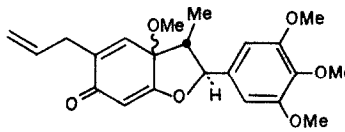
(**7a**) R+R' = CH_2, Y = H
(**7b**) R = R' = Me, Y = OMe

Cyclohexadienone **7b** serves as a model for the assignment of the shifts of eusiderin (**8**) [17] except those of the aromatic carbons of the bicycle. The latter were determined by selective decoupling of proton regions [12].



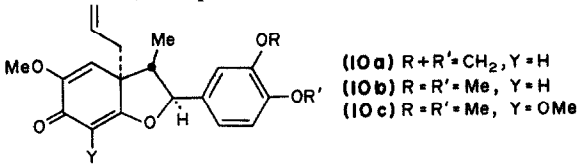
(**8**)

Mirandin A (**9a**) [18] and B (**9b**) [18] are angularly methoxylated cross-conjugated cyclohexadienones. Their ^{13}C NMR analysis depends on compounds **7b** and **8** serving as models for the trimethoxylated C_6–C_3 unit and dehydrogriseofulvin [16] as a backdrop for the cyclohexadienone moiety. All shifts of the mirandins are in Table 2.



(**9a**) 3aβ
(**9b**) 3aα

Burchellin (**10a**) [19] and other natural, angularly allylated cyclohexadienones **10b** [20] and **10c** [20] can be analyzed by the utilization of the aromatic carbon shifts of **7a** and **7b** for the evaluation of the δ values of the aromatic C_6–C_3 unit. The shift designation of the cyclohexadienyl C_6–C_3 moiety is based on that of mirandin B (**9b**) and 2-methoxy-2-cyclohexenone [21]. Expectedly, the 3-Me group of compounds **10** is shielded less strongly than that of mirandin B (**9b**) in view of the lower γ-effect of the angular allyl group than that of the angular OMe function. The shifts of burchellin (**10a**) and its relatives (**10b** and **10c**) are quoted in Table 3.



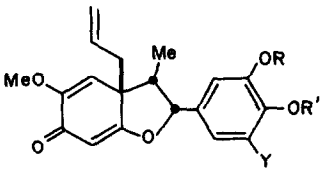
(**10a**) R+R' = CH_2, Y = H
(**10b**) R = R' = Me, Y = H
(**10c**) R = R' = Me, Y = OMe

Table 3. Carbon shifts of natural, angular allyl compounds*

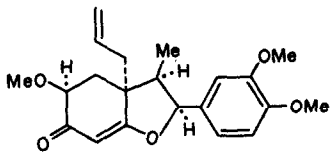
Carbons	10a†	10b‡	10c‡§	11a†	11b†¶	11c‖	12‡
2	90.9	91.0	91.5	87.2	87.1	87.2	87.2
3	49.5	49.3	49.6	44.6	44.5	44.5	42.5
3a	50.9	51.0	49.8	53.9	53.8	53.9	50.2
4	107 8	107.8	107.2	109.0	108.9	108 9	32.0
5	153.3	153.3	152.7	152.7	152.6	152.6	76.8
6	182.8	182.6	189.7	182.4	182.3	182.4	196.6
7	101.8	101.9	166 0	101.8	101.8	102.0	100.1
7a	181.4	181.3	183.9	181.2	181.0	181.1	183.4
3-Me	8.3	8.5	8.5	12.0	11.9	12.0	11.6
5-OMe	55.8	55.2	55.3	55.2	55.1	55.2	58.7
1′	131.5	129.8	130.1	130.2	134.6	130.7	128.3
2′	106.5	109.1	109.2	106.0	99.7	102.4	108.6
3′	148.1	149.6	149.5	147.7	148.9	153.2	148.8
4′	148.1	149.2	149.2	147.1	131.0	132.1	148.5
5′	107.8	110.9	110.9	108.1	143.4	153.2	110.9
6′	120.5	119.3	119.2	118.7	105.0	102.4	117.8
α	36.6	36.7	36.7	43.9	43.8	43 9	39.0
β	130.9	130.7	130.7	131.5	131.5	131.5	132.5
γ	120.0	119.9	119.8	120.0	120.0	120.1	119.7

* The δ values are in ppm downfield from TMS; δ(TMS) = $\delta(CDCl_3)$ + 76.9 ppm. † δ(3′,4′-O_2CH_2) of **10a**, **11a** and **11b** is 101.2, 101.0 and 101.4 ppm, respectively. ‡ δ(OMe) = 55.9 ppm. § δ(7-OMe) = 60.4 ppm. ¶ δ(5′-OMe) = 56.7 ppm. ‖ δ(3′-OMe) = 56.1 and δ(4′-OMe) = 60.7 ppm.

Cyclohexadienone **11a** [14] is a stereoisomer of burchellin (**10a**). The change of stereochemistry is insufficient to complicate the shift assignment of **11a** or its relatives **11b** [15] and **11c** [15] as well as the natural dihydro product porosin (**12**) [22].* The methylenes of the allyl and cyclohexenone units of the latter are distinguished by the difference of their residual coupling [12]. All shifts are listed in Table 3.

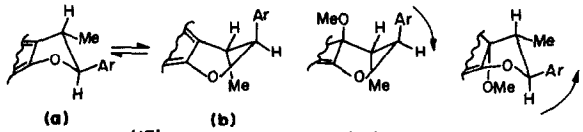


(**11a**) R+R′=CH_2, Y = H
(**11b**) R+R′=CH_2, Y = OMe
(**11c**) R = R′ = Me, Y = OMe

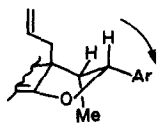


(12)

The ^{13}C NMR data reveal much about the configuration and some information about the conformation of the neolignans. The 3-Me shift especially is of diagnostic importance. Its similarity in the licarins (**4**) and the cyclohexadienones **7**, both types of substances containing nearly planar benzofuranoid rings in which only C(2) can be non-coplanar, shows the aryl group to contribute no significant γ-effect on the Me unit. While the reported H(2)–H(3) coupling constants of 9 Hz [13] and 3 Hz [14,15] reflect the adoption of predominantly the conformation **13a** and **13b** by the licarins (**4**) and the cyclohexadienones **7**, respectively, the *pseudo*-equatorial Me group of compounds **4** must be mostly beyond nonbonded interaction range of the neighboring aryl sidechain. The identity of the 3-Me shift of mirandin A (**9a**) with that of compounds **7** shows this angularly methoxylated substance to possess a conformation related to **13b**, i.e. a conformer like **14** in which the 1,3-diaxial interaction of the OMe and the aryl groups is relieved (see arrow on **14**), in conformity with the known small H(2)–H(3) coupling constant (less than 0.5 Hz) [18]. Contrastingly, mirandin B (**9b**) reveals its Me group over 9 ppm upfield of that of its isomer A (**9a**) and its H(2)–H(3) coupling to be large (9.5 Hz) [18]. A relaxed version of conformer **15** (see arrow) can account for these facts, especially in view of its support of the presence of at least two γ-effects on the Me group exerted by its neighbors. The non-bonded interaction of the C(2) and C(3) substituents is shown also by the shielded position of C(1′) in **9b** vs **9a**. The ^{13}C NMR analysis of the mirandins identifies them clearly as 3a-epimers.



Burchellin (**10a**) and its relatives **10b** and **10c** possess the same relative configuration of the substituents of the furanoid ring as mirandin B and hence would be expected to prefer a conformation as in **15**. In accord therewith the three substances were shown to exhibit 9.5 Hz H(2)–H(3) coupling [19,20] and an upfield 3-Me signal. The *ca* 1.5 ppm decrease of shielding of the 3-Me group of compounds **10** vs that of mirandin B may be due mostly to the known higher γ-shift by alkoxy over alkyl groups. In view of the reciprocity of the γ-effect the α-methylene of the allyl group of substances **10** is shielded by *ca* 7 ppm contrasted with this subunit in the 3-epimer (**11**). The cyclohexadienones **11**, confined to conformation **16** with a flattened five-membered ring (see arrow), cause their 3-Me group to feel one less γ-effect than the C(3) substituent in substances **10** and hence to be deshielded (*ca* 3.5 ppm). Having the furanoid substituents in the same relative configuration as the C(2), C(3) and C(3a) substituents of compounds **11**, porosin (**12**) is restricted to conformation **17**. In view of this constraint and the reported PMR data revealing the axiality of H(5) (J = 5 and 12 Hz) [22,23] the C(5) stereochemistry is as depicted in **12** and **17**. This feature is confirmed by the shielding of the α-methylene of the angular allyl group of porosin (**12**) with respect to the field position of this subunit in cyclohexadienones **11**, induced by a γ-effect from H(5).



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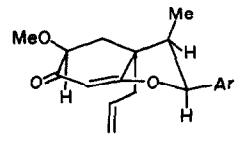


(17)

In the absence of many ^{13}C NMR facts on lignans [24–26] the following carbon shift assignment of pluviatolide (**18a**) [27], its acetate (**18b**) and hinokinin (**18c**) [28]† represents an early ^{13}C NMR analysis in this field of natural products. The non-aromatic carbon signals were distributed on the basis of standard shift

* The structure of porosin had been considered earlier to be the 4,5-dehydro-7,7a-dihydro form of **12** [23]. The revision was necessitated initially by the ^{13}C NMR analysis of the natural product.

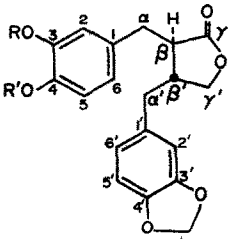
† Pluviatolide (**18a**) and hinokinin (**18c**) were isolated recently from the heartwood of *Libocedrus formosana* Florin (E. Wenkert and N. C. Franca, unpublished observations).

Table 4. Carbon shifts of lignans 18*

Carbons	18a†	18b†‡	18c§
1	129.5	136.7	131.2¶
2	110.9	112.5	108.4
3	146.1	151.0	147.4
4	144.2	138.4	145.8
5	114.3	120.4	107.8
6	121.0	122.7	121.1
α	34.6	34.4	34.4
β	46.3	46.5	46.1
γ	178.2	178.0	177.9
1′	131.1	131.1	131.0¶
2′	109.2	109.3	109.0
3′	147.5	147.7	147.4
4′	146.4	146.3	146.0
5′	107.9	108.1	107.8
6′	122.0	122.1	121.8
α′	38.1	38.5	37.9
β′	41.2	41.0	41.0
γ′	71.0	71.0	70.7
O_2CH_2	100.8	100.9	100.6

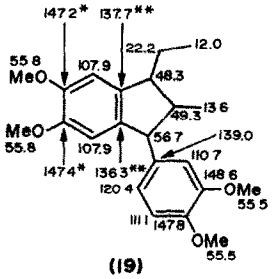
*The δ values are in ppm downfield from TMS; δ(TMS) = δ(CDCl₃) + 76.9 ppm. †δ(OMe) = 55.7 ppm. ‡δ^{Ac} (C=O) = 168.7 ppm and δ^{Ac} (Me) = 20.6 ppm. §δ(O_2CH_2) = 100.6 ppm. ¶Signals may be interchanged.

theory [4], while the aromatic carbons could be distinguished by the three compounds acting as models of each other. All shifts are shown in Table 4.

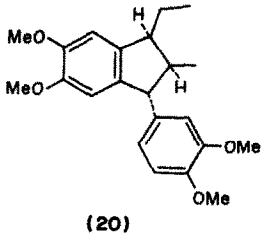


(18a) R = Me, R′ = H
(18b) R = Me, R′ = Ac
(18c) R+R′ = CH_2

Styrenes or alkyl aryl carbinols are known to give dimers of the 1-arylindane type on exposure to acid [29–34]. This facile reaction was encountered also in the preparation of carbinols **3e** and **3f** on route to the model ethers **3g** and **3h**, respectively (*vide supra*). As a consequence it was of interest to check the stereochemistry of the indane isomer, the α-isomer **19** derived from **3e** [33], by ^{13}C NMR analysis. Stereostructure **20** had been suggested for this compound on the basis of an exhaustive PMR determination [34].



(19)



(20)

The carbon shifts depicted on formula **19** were established in the following fashion. The dimethoxyphenyl shifts are based on those of **3g** and the remaining aromatic carbon and OMe shifts by difference. The methylene part of the Et group is unique, while the Me part can be differentiated from the other Me group by taking cognizance of the known 12.1 ppm shift of the Me function of ethylcyclohexane [4]. The benzylic methines can be distinguished from the remaining cyclopentane carbon by the difference of their residual coupling [12], while the distinction of the benzyl carbons themselves is founded on the fact of the arylated center being deshielded by an added β-effect not experienced by the ethlated site.

In order to assess the relative configuration of the Et, Me and 3,4-dimethoxyphenyl groups of **19**, several points need to be recognized. Firstly, as a comparison of the Me shifts of methylcyclopentane (20.1 ppm), *cis*-1,2-dimethylcyclopentane (14.8 ppm) and *trans*-1,2-dimethylcyclopentane (18.4 ppm) [35] indicates, the γ-effect of a Me group on its Me neighbor in a cyclopentane system is normal in a *cis* relationship but very low in a *trans* case. Secondly, comparison of the Me shift of the 1,3-dimethylindane (19.9 ppm) [4] and 1,3-dimethylcyclopentane systems (*ca* 21 ppm) [35] reveals the benzene ring to offer only a minimal *peri* effect, i.e. a γ-effect of *ca* 1 ppm. Thirdly, as the 3-Me shift of the licarins (**4**) (17.4 ppm), a dihydrobenzofuran system structurally related to the indane moiety, indicates, the γ-effect of a vicinal aryl group on a Me substituent is similar in magnitude to that of a Me group. Finally, the methylene of an Et group thus can be expected also to induce a γ-shift of a similar size on its neighboring Me sidechain in the five-membered ring of the substituted indane. Calculation of the benzylic Me shift for a compound like **19** in which the Et group is replaced by a Me function, using the known Δδ value of 7.2 ppm for the carbon directly attached to the ring in a ethylcyclohexane → methylcyclohexane change [4], leads to a δ value of 15.0 ppm, in accord only with a *cis*-1,2-diMe arrangement. As a consequence the Et and Me groups of **19** must be *cis* to each other. Since the latter is shielded only by *ca* 1 ppm, when compared with the Me groups of *cis*-1.2-dimethylcyclopentane (*vide supra*), it possesses a *trans* relationship to its aryl neighbor. The stereostructure **20** is in full agreement with the ^{13}C NMR analysis.

EXPERIMENTAL

IR spectra were recorded as films and PMR spectra of $CDCl_3$ solns containing TMS (δ = 0 ppm) at 60 MHz. ^{13}C NMR spectra were obtained at 25.2 MHz in the Fourier transform mode. The shifts denoted on formulas **1**, **2**, **5**, **6**, **8** and **19** are from $CDCl_3$ solns; δ(TMS) = δ($CDCl_3$) + 76.9 ppm. The stars on formulas **1**, **8** and **19** indicate permissible signal reversals.

1-(3,4-*Dimethoxyphenyl*-)1-*ethoxypropane* (**3g**). A mixture of 7.32 g of alcohol **3e** and 0.85 g of Na in 15 ml of toluene was refluxed under N_2 for 4 hr. After cooling, a soln of 34.8 g EtI in 20 ml of toluene was added and the mixture refluxed under N_2 for an additional 4 hr. It was then poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried and evaporated. Residue was chromatographed on Si gel and eluted with C_6H_6–$CHCl_3$ (1:1). Distillation of the eluate yielded 5.32 g of ether **3g**: bp 115°/18 Torr. (Found: C, 69.39; H, 8.81; $C_{13}H_{20}O_3$ requires: C, 69.91; H, 8.99%.) ν(cm^{-1}) 1605, 1595 (C=C); δ 0.84 (*t*, 3, *J* 7 Hz, Me), 1.13 (*t*, 3, *J* 7 Hz, ethoxy Me), 1.4–2.0 (*m*, 2, CH_2), 3.32 (*q*, 2, *J* 7 Hz, ethoxy CH_2), 3.90 [*s*, 6, $(OMe)_2$], 4.01 (*t*, 1, *J* 6 Hz, CH), 6.7–6.9 (*m*, 3, aromatic Hs).

1-(3,4-*Methylenedioxyphenyl*-)1-*ethoxypropane* (**3h**). A mixture of 5.12 g of alcohol **3f** and 0.65 g of Na in 20 ml of toluene was refluxed under N_2 for 7 hr. After cooling a soln of 26.4 g of EtI in 10 ml of toluene was added and the mixture refluxed under N_2 for 4 hr. After work-up the product was distilled yielding 4.20 g of ether **3h**: bp 82°/1 Torr. (Found: C, 68.98; H, 7.65; $C_{12}H_{16}O_3$ requires: C, 69.21; H, 7.74%.) ν(cm^{-1})

1630, 1610 (C=C); δ 0.84 (*t*, 3, *J* 7 Hz, Me), 1.13 (*t*, 3, *J* 7 Hz, ethoxy Me), 1.4–2.0 (*m*, 2, CH_2), 3.32 (*q*, 2, *J* 7 Hz, ethoxy CH_2), 4.01 (*t*, 1, *J* 6 Hz, CH), 5.92 (*s*, 2, OCH_2O), 6.7–6.9 (*m*, 3, aromatic Hs).

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