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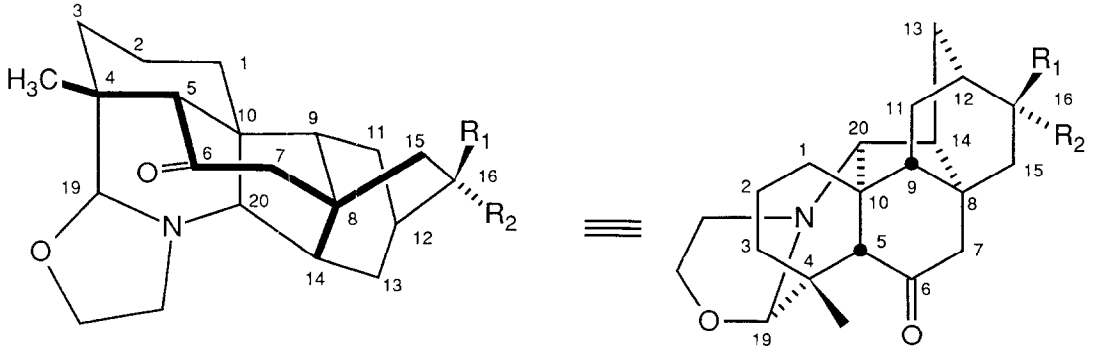
THE STRUCTURES OF SPIRASINE V AND SPIRASINE VI

SUN Fang, LIANG Xiao-tian*, and YU Dequan
Institute of Materia Medica, Chinese Academy of Medical Sciences
Nan-wei Road, Beijing 100050, CHINA

XU Chang-fu and Jon CLARDY*
Department of Chemistry - Baker Laboratory
Cornell University, Ithaca, NY 14853-1301, USA

Summary: The title alkaloids were isolated from *Spiraea japonica*, and their absolute stereostructures were elucidated by chemical, spectral, and x-ray crystallographic methods as **1** and **2**. Although both **1** and **2** exist as a single epimer with the 19(S) configuration in the solid state, fast equilibration occurs in solution to form a pair of C19 epimers in an approximate ratio of 1:1.

As part of our continuing research on Chinese medicinal plants, we have recently isolated eighteen C_{20}-type diterpene alkaloids from *Spiraea japonica* L. f. var. fortunei (planchon) Rehd. Fifteen of these alkaloids had previously unreported structures and were designated as spirasine I to XV. Of the three remaining alkaloids, two are the previously reported spiradine A[1] and spiredine.[2] The third, the N-chloromethyl quaternary salt of spirasine IX, is tentatively regarded as an artifact since CH_2Cl_2 was used in the extraction. It should be noted however that spirasine IX failed to react with CH_2Cl_2 after prolonged reflux. In this note we wish to discuss the structures of spirasine V(**1**) and VI(**2**), a pair of C-16 stereoisomers.



1 R_1=CH_3, R_2=OH
2 R_1=OH, R_2=CH_3

Molecular formulas of both spirasine V and VI were determined as $C_{22}H_{31}NO_3$ by high resolution mass spectrometry. The spiredine-type skeleton common to both alkaloids was established through comparison of ^{13}C NMR chemical shift values with literature data.[3] Spirasine V had m.p. 177-179°; $[\alpha]_D^{28}$ -47° (c. 0.77, $CHCl_3$); IR (KBr) 3515 (OH) and 1680 (C=O) cm^{-1}; and CD $\Delta\epsilon$ -1.65 (294 nm, EtOH). Spirasine VI had m.p. 202-203°; $[\alpha]_D^{21}$ -107° (c. 1.0, $CHCl_3$), IR KBr 3495 (OH) and 1674 (C=O) cm^{-1}; and CD $\Delta\epsilon$ -1.41 (294 nm, EtOH). The structure of spirasine VI (**2**) was established through an x-ray diffraction experiment. It crystallized in the orthorhombic crystal system with accurate lattice constants, determined by a least-squares fit of fifteen diffractometer measured 2θ-values, of a=8.463(2), b=9.306(1), and c=23.236(3) Å. The crystal density, optical activity, and systematic extinctions were uniquely accommodated by space group $P2_12_12_1$ with one molecule of $C_{22}H_{31}NO_3$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer controlled diffractometer with graphite monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å) and variable speed, 1° w-scans. A total of 1478 reflections were collected in this fashion, and after correction for Lorentz, polarization, and background effects, 1368 (93%) were judged observed ($|F_o| \geq 3\sigma(F_o)$).[4] A phasing model, which showed all of the nonhydrogen atoms, was found routinely using the MULTAN series of programs. Hydrogens were located on a ΔF-synthesis following partial refinement. Block diagonal least-squares refinement with anisotropic heavy atoms, and isotropic hydrogens have converged to a conventional crystallographic residual of 0.066 for the observed reflections.[5] A computer generated perspective drawing of the final x-ray model is presented below.

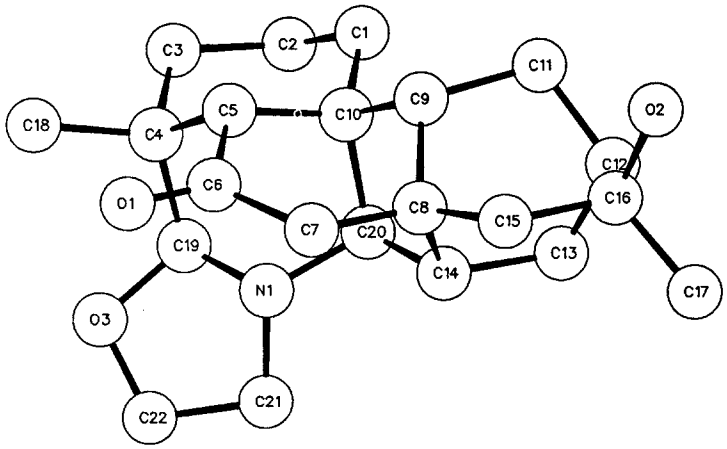
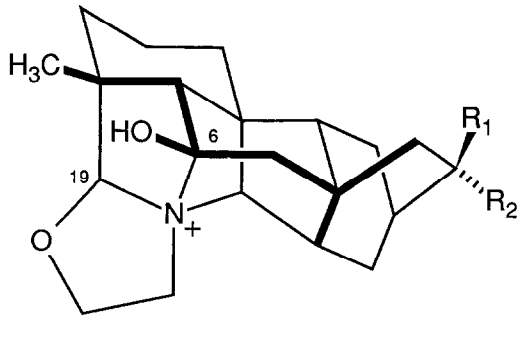


Figure 1. A computer generated perspective drawing of the final x-ray model of spirasine VI (**2**). Hydrogens are omitted for clarity, and the absolute configuration was determined by chiroptical methods.

The NMR spectra of spirasine VI was completely consistent with structure **2**, but the spectra of both spirasine V and VI were complicated by C19 epimeric forms in solution. The 1H NMR spectra showed this quite clearly, and the existence of an epimeric pair is best exemplified by a pair of signals at δ4.25 [19(S)] and 3.68 [19(R)] for the C19 proton in a ratio of approximately 1:1. Comparison of the multiplet pattern between 2.8-4.2 ppm (5H's) with that of spiredine confirmed the presence of an iso-type oxazolidine ring in spirasine V and VI. Treatment of spirasine V(**1**) or VI(**2**) with ethanolic HCl gave the corresponding salt of the carbinolamine type (**3**)[6] where only one epimeric form [19(S)] is possible because of the constraint of the newly formed N to C-6 bond. Apparently the 19(R) epimer was converted to the 19(S) *via* the intermediate immonium ion formed by opening the oxazolidine ring. The salt shows no carbonyl absorption in the IR and can be converted back to the free base by treatment with silver oxide.

The relation of spirasine V(**1**) and VI(**2**) was shown to involve the stereochemistry of the hydroxyl group at C-16. When spirasine V (**1**) was dissolved in acetic acid containing perchloric acid and allowed to stand at room temperature overnight, dehydration product **4** and some spirasine VI (**2**) were formed in addition to starting material. Spirasine VI (**2**) behaved similarly. The ^{13}C NMR spectra of both spirasine V and VI displayed a number of signals for C-19 and its close neighbors which were doubled due to the presence of a C-19 epimeric mixture. The δ_C values of the stereochemically homogeneous HCl salts are given in Table 1. The preferential shielding of the γ-carbons[7] (C-11 and C-13 in both V and VI) which are in close proximity to the C-17 methyl group can be used as guides in the assignment of the stereochemistry at C-16. However, this is a subtle analysis and subject to misinterpretation. The x-ray analysis, which showed that the B-ring of spirasine VI had a half-chair conformation, was crucial in this regard. Atoms C-5, C-6, C-7, and C-10 are essentially planar, and, in the conventional view, atom C-9 is above this plane and C-8, below. If this conformational preference persisted in solution, it would satisfactorily account for the difference in $\Delta\epsilon$ values (0.24) since the α-hydroxyl at C16 (structure **1**) is expected to give a more negative contribution. It is also interesting that in the solid state the free base of spirasine VI (**2**) exists exclusively as the 19(S) epimer. Cases of a crystalline mixture of epimers are known.[8]



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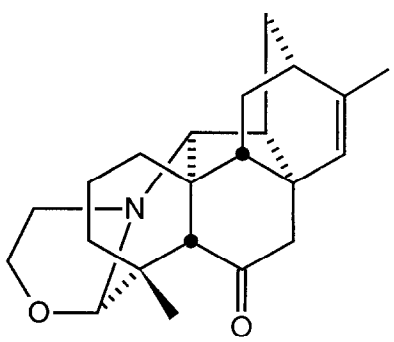

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All of the 6-keto containing spirasines showed a negative CD extremum at *ca.* 290 nm which was quenched by the addition of acid. Correlation with known structures[9] has led to the assignment of the absolute configurations for spirasines V and VI embodied in the structural formulas **1** and **2**.

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Table 1. ^{13}C NMR data for spirasine V (**1**) and spirasine VI (**2**) HCl salts*

Carbon	1	2	3	4	5	6	7	8	9	10	11
1	40.4	17.3	33.8	38.9	59.8	104.8	26.3	39.9	34.4	47.8	22.8
2	41.4	17.8	34.5	40.9	60.4	105.6	27.0	40.9	35.3	48.5	27.6

Carbon	12	13	14	15	16	17	18	19	20	21	22
1	47.6	24.4	39.3	40.1	68.5	27.2	21.3	104.8	73.3	43.3	68.5
2	48.0	20.8	39.9	41.4	69.4	28.8	22.1	105.2	73.7	44.2	69.1

*Chemical shifts in ppm downfield from TMS; solvent CD_3OH; 25.1 MHz

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4. All crystallographic calculations were done on a PRIME 9950 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from x-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, University of York, England, 1978 and 1980; BLS78A, an anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu and G. Van Duyne, Cornell University, 1985.

5. Crystallographic parameters have been deposited with the Cambridge Crystallographic Data File, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, ENGLAND and are available from them. Please give a complete literature citation when ordering.

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