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Characterization of Spiro-Bislactonic Phenolic Metabolites of Proteaceae by ^{13}C Nuclear Magnetic Resonance

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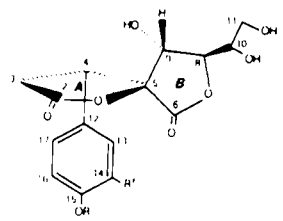
The ^{13}C NMR characteristics of a group of spiro-bislactonic phenolic metabolites of *Leucadendron* and *Leucospermum* species of the Proteaceae have been studied. The structure of a new member of this group, leudrin, has been established.

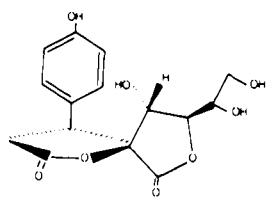
The great promise which ^{13}C NMR spectra have held for the characterization of natural products[2] has been richly fulfilled by the many studies now appearing. This tool has been used to establish the nature of alkyl chains unambiguously,[3] to demonstrate functional groups in puzzling circumstances,[4] to confirm or correct empirical formulas, and, in happy circumstances, to establish, together with ^1H NMR, the structures of surprisingly complex molecules without degradative or x-ray crystal studies.[5] However, in general, fruitful study of complex natural products has been possible only within the context of a series of closely related materials,[6] for knowledge of the factors which determine the chemical shifts of carbons in alicyclic and heterocyclic systems is still growing.[7] We describe here ^{13}C NMR studies of a group of plant phenolics not previously so studied which exemplify these problems, and which, with the support of the data of ^1H spectra taken at the field of a superconducting magnet, have led to the structure of a novel compound.

Previous studies on the phenolic constituents of the family Proteaceae have elucidated the structures and the stereochemistry[8] of leucodrin (**1**),[9] conocarpin (**4**),[10] conocarpic acid (**8**), and its methyl ester reflexin (**9**).[11] The structure and stereochemistry of leucodrin have been confirmed by an x-ray crystallographic study,[12] but those of the other compounds are based on interconversion and degradative studies, and on the spectral properties of the products. The configurations of C-4 in **1** and **4** have been established as *R* and *S*, respectively, by degradation of each to the corresponding *p*-methoxyphenylsuccinic acid, while that of C-10 is *S* in each case, as the chain of atoms C-8, C-10, and C-11 can be excised from both molecules in the form of L-glyceraldehyde. A key transformation in these studies is the conversion of conocarpin by bromine water to the spiroquinomethide ether (**5**), possible only for the configurations of C-4, C-5, and C-9 shown. The dienone–phenol rearrangement of **5** to a chroman such as **6** is attended by an upfield shift of H-8 in that compound,[10] which seems best accommodated by the configuration shown. Thus the configurations of all centers of the conocarpin series are firmly established with the exception of that at C-8. This paper particularly examines the ^{13}C NMR characteristics of this series of compounds.

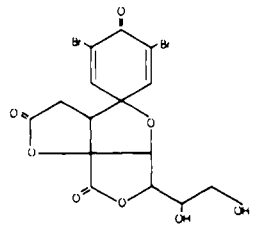
^{13}C Characteristics. The ^{13}C resonances observed in the ^1H noise-decoupled spectra are readily divided into several functional group categories[2] and methine and methylene carbons are readily recognized by off-resonance decoupled spectra. Within the aromatic group, C-15 is readily differen-



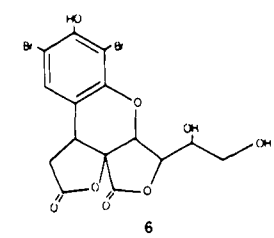
1. leucodrin, R = R′ = H
2. leucodrin methyl ether, R = CH_3, R′ = H
3. dimethylleudrin, R = CH_3, R′ = OCH_3



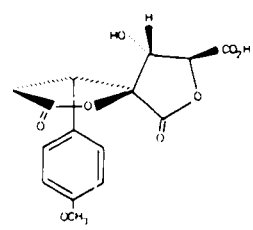
4. conocarpin



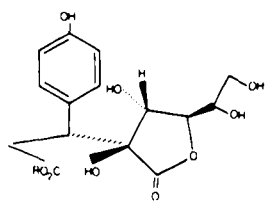
5



6



7. norleucodrinic acid methyl ether



8. conocarpic acid, R = H
9. reflexin, R = CH_3

Table I. Chemical Shifts in Dimethyl Sulfoxide Solution (ppm from Me_4Si)

Compd	Carbon atoms															
	2	3	4	5	6	8	9	10	11	12	13	14	15	16		17
Leucodrin (1)	175.0	33.6	41.3	90.3	172.3	80.2	69.5	68.4	61.6	123.7	130.3	115.8	157.4	115.8		130.3
Leucodrin methyl ether (2)	174.9	33.5	41.3	90.2	172.2	80.3	69.6	68.4	61.7	125.6	130.4	114.4	159.4	114.4		130.4
															OCH_3	55.4
Norleucodrinic acid methyl ether (7)	174.6	33.3	41.3	89.3	171.2	77.4	72.4	168.7		125.2	130.4	114.5	159.6	114.5		130.4
															OCH_3	55.4
Dimethyl-leudrin (3)	174.9	33.4	41.5	90.2	172.2	80.3	69.5	68.4	61.5	125.9	111.9	148.9[a]	148.7[a]	112.8		121.4
															OCH_3	55.6
Conocarpin (4)	174.7	32.7	47.6	88.0	172.7	79.4	73.4	67.8	61.8	122.8	130.5	115.3	157.2	115.3		130.5
Reflexin (9)	177.7	34.0	46.8	79.7	173.2	80.3	75.9	69.1	62.3	127.8	131.4	115.0	156.6	115.0		131.4
															OCH_3	51.5
Conocarpic acid (8)	169.5	31.2	44.8	74.9	173.9	82.7	79.0	69.4	61.4	126.6	129.6	115.6	157.1	115.6	129.6	

[a] These values can be interchanged.

tiated from C-12 and C-14/16 from C-13/17 by established hydroxyl substitution values.[2] The corresponding peaks of the phenol ethers, **2** and **7**, show the anticipated downfield shifts for C-15 and upfield shifts for C-14 and C-16. Of the methylene carbons recognized in the off-resonance spectra, that at high field is readily assigned to C-3, and that in midfield to C-11; the latter is, of course, absent in the spectrum of **7**. The two carbonyl peaks present in all of the spectra are differentiated by the observation that the one near 172 ppm (C-6) remains fairly constant throughout the series, while that at 175 ppm in the dilactones (C-2) is shifted in the compounds with ring A open. The remaining singlet at midfield is the signal of C-5. Four methine carbons are recognized by off-resonance spectra; that at high field clearly corresponds to C-4, but the distinction of C-8, C-9, and C-10 poses a more difficult problem. Because H-9 in the ^1H NMR spectra of this series of compounds is a doublet well separated from the signals of the other ^1H nuclei, it is possible to demonstrate by single frequency decoupling at the H-9 ^1H frequency that the signal near 70 ppm in the ^{13}C NMR spectra corresponds to C-9; the ^1H resonances of H-8 and H-10 are, however, closely coupled. Assignment of the resonances of carbon atoms C-8 and C-10 is based on the observation that the resonance at lower field shows more variation with stereochemical and structural changes; it is therefore C-8. The resonance at higher field is more nearly constant throughout the series, and is more suitable for C-10, distant from the site of these changes. The choice is consistent with the effects anticipated from the larger number of heavy atoms separated by two bonds from C-8.

The spectra of these compounds in dimethyl sulfoxide show the intriguing characteristic of broadened lines for the unsubstituted aromatic carbon atoms, C-13/17 and C-14/16, reflected to a lesser extent by other peaks. That this broadening results from an exchange of chemical shifts is supported by the spectra at higher temperatures in which the peaks are sharpened to widths characteristic of the resolution of the spectrometer. The phenomenon is dependent on the solvent, for the spectra of leucodrin (**1**) in methanol are sharp at room temperature, but broaden on chilling to −40 °C. Although the effect may result only from viscosity effects and more effective relaxation, earlier findings[11] indicated unusual steric crowding between the aromatic ring and the 9-hydroxyl of conocarpin. Inspection of Dreiding molecular models of this series of compounds clearly shows further strong steric interactions of the aromatic atoms C-13/17 and H-13/17 with the atoms at position 9 and, in the ring A opened compounds, at position 5. It was therefore interesting to compare the spectrum of conocarpin with that of leucodrin in a mobile solvent. Methanol is unsatisfactory for this purpose, however, as the more strained lactone system of conocarpin readily opens in methanol.[11] This difficulty was obviated by conversion of conocarpin to its tetrakistrimethylsilyl ether by reaction with trimethylsilylimidazole. A chloroform solution of this derivative shows aromatic peaks of normal half-width for all carbon atoms. The broadening of the peaks for C-13/17 and C-14/16 thus may be ascribed to the solvation of the oxygen-containing groups in the parent compounds.

Discussion

It is clear from the evolving knowledge of the relation of ^{13}C chemical shifts to the structures of cyclic systems that the effects of substituents and stereochemistry are subtle and complex.[7] Apparently, beyond the carbon directly substituted, the stereochemistry of a substituent is more important than its electronegativity.[7f] The effect of ring size may depend primarily on the dihedral angles of the ring atoms and the attached ^1H.[7g] In any event, the steric compression of attached ^1H can give rise to either shielding or deshielding.[7c,f]

In the series studied here, such effects produce chemical shift differences which cannot be completely explained. Gross structural changes do indeed produce anticipated major changes in the spectra. Thus, the opening of the lactone ring (4 vs. 8) results in an upfield shift of the carbinyl carbon, C-5, of 13.5 ppm and an upfield shift of 5.2 ppm in the carboxyl carbonyl. However, C-8, C-9, and C-12 are shifted substantially downfield, 3.3, 5.6, and 3.8 ppm. Of these, C-9 is two bonds away from the site of change, and might be expected to show a downfield shift. (The chemical shift of C-2 of butyl acetate is 31.2, while that of 1-butanol is 35.3.) However, the more distant C-8 and C-12 clearly show effects not paralleled in acyclic compounds. Comparison of leucodrin (**1**) to conocarpin (**4**) allows an evaluation of the effect of the steric compression noted in the chemistry of these compounds.[11] Two of the carbon atoms at the site of compression, C-4 and C-9, show downfield shifts (6.3 and 3.9 ppm) in conocarpin, while two show upfield shifts (C-5, 2.3, and C-12, 0.9 ppm). The remaining carbon atoms of the two diastereomers show essentially the same chemical shifts. It is perhaps even more surprising that the simple conversion of conocarpic acid (**8**) to its ester, reflexin (**9**), is accompanied by substantial alteration of the shifts in the unaffected lactone ring and aromatic system: C-5 and C-12 are shifted downfield 4.8 and 1.2 ppm, while C-8, C-9, and C-13/17 are shifted upfield, 2.4, 3.1, and 1.8 ppm.

If the changes produced by minor modifications of these structures are not readily intelligible, however, it is indeed clear that the chemical shifts very sensitively reflect the exact structural arrangement and shape of these molecules, and can be used as a fingerprint of the structural moieties involved.

An opportunity to utilize this empirical observation arose

Table II. ^{1}H Characteristics (in $CDCl_3$ Solution) of the Trimethylsilyl Ether Derivatives

	^{1}H chemical shifts												Trimethylsilyl ethers		
Compd	3a	3b	4	8	9	10	11a	11b	13	14	16	17	C-9	C-15	C-10,11
Leucodrin (1)	2.88	3.34	4.19	3.65	4.87	3.81	3.54	3.38	7.30	6.83	6.83	7.30	0.33	0.32	0.17, −0.04
Dimethylleudrin (3)	2.83	3.30	4.14	3.66	4.86	3.76	3.51	3.35	6.95		6.85	6.90	0.27	0.12	−0.03
Conocarpin (4)	2.83	3.33	3.88	4.02	4.69	3.88	3.51	3.68	7.25	6.90	6.90	7.25	0.26	0.13	−0.06, 0.11
Norleucodrinic acid methyl ether (7)	2.72	3.15	4.12	3.78	4.73				7.33	6.90	6.90	7.33	0.25		
Conocarpic acid (8)	2.85	3.31	3.78	3.78	5.05	3.56	3.36	3.46	7.11	6.76	6.76	7.11	0.22	0.20	−0.06, 0.09

	^{1}H coupling constants, Hz								
Compd	3a,3b	3a,4	3b,4	8,9	8,10	10,11a	10,11b	11a,11b	13,14
Leucodrin (1)	−17.1[a]	8.9[a]	13.4[a]	8.4[a]	1.7[a]	6.8	7.5	−10.0	8.7
Dimethylleudrin (3)	−17.5	8.7	13.2	8.2[a]	1.4[a]	6.8	8.0	−10.0	2.0 (13,17) 9.0 (16,17)
Conocarpin (4)	−17.1	5.8	8.3	3.5[a]	5.9[a]	6.5	4.5	−10.8	
Norleucodrinic acid methyl ether (7)	−17.1[a]	8.6[a]	13.0[a]	8.2[a]					
Conocarpic acid (8)	−17.5	2.0	5.9	8.5	2.0	8.2	6.3	−9.4	8.8 (J(4,9) = 1.5)

[a] Verified by INDOR.

in the study of a phenolic dilactone leudrin.[13] Preliminary characterization of this compound suggests that it shares many structural characteristics common to the dilactones of the leucodrin series and that its structure could be that of leucodrin carrying a further hydroxy substituent at position 14. In particular, the ^{1}H NMR spectrum at 220 MHz allows the determination of the chemical shifts and coupling constants of the alicyclic system, which correspond closely to those earlier observed for leucodrin. To allow a close comparison of such values, and an evaluation of their significance, the ^{1}H spectra of a group of compounds within the series were studied as their trimethylsilyl ether derivatives, and the results are collected in Table II. However, the close correlation of the ^{13}C chemical shifts of Table I, in the context of the strong dependence of these values demonstrated above, not only supports the proposed structure of dimethylleudrin but also indicates its stereochemistry.

Experimental Section

^{13}C spectra were determined on a Varian XL-100 NMR spectrometer equipped with a Digi-Lab Fourier transform accessory. Exciting pulses at approximately 300 Hz below the frequency of tetramethysilane were used, the free induction decay being sampled at 12 kHz, to fill an 8K data table, giving an effective resolution of 1.5 Hz. Typically, 70 000 FID's were collected overnight. Homonuclear INDOR experiments were conducted on the XL-100 at 100 MHz. High-field spectra were obtained on a Varian HR-220 spectrometer.[14]

Trimethylsilyl ethers were formed by mixing the phenols with approximately threefold (by weight) quantities of trimethylsilylimidazole at room temperature. Mass spectra were determined after a few hours on an LKB-2000 mass spectrometer. Solutions so prepared were stable for several days.

Leucodrin (1): m/e (rel intensity) 614 (1), 613 (3), 612 (5, $C_{27}H_{48}Si_4O_8$), 597 (1), 540 (1), 525 (1), 509 (2), 480 (4), 465 (1), 464 (2), 463 (7), 451 (1), 423 (5), 408 (1), 391 (2), 219 (16), 218 (8), 217 (35), 205 (9), 192 (20), 177 (11), 147 (15), 133 (4), 124 (3), 120 (5), 117 (10), 103 (12), 75 (11), 74 (10), 73 (100), 45 (8).

Norleucodrinic acid methyl ether (7): m/e (rel intensity) 466 ($C_{21}H_{30}O_8Si_2$, 1), 451 (1), 361 (1), 291 (1), 149 (2), 148 (3), 147 (25), 134 (4), 125 (11), 98 (15), 89 (3), 88 (6), 86 (39), 85 (4), 84 (57), 83 (6), 75 (3), 74 (3), 73 (37), 70 (4), 69 (7), 68 (100), 67 (10), 59 (5), 49 (13), 47 (19), 45 (9), 43 (11), 41 (70), 40 (37), 39 (12), 38 (9), 35 (8), 28 (25).

Conocarpin (4): m/e (rel intensity) 614 (1), 613 (3), 612 ($C_{27}H_{48}Si_4O_8$, 5), 597 (2), 509 (2), 480 (4), 463 (3), 451 (3), 423 (6), 292 (2), 293 (2), 219 (20), 217 (28), 205 (12), 193 (4), 192 (18), 177 (8), 147 (16), 133 (4), 129 (2), 120 (5), 117 (11), 103 (11), 75 (12), 74 (9), 73 (100), 68 (5), 59 (3), 45 (6), 41 (3), 28 (6).

Dimethylleudrin (3): m/e (rel intensity) 585 (2), 584 ($C_{26}H_{44}O_9Si_3$, 5), 217 (5), 191 (2), 164 (5), 149 (3), 148 (3), 147 (18), 141 (2), 140 (17), 125 (12), 103 (2), 98 (16), 88 (2), 86 (50), 84 (70), 75 (4), 74 (4), 73 (46), 70 (3), 69 (7), 68 (100), 67 (11), 59 (2), 51 (2), 49 (14), 47 (20), 45 (7), 43 (8), 42 (5), 41 (64), 40 (34), 39 (7), 38 (5), 35 (5), 28 (24).

Registry No.—**1**, 14225-07-1; **1** trimethylsilyl derivative, 59873-48-2; **2**, 59873-49-3; **3**, 59873-50-6; **3** trimethylsilyl derivative, 59873-51-7; **4**, 30358-74-8; **4** trimethylsilyl derivative, 59905-86-1; **7**, 13565-22-5; **7** trimethylsilyl derivative, 59873-52-8; **8**, 39236-59-4; **8** trimethylsilyl derivative, 59873-53-9; **9**, 40036-19-9.

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(13) Leudrin has been found (G.W.P.) to occur in a number of *Leucadendron* species which also produce leucodrin, but not in *Leucospermum* species which produce the diastereomer, conocarpin. The chemical degradation of leudrin and a synthetic route for leucodrin to leudrin are being published elsewhere. Its 14,15-dimethyl ether, mp 222 °C, is the stable and highly crystalline derivative (**3**) discussed in this paper.
(14) We are indebted to Mr. R. B. Bradley of the National Institute of Arthritis, Metabolism and Digestive Diseases and Professor J. M. Edwards of the University of Connecticut for these spectra.