drochloride, 645-33-0; *p*-hydroxyphenylpyruvic acid, 156-39-8; benzoyl chloride, 98-88-4; 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 15357-92-3; *N*-benzoyl-7-benzyloxy-6-methoxy-1-cyano-1,2,3,4-tetrahydroisoquinoline, 57256-43-6; benzyl chloride, 100-44-7; *N*-benzoyl-7-benzyloxy-1-benzyl-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 57256-44-7; *N*-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 10174-83-1; *N*-benzoyl-1-(*p*-benzyloxylbenzyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 57256-45-8; acetyl chloride, 75-36-5; diazomethane, 334-88-3.

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The Polyphenolic Acids of *Lithospermum ruderale*. II. Carbon-13 Nuclear Magnetic Resonance of Lithospermic and Rosmarinic Acids

Charles J. Kelley, Richard C. Harruff, and Marvin Carmack*

Contribution No. 2739 from the Department of Chemistry
Indiana University, Bloomington, Indiana 47401

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The ^{13}C NMR spectra of caffeic acid (**3a**) and 3-(3,4-dihydroxyphenyl)lactic acid (**4a**) and a series of their O-alkylated derivatives in neutral aqueous solutions are fully assigned. These chemical shifts are used to assign the carbons of rosmarinic (**2**) and chlorogenic (**5**) acids. The foregoing compounds serve as models to interpret the ^{13}C NMR spectrum of lithospermic acid (**1**), $C_{27}H_{22}O_{12}$. Also discussed are the ^{13}C NMR spectra of quinic acid (**6**) and two morphinane derivatives, oxymorphone (**10**), and oxycodone (**11**), containing aromatic rings structurally similar to **1**.

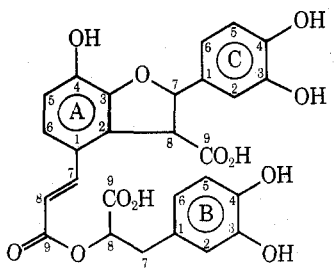
In recent work on the constituents of the roots of *Lithospermum ruderale* (Dougl. ex Lehm.), we postulated structure **1** for lithospermic acid, the principal polyphenolic acid in the plant.[1] Rosmarinic acid (**2**) was also identified as a minor plant constituent. Evidence for structure **1** and for the presence of **2** in *L. ruderale* rested largely on ^1H NMR and mass spectral data from derivatives of **1** and **2**. To obtain further confirmation for structure **1** and to develop an analytical method for the assay of fractionated aqueous extracts from the plant, we undertook a study of the ^{13}C NMR spectra of **1**, **2**, and a series of model compounds.

Compounds **1** and **2** are composed of phenylpropanoid subunits. For convenience in comparing chemical shift data, each subunit (the aromatic ring and the attached

Table I
Carbon-13 Chemical Shift Assignments of Catechol-Containing Acids[a]

Acid	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Cation	pH	M
(1) Lithospermic acid[c]										K, etc.	5.5[b]	0.3
Unit A	123.5	128.6	146.8	144.2	117.6	121.4	142.4	115.6	168.3			
Unit B	130.3	116.9	144.0	142.7	116.3	121.6	37.2	76.6	176.9			
Unit C	133.3	113.4	144.2	142.4	116.3	118.1	88.9	59.0	178.8			
(2) Rosmarinic acid										Na	7.5[b]	0.6
Unit A	126.5	113.6	143.7	146.7	115.9	122.4	145.8	115.0	168.6			
Unit B	129.9	117.1	143.7	142.4	115.9	121.8	36.8	76.2	177.2			
(3a) Caffeic acid	127.8	114.5	144.1	145.9	116.1	121.4	141.0	121.2	176.0	Li	7.4	1.0
(4a) 3-(3,4-Dihydroxyphenyl)lactic acid	130.8	117.2	143.7	142.4	116.1	121.7	39.7	73.5	180.5	Na	6.2	1.0
	129.3	117.2	143.7	142.8	116.2	121.8	38.9	71.3	177.1	(HCl)	0.3	1.0
(5) Chlorogenic acid										Na	4.5	0.5
Unit A	126.6	114.1	144.2	147.0	116.0	122.6	145.9	115.2	168.9			
Unit B	76.6	38.3	70.6	72.8	71.0	37.3	180.1					
(6) Quinic acid	77.0	40.7	67.1	75.2	70.5	37.4	181.2			Li	4.6	1.2
	74.9	40.3	66.5	75.7	70.1	36.9	177.7			(HCl)	0.7	1.1
(7) Dopa [3-(3,4-Dihydroxyphenyl)alanine]	126.4	117.1	144.3	143.7	116.6	121.9	35.1	54.5	171.7	(HCl)	1.0	0.8
(8) 3,4-Dihydroxyphenylacetic acid	129.7	117.2	143.9	142.5	116.4	121.6	43.4	181.0		Li	5.2	1.0

[a] Spectra were obtained at 15.1 MHz (1 at 25.2 MHz) in H_2O (1 and 2 in D_2O). [b] These values are pD's, i.e., glass electrode measured pH + 0.4. [c] Most of the carbon resonances of 1 fall in groups where alternate assignments are possible. Many of our reasons for assigning the carbons as they appear in this table are discussed in the last section of the paper.



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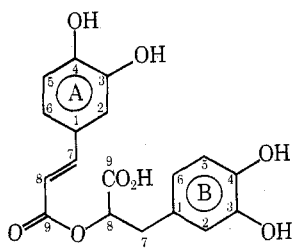

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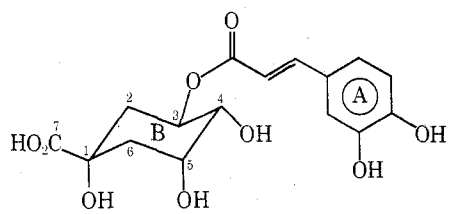

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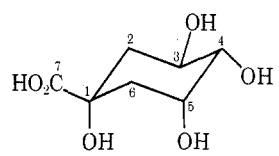

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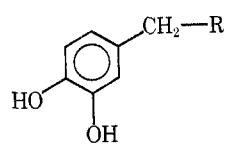
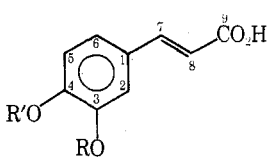


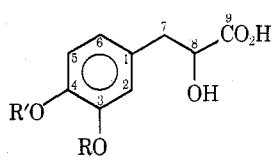
7, R = $CHCO_2H$ | NH_2

8, R = CO_2H

three-carbon side chain) has been labeled with a letter, A, B, or C. Within each subunit, the carbon atoms are numbered from C-1 to C-9. The model compounds, caffeic acid (**3a**) and 3-(3,4-dihydroxyphenyl)lactic acid (**4a**), are numbered by the same system.



3a, R = R′ = H
b, R = Me; R′ = H
c, R = H; R′ = Me
d, R = R′ = Me
e, R-R′ = $-CH_2-$
f, R-R′ = $-CMe_2-$



4a, R = R′ = H
b, R = Me; R′ = H
c, R = H; R′ = Me
d, R = R′ = Me
e, R-R′ = $-CH_2-$
f, R-R′ = $-CMe_2-$

Table I contains assignments of the ^{13}C NMR chemical shifts observed for compounds **1** and **2**, the assignments for model compounds **3a, 4a,** chlorogenic acid (**5**), quinic acid (**6**), and 3,4-dihydroxyphenylacetic acid (**8**)—all in neutral solution as alkali metal salts—and for comparison the chemical shifts of **4a, 6,** and Dopa (**7**) in acidic solution.

Chemical Shift Assignments for Monomeric Phenylpropanoids. Since both natural products **1** and **2** contain units like model compounds **3a** and **4a,** we put a special effort into correctly assigning the individual carbon resonances in these two models. Using chemical shift theory[2] and residually coupled ^{13}C NMR spectra obtained by the off-resonance decoupling technique, we assigned carbons 1, 7, and 9 of **3a** and 1 and 6–9 of **4a.** Pairs of similar carbons 2, 5 and 3, 4 in **3a** and **4a** and 6, 8 of **3a** were not distinguishable.

Another way to establish carbon assignments is by analysis of the fine structure of fully coupled ^{13}C NMR spectra. Coupled spectra can be obtained with NOE enhancement by alternatively pulsing carbon and proton frequencies, a technique called gated decoupling.[2b,3] The 1,3,4-trisubstituted benzene derivatives studied here are easily analyzed by this technique because of the pattern of long-range coupling constants generally observed in benzene rings.[4] The magnitude of the three-bond coupling constant (^3J) is so much greater than either ^2J or ^4J that it will be the dominant factor in determining the fine structure of the carbon resonances. Spectral parameters for **3a** and **4a** obtained by gated decoupling are presented in Table II. By inspection, C-2 will have two ^3J's in **3a** and three ^3J's in **4a,** while C-5 will experience no ^3J's in either compound. Thus in the undecoupled spectra of **3a** and **4a,** C-5 appears as a pair (^1J = 160 Hz) of very sharp lines, while C-2 is a pair of triplets in **3a** and a pair of quartets in **4a.**

A similar analysis can be used to distinguish the pair of carbons 3, 4 in both models. C-3 should have only a single ^3J while C-4 should have two ^3J's. C-4 appears as a clean triplet with no discernible ^2J in both **3a** and **4a.** Unfortunately the fine structure of C-3 in **3a** is obscured by acci-

Table II
Fully Coupled ^{13}C NMR Spectra of 3a and 4a

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
3a multiplicity, $^1J_{CH}$, Hz	s	d, 157	s	s	d, 160	d, 160	a	d, 155	s
Fine structure, $^2J_{CCH}$, $^3J_{CCCH}$, Hz	m	t, 5.4	a	t, 7.0	s	dd, 6,7	m	s	dd, 3, 7
4a multiplicity, $^1J_{CH}$, Hz	s	d, 162	s	s	d, 164	d, 164	t, 132	d, 151	s
Fine structure, $^2J_{CCH}$, $^3J_{CCCH}$, Hz	tt, 2+ 7	q, 6	dd, 3 7	t, 7+	s	q, 6	t 4	t, 4	b

[a] Not analyzable owing to accidental overlap of C-3 resonance with the low-field leg of C-7 resonance. [b] Not measured.

Table III
Carbon-13 Chemical Shifts of Alkylated Catechol Acids[a]

Acid	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C–O	C–C–O	Cat-ion	pH
(3b) Ferulic acid[b,c]	127.7	110.5	147.1	146.4	115.3	121.9	141.3	121.1	175.8	55.6		Li	6.6
(3c) Isoferulic acid	128.0	113.5	144.7	148.5	111.6	121.5	140.8	121.3	175.7	55.5		Li	7.0
(3d) 3,4-Dimethoxycinnamic acid	127.8	109.2	147.5	148.8	110.7	121.6	140.9	121.6	175.7	55.1		Na	11.0
(3e) 3,4-Methylenedioxy-cinnamic acid[d]	129.6	106.3	147.4	148.1	108.3	123.6	140.7	122.1	175.7	101.4		Li	7.4
(3f) 3,4-Isopropylidene-dioxycinnamic acid[e]	129.1	106.3	147.0	147.7	108.3	123.2	140.8	122.1	175.3	118.8	25.0	Li	7.3
(4b) Vanillactic acid	130.7	113.6	147.1	143.4	115.4	122.1	40.0	73.5	180.6	56.0		Na	8.2
(4c) Isovanillactic acid[e,f]	131.4	116.5	144.5	145.9	112.6	121.4	39.7	73.4	180.4	56.1		Na	7.2
(4d) 3-(3,4-Dimethoxy-phenyl)lactic acid	131.3	113.0	147.6	146.5	111.6	121.9	40.1	73.5	180.6	55.7		Na	5.6
(4e) 3-(3,4-Methylene-dioxyphenyl)lactic acid	132.0	109.7	146.8	145.3	108.2	122.5	40.1	73.4	180.5	100.8		Li	6.8
(4f) 3-(3,4-Isopropyli-denedioxyphenyl)-lactic acid[e]	131.8	109.7	146.4	145.1	108.2	122.2	40.2	73.5	180.5	118.3	24.8	Li	6.6

[a] Spectra obtained at 15.1 MHz on 0.8–1.0 *M* solutions in H_2O. [b] ^{13}C NMR reported in acetone-d_6–D_2O (9:1) with shifts of carbons 3, 4 reversed.[8] [c] Assignments of carbons 3, 4 verified by pH change 7.5 → 8.6; $\Delta\delta_{C-4}$ = +2.0 ppm; $\Delta\delta_{C-3}$ = +0.6 ppm with that 1.1-unit pH change; $\delta_{C-3} = \delta_{C-4}$ = 147.4 ppm at pH 8.2. [d] ^{13}C NMR of amide reported.[6] [e] Assignments of carbons 2, 5 confirmed by gated decoupling. [f] Change of pH from 7.2 to 8.6 results in a downfield shift of C-3 (0.3 ppm) but no change in any other resonance.

dental overlap with the downfield leg of the C-7 resonance. In **4a**, however, the fine structure of C-3 is a doublet of doublets. The doublet with J = 7 Hz is clearly the ^3J coupling with H-5, while the second doublet with J = 3 Hz most likely arises from an unusually large ^2J to H-2.

In compound **3a**, C-8 is easily distinguished from C-6 since the resonance of the former is a pair (^1J = 155 Hz) of sharp peaks with no three- (or large two-) bond couplings, while the latter is a pair (^1J = 160 Hz) of doubled doublets due to slightly unequal ^3J's to H-2 and H-7. The carboxylate carbon (C-9) in **3a** appears as a doublet of doublets, $^3J > {}^2J$, in the ^{13}C NMR spectrum as expected from the observed ^1H NMR spectrum of ^{13}C-labeled *trans*-crotonic acid.[5]

The distinguishing features of the ^{13}C NMR spectra of the 3,4-dihydroxybenzene rings of **3a** and **4a** then are the reversals observed in the relative chemical shifts of carbons 2, 5 and 3, 4 on going from the unsaturated to the saturated side chains. This effect may be produced by the shielding of C-2 and a deshielding of C-4 by the unsaturated side chain in **3a**. Carbons 3, 5, and 6 remain relatively unaffected by the nature of the C-1 side chain. The selective shielding of C-2 but not C-6 in **3a** apparently reflects a conformational preference in solution. For example, preferred rotamers have been postulated to explain selective shieldings in the ^{13}C NMR spectrum of the alkaloid piperine.[6]

Although assignments of carbon resonances by gated decoupling are sufficiently unambiguous, we sought to confirm these assignments in a series of compounds in which the phenolic groups are alkylated. Compilations of these data would be useful in assigning alkylation patterns for related series of compounds from their ^{13}C NMR spectra. Previous additivity schemes for these types of aromatic rings have given admittedly ambiguous predictions for vanil and isovanil rings.[7]

Table III contains the ^{13}C NMR data for similar series of cinnamate (**3b–f**) and phenyllactate (**4b–f**) derivatives. The shifts observed in these series are in agreement with chemical shift theory if one makes the reasonable assumption that for the caffeate derivatives the shielding of C-2 and the deshielding of C-4 by the unsaturated side chain at C-1 in **3a** are maintained throughout the series.

Independent assignments of carbons 3, 4 in **3b** were obtained by varying the pH of the solution. Since even partial ionization of a phenolic hydroxyl group results in a strong deshielding of the phenolic carbon resonance, titration over only a small pH range serves to identify the individual carbons. Comparison of the $\Delta\delta$ values for **3b** on titration to pH 8.6 (see Table III, footnote *c*) with the published ^{13}C NMR titration of a tyrosine dipeptide[9] indicates that the phenolic function of **3b**, which has an unsaturated group para to it, is somewhat more acidic than the phenolic group of tyrosine. The ^{13}C NMR spectrum of **4b** at pH 8.2 (Table III) by analogy to the tyrosine titration curve[9] should not show any effects of phenolic ionization.

Independent confirmation of the assignments of carbons 2, 5 in **3f**, **4c**, and **4f** were obtained by gated decoupling. The same technique confirmed the assignment of carbons 3, 4 in **4c**, but the resolution of the fine structure of the resonances of these carbons in **3f** and **4f** was so poor, possibly through four-bond coupling to the methyl protons, that

Table IV
^{13}C NMR Chemical Shifts in Morphinane Aromatic Rings

	C-①	C-②	C-③	C-④	C-⑤	C-⑥
Oxymorphone (10)	121.7	127.1	143.0	138.9	118.6	121.0
Oxycodone (11)	122.6	127.1	144.0	142.6	115.4	121.0

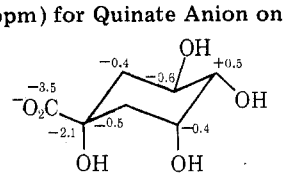
these assignments could not be confirmed by this method.

Chemical Shift Assignments for Natural Products. A. Caffeate Esters. To help in assigning the natural products 1 and 2, we desired a model ester of caffeic acid to complement the data obtained for the caffeate salt **3a.** Such a model was found in chlorogenic acid (**5**), a caffeate ester of quinic acid (**6**). The deshielding of carbons 1, 8, and 9 and the shielding of C-7 in the salt **3a** as compared with the ester **5** are completely consonant with the observation[10] that the introduction of a charge into an α,β-unsaturated carboxylate system imposes strong shifts of alternating polarity along the unsaturated chain.

A detailed analysis of the ^{1}H NMR spectra of chlorogenic and quinic acids left no doubt that in solution the cyclohexane rings are in those chair conformations depicted in structures **5** and **6**.[11] The ^{13}C NMR spectra of chlorogenic and quinic acids (Table I) are in full agreement with this picture.

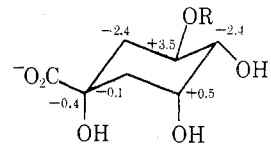
In quinic acid (**6**), the axial proton H-3 is 1,3-diaxially disposed to two OH groups (at C-1 and C-5). This relationship causes a strong deshielding[12] of the resonance of C-3 and allows its unambiguous assignment in **6**. The oxygenated carbon at 75.2 ppm in the quinate salt was identified as C-4 since the intensity of this resonance was least affected by the addition of 1 mol % of Mn(II) acetate to the quinate solution.[13] The paramagnetic Mn(II) ion, which would coordinate with the carboxylate anion in **6**, broadens the resonances of carbons 1 and 7 so that they are not observable, while the resonances of carbons 2, 3, 5, and 6 are truncated with intensities about one-third that observed for the 75.2-ppm resonance. The remaining oxygenated methine, C-5, must resonate at 70.5 ppm in the quinate salt. The two methylene carbons (2, 6) in **6** differ only in that C-2 experiences a β effect from an equatorial OH and C-6 experiences a β effect of an axial OH. Chemical shift theory thus places C-2 at lower field than C-6.[14] Carbon 1 was identified by off-resonance decoupling. These assignments of the resonances of quinate anion are completely consistent with the change in the chemical shifts ($\Delta\delta$) observed on passing from the anion to the fully protonated acid (cf. Chart I). The chemical shift changes observed upon protonation of quinate anion are analogous to those occurring with the protonation of the α-hydroxy acid **4a** [compare carbons 7–9 in **4a** at pH 6.2 and at pH 0.3 (Table I)].

Chart I
$\Delta\delta$ Values (ppm) for Quinate Anion on Protonation



The assignments of carbon resonances for chlorogenic acid (**5**) are based on similar arguments, and are supported by specific proton–carbon decoupling experiments employing known ^{1}H NMR chemical shifts for H-3, H-4, and H-5 of **5**.[10] Moreover, a comparison of the changes ($\Delta\delta$) in the carbon resonances of the quinate anion on replacing the C-3 hydroxyl with a caffeyloxy group (see Chart II) shows a strong deshielding of the acylated carbon and symmetrically disposed shieldings for the β carbons. The dissymmetry of the γ effect may indicate a preferred orientation for the caffeyl group in **5** with respect to the quinate ring.

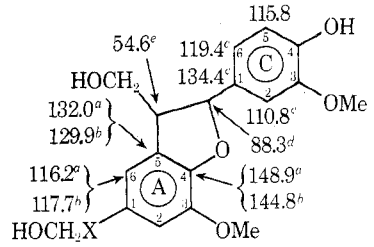
Chart II
$\Delta\delta$ Values (ppm) for Quinate Anion on Acylation at C-3



Having assigned the carbons of the quinic acid ester of caffeic acid, it then becomes a simple matter to assign the caffeate (unit A) carbons of rosmarinic acid (**2**) by comparison. The phenyllactate portion of rosmarinic acid (unit B) can be assigned by comparison to the chemical shifts of the corresponding carbons of **4a.** The significant differences which exist between carbons C-1 and C-7–C-9 of **2** and of **4a** correspond in magnitude to the differences observed in the quinate anion on acylation as shown in Chart II.

B. Lignan and Morphinane Models. The distinctive structural features of **1**, the 1,2,3,4-tetrasubstituted ring A and the dihydrobenzofuran (coumaran) ring, are not duplicated in any of the compounds heretofore mentioned. ^{13}C NMR spectra of several lignan model compounds containing a dihydrobenzo[*b*]furan ring system have been reported, but these differ significantly from **1** in that the point of attachment of the three-carbon side chain is not ortho to the fused dihydrofuran ring.[8] To aid in the discussion of the assignments of the carbon resonances of **1**, the literature assignments for the two lignan models, **9a** and **9b,** are included in Chart III. The rings are labeled A and C to correspond with **1**, but it should be noted that the numbering system within ring A does not correspond to that employed in **1**.

Chart III
Selected ^{13}C NMR Chemical Shifts for Dihydrobenzo[*b*]furans in Acetone-d_6–D_2O (9:1)[8]



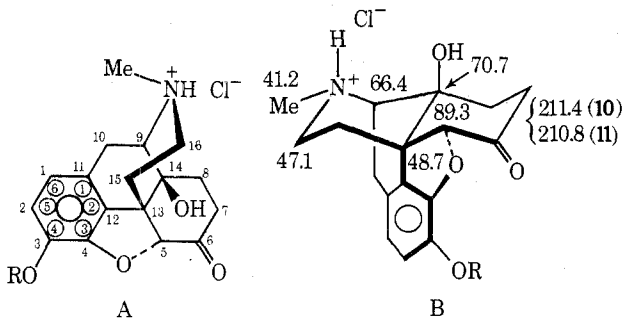
9a, X = CH=CH
b, X = CH_2CH_2

[a] for **9a**. [b] for **9b**. [c] ±0.1 ppm. [d] ±0.2 ppm. [e] ±0.3 ppm.

Somewhat surprisingly, a more closely congruent model for the A ring of **1** is present in an important alkaloidal family, the morphinanes. The model compounds which we have chosen, oxymorphone (**10**) and oxycodone (**11**), contain both a 1,2,3,4-tetrasubstituted benzene ring with 1,2-carbon substitution and 3,4-oxygen substitution; the 2,3 positions are the carbon and oxygen, respectively, of a dihydrofuran ring.

^{13}C NMR spectra of **10** and **11** in the form of their hydrochloride salts were recorded at 25.2 MHz in aqueous solu-

tions, and a gated decoupled spectrum of **10** was obtained. Assignments for the chemical shifts of the aromatic carbons are listed in Table IV, while the shifts of those aliphatic carbons assignable on the basis of multiplicity and chemical shift theory appear in formula B.[15] The number-



10, R = H, oxymorphone
11, R = Me, oxycodone

ing system for the morphinane skeleton appears on formula A, but in addition another set of circled numbers *within* the aromatic ring is added to designate those carbon atoms equivalent to the same-numbered aromatic carbon atoms in ring A of **1**. This latter set of numbers enclosed in circles is used exclusively in Table IV and in the following discussion.

Three pairs of aromatic carbons, quaternary, C-(1,2), oxygenated, C-(3,4), and protonated, C-(5,6), are easily distinguished from the spectra in Table IV and the gated decoupled spectrum of **10**. Individual carbons within the pairs 1,2 and 5,6 are identified by recourse to empirical shielding parameters[7] which predict that on O-methylation of a phenol, ortho and para carbons experience changes in chemical shift while carbons meta to the phenolic center remain invariant. An analogy which allows one to distinguish C-(3) from C-(4) was derived from examination of spectra in Tables I and II. As is exemplified by many pairs of compounds, e.g., **3a** → **3b**, **3a** → **3c**, **3b** → **3d**, etc., O-methylation of one oxygen function of a catechol ring causes *both* oxygenated carbons to be deshielded. In going from **10** to **11**, then, deshielding of both oxygenated carbons would be expected. This happens only if C-(3) and C-(4) in **11** are as assigned in Table IV.[16]

C. Lithospermic Acid. ^{13}C NMR spectra of lithospermic acid salts were obtained at 15.1 MHz in water and 25.2 MHz in D_2O. Resolution of 26 of the 27 carbons present was obtained in the latter measurement. The only unresolved resonance (at 116.3 ppm) is clearly due to two carbons on the basis of its intensity. In discussing the assignments of the resonances of **1**, we have found it convenient to break up the 27 carbons into six groups of resonances based on chemical shift, and thus to a large extent functional type. In some cases chemical shift theory and model compounds are sufficient to provide unambiguous assignment of individual carbons. In many cases, however, the similarity of chemical environment of several carbons precluded their definitive assignment. The following six paragraphs contain a discussion of the assignments of the resonances within the various groups of resonances of lithospermic acid.

The three carboxylate carbons (two anions and an ester) were assigned on the basis of the close correspondence of two of these chemical shifts to those of the two carboxylates in **2**.

Six oxygenated aromatic carbons and one protonated vinyl carbon, C-7(A), resonate between 142 and 147 ppm. The latter carbon was easily assigned by off-resonance decoupling. The oxygenated aromatics include five phenolic carbons and one alkylated ether. The most deshielded of these resonances, 146.8 ppm, is assigned to the aromatic ether carbon, C-3(A), in agreement with the assignments of **3b** (Table III), and the morphinanes, **10** and **11** (Table IV). Carbon 4(A) in **1**, which might be expected to resonate at lower field like C-4(A) in **2** and **5**, is assigned in agreement with the observed shieldings for carbons ortho to fused carbocyclic[2a] and fused heterocyclic five-membered rings (compare carbons 2, 5 of model compounds **3e/3f** and **4e/4f** with **3d** and **4d** in Table III).

The four quaternary aromatic carbons in **1** resonate between 123 and 134 ppm. The most deshielded of these is assigned as C-1(C) on the basis of the chemical shift of carbon C-1(C) in models **9a** and **9b**. The resonance of C-1(B) is little changed from the corresponding resonance in **2**. In fact, in the 15.1-MHz ^{13}C NMR spectrum of mixtures of **1** and **2** from *L. ruderale*,[1] the resonances of C-1(B) for both compounds appear as a broadened singlet. The remaining two quaternary carbons, C-1(A) and C-2(A), are assigned by comparison with the corresponding carbons in the morphinane aromatic rings of **10** and **11**.[19]

Lithospermic acid (**1**) contains three carbons of the C-6 type. Two of these carbons resonate in the normal range, i.e., between 121 and 122 ppm. The third C-6 carbon, which resonates at 118.1 ppm, is shielded by a full 3 ppm. Two possibilities exist for the assignment of this shielded carbon. On the basis of the chemical shifts observed for carbons C-6(C) in models **9a** and **9b** and also the shift of C-6 in epinephrine,[21] carbon C-6(C) in **1** should be shielded by 1–2 ppm owing to the presence of the α oxygen atom on C-7(C). This shielding is somewhat less than that required to fully explain the 118.1-ppm resonance. Alternatively, the shielding by about 3 ppm of C-2 in caffeic acids and their esters, which we explained by a preferred orientation of the unsaturated side chain, might in **1** be felt by C-6(A) because the bulky substituents at C-2(A) would cause a reorientation of the unsaturated group toward C-6(A). Such a reorientation would also be felt by C-7(A) in **1** which in fact is found to be shielded by more than 3 ppm relative to C-7(A) in **2** and **5**. If this latter explanation were accepted, however, the lack of any enhanced shielding for C-6(C) would remain to be explained.

The remaining protonated, unsaturated carbons in **1**, which include five aromatic carbons with ortho oxygen substituents and the vinyl carbon C-8(A), resonate between 113.4 and 117.6 ppm. Gated decoupling experiments with **1** did not provide sufficient evidence to allow unambiguous assignments within this group of resonances. These resonances are tentatively assigned in Table I, however, by reference to model compounds. A purer sample of **1** and additional model compounds will be required to make definitive assignments.

The assignments of the four aliphatic carbons, three methine and one methylene groups, are in **1** unambiguous with **2** and **9a,b** as models.

In solving the structure of lithospermic acid, we synthesized a variety of fully methylated esters of model compounds.[1] ^{13}C NMR spectra, measured in $CHCl_3$ at 15.1 MHz, of a selected set of these compounds are reported in Table V. Chemical shift assignments in Table V are internally consistent and are in complete agreement with the assignments made for the sets of phenolic model compounds recorded in aqueous solution.

Experimental Section

^{13}C NMR spectra were measured at 15.1 MHz in a Varian spectrometer operating in the pulsed Fourier mode. Samples of 2-ml volume were measured in spinning 13-mm tubes at an operating

Table V
^{13}C NMR Chemical Shifts for Fully Methylated Derivatives[a]

Registry no.		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	OMe (ether)	OMe (ester)	Other
5396-64-5	Methyl 3,4-dimethoxycinnamate[b]	127.2	109.7	149.1	151.1	111.0	122.4	144.6	115.4	167.5	55.8	51.4	
57362-39-7	Pentamethyl rosmarinate												
	Unit A	127.1	109.8	149.2	151.3	111.0	122.9	145.9	114.6	166.2	55.9		
	Unit B	128.3	112.6	148.7	148.1	111.3	121.4	37.2	72.9	170.2	55.9	52.3	
54640-00-5	Methyl 3-(3,4-dimethoxyphenyl)lactate	128.8 [130.0	112.8 113.6	148.7 149.1	147.9 148.2	111.3 111.9	121.4 121.7	40.1 40.2	71.3 71.9	174.7 174.1	56.0 55.4	52.3 51.5][b-d]	
57362-40-0	Methyl 2-acetoxy-3-(3,4-dimethoxyphenyl)-propanoate	128.3	112.5	148.7	148.0	111.3	121.4	36.9	73.0	170.1	55.8	52.2	170.1 (C=O), 17.6 (Me)

[a] Recorded at 15.1 MHz in $CHCl_3$; $\delta(CHCl_3) = 77.2$ ppm. [b] Assignments of carbons 2, 5 confirmed by gated decoupling; fine structure of carbons 3, 4 obscured by ^3J to Me protons. [c] Spectrum recorded in acetone-d_6 at 25.2 MHz; $\delta(CD_3$ of solvent) = 29.2 ppm. [2b] [d] Downfield shifts for aromatic carbons in acetone-d_6 with respect to $CHCl_3$ have been noted before.[8]

probe temperature of 36 ± 3°. Chemical shifts were recorded from spectra with a digital resolution of 0.13 ppm. All chemical shifts in aqueous solutions were measured with respect to an internal standard of 1% dioxane: δ(dioxane) = 66.5 ppm in water with respect to external Me_4Si in $CHCl_3$ (1:4 by volume); $\delta(Me_4Si) = 0.0$ and $\delta(CHCl_3) = 77.2$ ppm.

The experiments with gated decoupling were performed in a Varian XL-100 spectrometer operating at 25.2 MHz. Carbon frequencies were pulsed every 5 sec and the proton decoupler was gated on for 3.73 sec prior to the ^{13}C observation pulse. Samples of 2-ml volume were measured in spinning 12-mm tubes at 34 ± 1°. An average of 400 pulses was used to accumulate data for the noise-decoupled spectra of the phenylpropanoid monomers and **10** and **11**. From 1500 to 4000 pulses were used to obtain decoupled spectra of **1**. From 1000 to 1500 pulses were required for the gated decoupling experiments.

The sample of **1** used in this study was obtained by fractionation of water-soluble portion of the roots of *L. ruderale* and was designated F3 in our earlier publication.[1] The organic material was at least 85% pure, in the form of metallic salts (mostly potassium). In our initial ^{13}C NMR spectrum of this plant fraction, the resonances of the carboxylate anions, C-9(B) and C-9(C), were very broad, as were, to a lesser extent, those of the neighboring carbons C-8(B) and C-8(C). Since traces of paramagnetic ions, e.g., Mn(II), Fe(III), and Cu(II), would cause this effect, we added 20 μl of 0.25 *M* disodium EDTA to our 2-ml samples to chelate any interfering ions. This treatment dramatically increased the peak heights of the anionic carboxylate resonances. Subsequently, EDTA was added to all solutions of natural plant materials before their ^{13}C NMR spectra were measured.

The synthetic carboxylic acids were measured as their sodium or lithium salts. At the concentrations employed (0.8–1.2 *M*) the sodium salts were not always soluble, e.g., **3a** and **3c**, so we used lithium salts routinely in later work. No specific effects for either cation were noted in the ^{13}C NMR spectra.

Registry No.—**1**, 28831-65-4; **2**, 20283-92-5; **3a**, 331-39-5; **3b**, 1135-24-6; **3c**, 537-73-5; **3d**, 2316-26-9; **3e**, 2373-80-0; **3f**, 57362-37-5; **4a**, 23028-17-3; **4b**, 2475-56-1; **4c**, 52262-43-8; **4d**, 32255-79-1; **4e**, 949-14-4; **4f**, 57362-38-6; **5**, 327-97-9; **6**, 36413-60-2; **7**, 59-92-7; **8**, 102-32-9; **10**, 76-41-5; **11**, 76-42-6.

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(15) Chemical shifts for the corresponding aliphatic carbons of **10** and **11** are within 0.15 ppm. Shifts for the carbonyl carbons differ as noted on formula B. The four methylene carbons in **10** and **11** which were not unambiguously assignable resonate at 23.3, 27.3, 30.7, and 34.7 ppm. The OMe carbon in **11** resonates at 56.7 ppm.
(16) Additionally, the assignments of the quaternary and the oxygenated aromatic carbons in the morphinanes **10** and **11** are in agreement with the relative shieldings of the corresponding ring carbons in codeine as deduced from spin-lattice relaxation data[17] and other considerations.[18]
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(19) Since the chemical shift differences ($\delta\Delta$) between C-(1) and C-(2) in **10** and **11** is $\simeq$ 4–5 ppm and the $\delta\Delta$ between C-1(A) and C-2(A) in **1** is 5.1 ppm, a reversal of the relative chemical shifts between the morphinanes and lithospermic acid would involve a shielding of C-2 by $\simeq$ 5 ppm and a simultaneous deshielding of C-1 by the same amount. The principal structural differences between **1** and **10/11**, i.e., the tertiary vs. quaternary center α to C-2 and the unsaturated side chain vs. the β-ammonium-substituted fused [C-(1) to C-(2)] cyclohexane ring, are in all probability insufficient to cause so large a chemical shift change.[20]
(20) In simple models, e.g., isopropylbenzene vs. *tert*-butylbenzene, the additional β effect of the third methyl group is <1 ppm, and similarly, the $\delta\Delta$ of C-1 between *o*-xylene and tetralin is also <1 ppm.[2a] Interestingly, in models lacking all substitution at C-2, i.e., Dopa (**8**), with a saturated side chain bearing a β-ammonium ion, vs. caffeate esters **2** and **5**, the resonances of C-1 and C-1(A) are virtually identical (see Table I). This observation further supports our use of morphinanes as models for ring A of **1**.
(21) Cf. ref 18, spectrum no. 356.

The 1-Hetera-4-cyclohexanone System. Proton and Carbon-13 Magnetic Resonance, Transannular Effects, and Conformational Analysis

Jerry A. Hirsch*[1] and E. Havinga

Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079, and the Gorlaeus Laboratories, Department of Organic Chemistry, University of Leiden, The Netherlands

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Proton (^{1}H NMR) and carbon-13 (^{13}C NMR) magnetic resonance have been applied to a series of 1-hetera-4-cyclohexanones in order to acquire information about ring conformations. The ^{1}H NMR results require evaluation of long-range couplings through the carbonyl groups prior to R-value analysis. Comparison of the ^{13}C NMR data with that from a series of 1-heteracyclohexanes and from acyclic analogues indicates (a) that the effects α and β to the heteroatom groups in the 1-hetera-4-cyclohexanones are proportional to the effects in the same positions in the 1-heteracyclohexanes except for cyclohexane-1,4-dione, and, therefore, indicate chair conformations; (b) that additivity relationships from the 1-heteracyclohexanes may be used as indications of chair or twist conformations in 1,4-diheteracyclohexanes and 1-hetera-4-cyclohexanones; and (c) that upfield carbonyl shifts in 1-hetera-4-cyclohexanones and related systems do not contain transannular electron-transfer components. Previous suggestions that upfield carbonyl shifts of approximately 10 ppm or less may be used to indicate transannular electron donation are refuted. An ordering of heteroatom group effects is presented based on ^{13}C NMR α shifts in these cyclic systems.

Cyclohexane and its derivatives have been subjected to extensive conformational analyses.[2] Numerous examples have been reported of both chair[2] and nonchair[2,3] preferences. In view of the predominantly twist nature of cyclohexane-1,4-dione[4,5] (**1a**) and its derivatives[4,6] and the predominantly chair nature of 1,4-dimethylenecyclohexane[4,7] and its analogues,[7,8] the question may be raised as to the extent to which sp^2-like hybridizations and electronic interactions cause this conformational dichotomy. A useful type of compound to help answer this question is the 1-hetera-4-cyclohexanone system (**1b–n**).

Various representative 1-hetera-4-cyclohexanones have been readily available for some time. Allinger and Jindal[9] investigated 1-acetyl-4-piperidone (**1b**) and 1-methyl-4-piperidone (**1c**) using Z values with n $\rightarrow \pi^*$ transitions, dipole moments, and infrared spectroscopy, and concluded that both compounds were predominantly in chair conformations. In particular, the N-acetyl system **1b** was not believed[9] to exhibit a transannular charge-transfer electrostatic interaction between the carbonyl groups in a boat conformation. However, no Z-value correlation was observed for this compound.

A series of papers by Katritzky and co-workers[10] has reported the cis–trans equilibrations of 3,5-dimethyl-1-hetera-4-cyclohexanones. These workers assumed that only chair conformations were significant; e.g., ". . . it is generally accepted that these compounds exist in a chair form".[10] Their base-catalyzed equilibrations were accomplished simultaneously with deuteration at the position α to the carbonyl group to simplify the proton magnetic resonance (^{1}H NMR) spectra, thereby eliminating the possibility of a concurrent R-value[4] type of conformational analysis.