166. The Configuration of Naturally Occurring Iridoid Glucosides at C(6) and C(8): A Complementary Assignment Aid by ^{13}C-NMR. Spectroscopy

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Summary

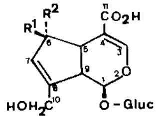
Evidence is presented which demonstrates that ^{13}C-NMR. spectroscopy can be used with confidence in evaluating the configuration of R^1R^2CHOH centers at C(6) and C(8) of iridoid glucosides.

The configurational analysis with the help of NMR. carried out so far in this series used the proton [1]. This nucleus, however, suffers from two deficiencies: (i) proton spectra are complicated by spin-spin coupling which produces frequent overlap and renders spectrum interpretation difficult; (ii) the chemical shift differences of a proton in only slightly different environments are small and in the same order of magnitude as the long-range shielding effects. Thanks to the sensitivity of the ^{13}C-chemical shifts to configurational changes, the method is ideally suited for distinguishing stereoisomers.

Several reports (*cf. e.g.* [2-4]) have appeared on the ^{13}C-NMR. spectra of iridoid glucosides. However, no attempt has yet been made in this series to utilize the striking sensitivity of the ^{13}C-chemical shifts to steric effects. We have recently reported the structure of some new ester iridoids by the aid of ^{13}C-NMR. spectra [5] [6]. In order to establish a data basis for future structural studies and for throwing some light on the stereochemical dependence of ^{13}C-chemical shifts, the ^{13}C-spectra of three stereoisomeric pairs of iridoids are examined.

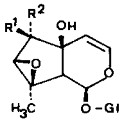
The ^{13}C-NMR. spectral analysis of iridoid glucosides **1**, **2**, **3**, **4**, **5** and **6** gave the needed stereochemical information. The spectra studied here are presented in the *Table*. The assignments [7] of the ^{13}C-NMR. signals were based on single frequency off-resonance decoupling technique, application of known chemical shift rules for hydroxy substitution and comparison among related compounds [8].

Inspection of the ^{13}C-NMR. spectra of C(6)-epimers shows that on going from equatorial to axial substitution, *e.g.*, **1** to **2** or **3** to **4** a shielding (γ-effect) ($\sim$ 3 ppm) is observed for the C(4) whereas the C(8) has experienced an approximately equivalent deshielding. A δ-effect of the substituent at C(6) exerted on C(3) in the



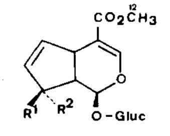
1 Scandoside:
$R^1=OH$; $R^2=H$

2 Desacetyl asperulosidic acid: $R^1=H$; $R^2=OH$



3 Antirrinoside:
$R^1=OH$; $R^2=H$

4 Procumbide:
$R^1=H$; $R^2=OH$



5 Gardenoside:
$R^1=OH$; $R^2=CH_2OH$

6 Monotropein methylester:
$R^1=CH_2OH$; $R^2=OH$

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Table. ^{13}*C-NMR. Data of Iridoids*[a])

C-Atom	**1**	**2**	**3**	**4**	**5**	**6**
1	98.80	101.53	94.56	95.56	94.41	95.15
3	153.98	155.62	142.90	144.12	152.02	152.48
4	111.02	108.27	107.45	104.45	111.60	110.53
5	46.97	42.57	74.52	80.01	38.92	38.80
6	82.38	75.33	77.29	77.69	135.80[b])	137.54
7	129.92	129.89	66.01	65.75	135.90[b])	133.65
8	147.31	151.32	64.18	66.83	86.34	85.89
9	45.94	45.73	52.72	52.88	52.40	45.42
10	61.06	61.61	17.53	17.59	67.17	68.26
11	172.07	170.92	-	-	169.69	168.97
12	-	-	-	-	51.62	51.58

[a]) The spectra were recorded in CD$_3$OD. Chemical shifts in ppm relative to internal (CH$_3$)$_4$Si. Additional signals arising from glucose. [b]) These values could be interchanged.

C(6)-epimers, although of lower extent (~1.5 ppm), is observed. The shielding effects can be rationalized on the basis of electric field effects [9] and find precedence in other systems [10]. It is of interest to point out the different chemical shift values for C(6) associated with the equatorial (**1**) and axial (**2**) hydroxyl function at this carbon atom.

Comparison of the C(1)-, C(6)-, C(7)- and C(9)-chemical shifts of one of the C(8)-epimers with those of the other distinguish the two compounds easily and reveal their C(8)-configurations as depicted in stereostructures **5** and **6**. Since the cyclopentane ring is frequently substituted, shifts caused to C(7) and C(6) with a change in configuration at C(8), may not be useful. It has recently been shown [4] [11] that changes in substituent or configuration at C(7) have little influence on the chemical shift value of C(9). Thus, the C(9)-chemical shift of C(8)-epimers is a diagnostic constant for revealing the C(8)-configuration of such natural products [11]. The shift induced on the β-carbon atom C(9) with the change of the configuration at C(8) can be rationalized on the basis of a C$_\beta$-electron-cloud distortion by the fluctuating C$_\alpha$-OH dipole [10].

These findings show clearly that ^{13}C-NMR. spectroscopy provides a useful sensitive method for determining the configuration of R^{1}R^{2}CHOH centers at C(6) and C(8) in iridoids.

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