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STEREOCHEMISTRY OF SPATHULIN*

WERNER HERZ and ASUR SRINIVASAN
Department of Chemistry, The Florida State University, Tallahassee, FL 32306, U.S.A.

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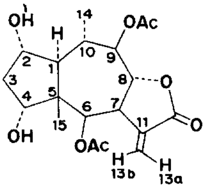
Key Word Index—Pseudoguaianolides; spathulin; *Gaillardia* species; NMR spectrometry.

Abstract—The stereochemistry of the pseudoguaianolide spathulin has been determined by NMR spectrometry at 270 mHz.

ALTHOUGH the gross structure of the pseudoguaianolide spathulin from *Gaillardia aristata* Pursh., *G. grandiflora* van Houtte, *G. mexicana* Gray, *G. spathulata* Gray and the Rio Grande form of *G. pulchella* Foug.[1] has been known for a number of years, determination of its stereochemistry was frustrated by superposition of signals in the NMR spectra of spathulin and its derivatives. Attempts to use chemical shift reagents to overcome this difficulty met with indifferent success and efforts to prepare material suitable for X-ray crystallography were hampered by shortage of material. We now report a solution to the problem by the use of NMR spectrometry at 270 mHz which has led to stereochemistry **1** for spathulin.



(**1**)

Table 1 lists chemical shifts and coupling constants for all protons of the spathulin structure which were determined by cw and FT techniques. Identification of the H-7 resonance was achieved by irradiating at the frequencies corresponding to H-13a and H-13b. Subsequent irradiation at the frequency of H-7 collapsed not only the H-13a and H-13b doublets, but converted the triplet at 4·50 ppm (H-8) to a doublet and the doublet at 5·98 ppm (H-6) to a singlet. Subsequent irradiation of H-8 collapsed a triplet at 4·86 ppm (H-9); irradiation at the frequency of H-9 collapsed the triplet of H-8 to a doublet and affected a multiplet (H-10) partially superimposed on one of the acetate signals. The center of this multiplet (1·88 ppm) was identified by performing an INDOR experiment using the methyl doublet; conversely, irradiation at 1·88 ppm collapsed the methyl doublet to a singlet and also the triplet of H-9 into a doublet.

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* Part XIII in the series "Constituents of *Gaillardia* Species." For Part XII, see HERZ, W. and SRINIVASAN A. (1974) *Phytochemistry* **13,** 1187.

[1] HERZ, W., LAKSHMIKANTHAM, M. V., RAULAIS, D. and SCHMID, J. J. (1967) *J. Org. Chem.* **32,** 1042.

Irradiation at the frequency of H-10 also simplified a multiplet at 2.30 ppm, which was therefore attributable to H-1, into a triplet. Identification of the H-2 signal was made possible by irradiating at the frequency of H-1; this collapsed a broadened triplet at 3·96 ppm to a broadened doublet, the broadening being due to coupling to an –O–H proton whose signal was superimposed on the frequency of H-8. Likewise a broadened doublet at 3.57 ppm was sharpened by irradiating at the frequency corresponding to a second –OH signal at 5·0 ppm, hence was that of H-4; irradiation at the frequencies of H-2 and H-4 affected two signals at 1·48 and 2·06 which were therefore those of H-3α and H-3β.

TABLE 1. NMR SPECTRUM OF SPATHULIN*

H-1	2·30*m*	$J_{1,2} = 8\cdot0$, $J_{1,10} = 10\cdot6$, $J_{1,3} \neq 0$
H-2	3·96*tbr*‡	$J_{2,3\alpha} = 7\cdot0$, $J_{2,3\beta} = 7.0$
H-3α	1·48*dbr*	$J_{3\alpha,3\beta} = 14.8$
H-3β	2·06*m*	
H-4	3·57*dbr*§	$J_{3\alpha,4} = 4\cdot5$, $J_{3\beta,4} = 0$
H-6	5·98*d*	$J_{6,7} = 2\cdot5$
H-7	3·46*m*	$J_{7,8} = 8\cdot5$
H-8	4·50*t*	$J_{8,9} = 9\cdot9$
H-9	4·86*t*	$J_{9,10} = 9\cdot8$
H-10	1·88*m*	
H-13a	6·09*d*	$J_{7,13a} = 3\cdot1$
H-13b	5·43*d*	$J_{7,13b} = 3\cdot0$
H-14†	1·07*d*	$J_{1,14} \neq 0$
H-15†	0·64	$J_{1,15} \neq 0$
Acetates†	1·96, 2·06	

* Signals are given in ppm, coupling constants in Hz. Multiplicities are indicated by the usual symbols: *d*—doublet; *t*—triplet, *m*—multiplet, *br*—broadened singlet. Unmarked signals are singlets.

† Intensity three protons.

‡ Broadening removed by irradiating at 4·50 ppm–2–O*H*.

§ Broadening removed by irradiating at 5·00–4–O*H*.

Comparison of the observed coupling constants with coupling constants deduced from Dreiding models led to the stereochemistry given in formula **1**. Thus the large values for $J_{7,8}$, $J_{8,9}$, $J_{9,10}$ and $J_{1,10}$ require the *trans*-diaxial arrangement of carbon-hydrogen bonds imposed by a *trans*-fused γ-lactone on the chair form of a pseudoguaianolide; this is in accordance with the generalization[2] that $J_{7,13}$ *trans* ≥ 3 Hz $\geq J_{7,13}$ *cis*, and, if H-7 is α as in all pseudoguaianolides of authenticated stereochemistry, with the observation of a positive Cotton effect near 265 nm associated with the n,π^*-transition of a *trans*-fused α,β-unsaturated lactone closed to C-8[4]. The magnitude of $J_{6,7}$ then requires α-orientation of H-6; the α-orientation of H-1 and the C-10 methyl group deduced by NMR spectrometry is also in harmony with the absolute configuration of all other pseudoguaianolides from *Gaillardia* and related species. The value of $J_{1,2}$ requires α-orientation of the hydroxyl group at C-2; since the two hydroxyl groups have been shown[1] to be *cis*, the complete stereochemistry of spathulin is defined.

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[2] SAMEK, Z. (1970) *Tetrahedron Letters* 671. Although some exceptions to the rule have been found,[3] it seems to be generally applicable to pseudoguaianolides.

[3] HERZ, W. and WAHLBERG, I. (1973) *J. Org. Chem.* **38**, 2485.

[4] STÖCKLIN, W., WADDELL, T. G. and GEISSMAN, T. A. (1970) *Tetrahedron* **26**, 2397. The exceptions to the rule involve compounds in which the carbon-oxygen bond of the lactone function is allyllic.[5]

[5] HERZ, W., BHAT, S. V. and HALL, A. L. (1970) *J. Org. Chem.* **35**, 1110; SUNDARARAMAN, P., MCEWEN, R. S. and HERZ, W. (1973) *Tetrahedron Letters* 3809.

EXPERIMENTAL

NMR spectra were run in DMSO-d_6 at 270 mHz on a Bruker HX-270 NMR spectrometer with tetramethylsilane as internal standard.

CD curve (MeOH, 0·64 mg/ml). $[\theta]_{300}$ 0; $[\theta]_{280}$ + 138; $[\theta]_{270}$ + 197 (max), $[\theta]_{260}$ + 138, $[\theta]_{255}$ 39; $[\theta]_{253}$ 0; $[\theta]_{245}$ − 158; $[\theta]_{230}$ − 788 (min); $[\theta]_{228}$ − 611 (last reading).

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