

The Structure and Stereochemistry of Hydroxyachillin

F. W. BACHELOR AND A. B. PARALIKAR¹

Department of Chemistry, University of Calgary, Calgary 44, Alberta

AND

SHÔ ITÔ

Department of Chemistry, Tohoku University, Sendai, Japan

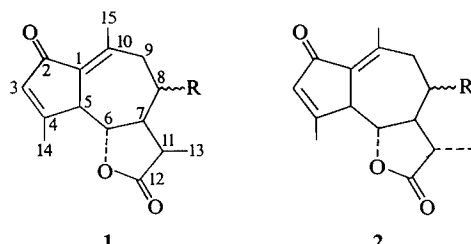
Received July 13, 1971

The sesquiterpene lactone hydroxyachillin has been isolated from *Artemisia frigida* Wild. The position and stereochemistry of the free hydroxyl group has been established by n.m.r. examination as well as the conformation of the molecule using nuclear Overhauser effects.

L'hydroxyachilline lactone sesquiterpénique a été isolée à partir de l'*Artemisia frigida* Wild. La position et la stéréochimie des groupes hydroxyles libres ont été déterminés par r.m.n.; il en a été de même pour la conformation de la molécule en se servant de l'effet nucléaire Overhauser.

Canadian Journal of Chemistry, 50, 333 (1972)

Although hydroxyachillin (**1a**) has been previously isolated from *Achillea lanulosa* by White and Winter (1), its structure is based on its conversion to achillin (**1d**) by removal of the free hydroxyl group. This was accomplished by preparing the nitrosylate (**1b**), converting this to the



- | | |
|--|---|
| a R = OH | a R = CH ₃ CO ₂ — |
| b R = p-NO ₂ C ₆ H ₄ SO ₂ O— | b R = H |
| c R = I | |
| d R = H | |
| e R = CH ₃ CO ₂ — | |

iodide (**1c**), and removing the iodine by reduction. This sequence still leaves the position of the hydroxyl group in doubt and although there are a sufficient number of analogies to suggest that the hydroxyl group is at C-8, including matricarin (**2a**) (2), which is found in the same plant, this is not sufficient to prove its location.²

¹Abstracted in part from the thesis of Mr. A. B. Paralihar submitted to the University of Calgary for the Ph.D. degree, 1970.

²A private communication from Prof. E. H. White informed us that the stability of the nitrosylate **1b** and the

In our investigation of local *Artemisia* species we have found hydroxyachillin to be the principal sesquiterpene lactone present in *Artemisia frigida* Wild. Comparison of the i.r. spectrum of our compound with an authentic specimen showed them to be identical.³ The recent stereospecific total syntheses of leukodin (**2b**) and achillin (**1d**) from α -santonin firmly establish the structures and stereochemistry of these molecules (4–6). There remains only the position and stereochemistry of the hydroxyl group of hydroxyachillin to be determined.

We have been able to complete the structure of hydroxyachillin by examination of the n.m.r. spectra of the free alcohol and its acetate. The n.m.r. data for these compounds are given in Table 1. Examination of these data shows that the hydroxyl group can only be located at C-8 or -9. As the new signal from the hydrogen on the alcohol carbon atom is found at 6.26 τ this places the hydroxyl group at C-8. If it were at C-9 it would be allylic and its position would be expected at lower field. For example the corresponding allylic hydrogen atom in geraniol is found at 5.85 τ (7). This hydrogen atom in hydroxyachillin is shifted to 5.24 τ in the acetate and is clearly seen as a triplet of doublets with

formation of an impure cyclopropane derivative obtained on reduction of the iodide **1c**, similar to that obtained from the corresponding compound in the matricarin series suggested to them that the hydroxyl was at C-8 (3).

³We wish to thank Dr. R. E. K. Winter for running the i.r. comparison of the two compounds.

TABLE 1. Proton chemical shifts of hydroxyachillin and related compounds

Compound	Position*							
	C-3	C-5	C-6	C-8	C-11	C-13	C-14	C-15
1a	3.85(s, broad)	6.60(d) $J = 10$	6.14(t) $J = 10$	6.26(dt) $J = 3, 10$		8.71(d) $J = 7$	7.69(d) $J = 1.5$	7.56(s)
1e†	3.83(c)	6.59(d) $J = 10$	6.10(t) $J = 10$	5.24(dt) $J = 3, 10$	7.18(quintet) $J = 7$	8.89(d) $J = 7$	7.70(d) $J = 1.5$	7.55(s)
1d‡	3.92(q) $J = 1.5, 1.5$	6.62(d, broad) $J = 10, 1.5$	6.21(t) $J = 10, 10$	8.88(c)	7.39(quintet) $J = 7.4$	8.90(d) $J = 7.4$	7.74(dd) $J = 1.5, 0.9$	7.60(d) $J = 0.9$
2b§	3.87	6.65	6.46			8.75	7.72	7.64

*All values are in τ relative to internal tetramethylsilane; s, singlet; d, doublet; t, triplet; q, quartet; dt, double triplet; c, complex.

†An additional signal appears at 7.91(s) for the acetyl methyl group.

‡See ref. 12.

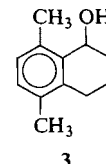
§See ref. 5.

coupling constants of 10 and 3 Hz. This splitting is also only compatible with the location of the hydroxyl group at C-8 having three hydrogen atoms on the adjacent carbon atoms.

Spin-spin decoupling on the acetate 1e firmly established the relationship of a number of the proton signals. Irradiation of the vinyl hydrogen at 3.83 τ caused the allylic splitting to disappear in the methyl signal at 7.70 τ thus establishing it as the C-14 methyl group. Decoupling of the methyl doublet at 8.89 τ caused the quintet at 7.18 τ to collapse to a doublet ($J = 7$ Hz) for the hydrogen at C-11. A quintet of this type with similar stereochemistry has been observed in β -santonin (8). Although the complexity of the region did not allow us to locate exactly the position of the hydrogen at C-7, irradiation at 7.3 τ caused the signal at 5.24 τ to collapse to a broad unresolved peak and the triplet at 6.10 τ became a doublet. Finally, decoupling of the allylic hydrogen at 6.59 τ reduced the hydrogen signal at 6.10 τ to a doublet and the vinyl hydrogen signal which showed complex allylic coupling became a simple quartet ($J = 1.5$ Hz). This evidence firmly establishes the relationship of the hydrogen atoms at C-3, -5, -6, -7, -8, -11, -13, -14, and -15.

Guaianolide lactones with a *trans* lactone at C₆—C₇ and *trans* hydrogens at C-5 and -6 are capable of ring inversion. This leaves the possibility for the stereochemistry of the C-8 hydroxyl of being either α or β , each of which could exist in one of two conformations, unless the conformations are freely interconvertible. Examination of models of the four different possibilities showed that they could easily be

distinguished from each other by determining the nuclear Overhauser effect (n.O.e.) of selected protons. Initially it must be remarked that there is a decided upfield shift of the C-13 methyl signal in the n.m.r. spectrum of hydroxyachillin acetate (1e) from that of hydroxyachillin (1a). This spatial interaction effect has been noted in the case of substituted tetralins (9). For example, in 1,4-dimethyl-5-hydroxydecalin (3), it was



found that acetylation caused an upfield shift of the peri methyl group of 0.17 p.p.m. We observe an upfield shift of 0.18 p.p.m. in hydroxyachillin acetate. This shift is not observed if the two groups are *trans* diaxial or pseudo *trans* diaxial as they would be in one conformation of hydroxyachillin where the hydroxyl group is α . All of the other three conformations would allow for this spatial interaction.

Of the remaining conformations, one α and one β conformation could account for the observed coupling constants. In the case of the conformer with the oxygen substituent α , the hydrogen atom at C-8 approaches very closely to that at C-6.⁴ Irradiation of either the hydrogen signal at C-6 or -8 of hydroxyachillin acetate (1e) pro-

⁴From Dreiding models the internuclear distance is estimated to be 2.13 Å. For comparison of this n.O.e. with compounds showing similar signal enhancements and similar proton relationships see refs. 10 and 11.

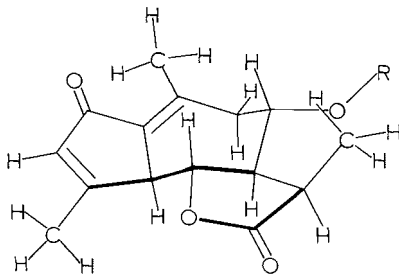


FIG. 1. The conformation of hydroxyachillin acetate ($R = \text{COCH}_3$).

duced a definite signal enhancement of approximately 10% in the other signal. This definitely establishes the hydrogen atom at C-8 as β and the conformation of the seven-membered ring such that the hydroxyl or acetate group is pseudo equatorial. This is in contrast to the oxygen functions at C-8 of the matricarin series which have been shown to have the α configuration (4). The complete conformational picture of hydroxyachillin acetate is given in Fig. 1. In addition to the n.o.e. at C-8 when radiating the C-6 proton signal, there was no observable enhancement of the signal due to the hydrogen atom at C-5. This verifies the *trans* relationship of these atoms.

The strong spatial interaction between the C-11 β -methyl group and the 8α -hydroxyl group is probably also responsible for the lack of reactivity of this hydroxyl group. Although it can be acetylated and the nitrosylate prepared, we have been unable to prepare the tosylate, brosylate, or iodoacetate. It is not oxidized to a ketone with the chromium trioxide-pyridine complex, but under more drastic conditions extensive oxidation takes place.

Experimental

The n.m.r. spectra were measured with a Varian HA-100 spectrometer with a frequency swept and tetramethylsilane-locked mode. Double and triple resonance experiments were performed by using the spectrometer in conjunction with two Hewlett-Packard HP-200ABR audio oscillators. The n.o.e. experiments were carried out by measuring the integrated intensities of a signal four times with and without irradiation at the resonance frequency of another signal at a sweep rate of 0.4 Hz/s. Samples were not degassed before carrying out n.o.e. measurements.

Extraction and Isolation of Hydroxyachillin

The aerial parts of *Artemisia frigida* Wild collected in the vicinity of Calgary, Alberta were dried and ground. The ground material (6 kg) was extracted successively with hex-

ane and chloroform. The chloroform extract was concentrated to dryness and the residual gum dissolved in 3 l of ethanol. The ethanolic solution was mixed with a solution of 75 g of lead acetate in 3 l of water and 20 ml of acetic acid. After 4 days the clear supernatant was decanted through glass wool and the residue washed twice with ethanol. The ethanol-water mixture was concentrated to a small volume and extracted thoroughly with chloroform. The chloroform extract was dried (Na_2SO_4), filtered, and concentrated at reduced pressure. The residual gum (56 g) was taken up in benzene and chromatographed over 1500 g of alumina. The column was eluted with benzene, benzene-chloroform (1:1), chloroform, chloroform-methanol (1:1) and methanol. The benzene-chloroform fractions showed characteristic bands in the i.r. at 1775 cm^{-1} for a γ -lactone and these were combined and concentrated yielding a residue of 8.7 g. This material was again chromatographed on alumina (320 g). Elution with benzene-chloroform gave 6.5 g of a brown gum. This gum was crystallized first from benzene and the crystalline material then recrystallized from ethyl acetate to give 1.4 g of hydroxyachillin, m.p. $159.5\text{--}160^\circ\text{C}$, $[\alpha]_D^{25} + 112^\circ$ (c 1.0 in CH_3OH); (lit. (4) m.p. $161\text{--}162^\circ$, $[\alpha]_D^{25} + 110^\circ$).

Hydroxyachillin Acetate

A solution of 0.1 g of hydroxyachillin in 1 ml of pyridine was mixed with 2 ml of acetic anhydride. The solution was warmed for 3 h on a steam bath, then left overnight at room temperature. The reaction mixture was then poured over ice and the resulting crystalline solid collected by filtration. Crystallization and recrystallization gave 0.06 g of hydroxyachillin acetate, m.p. $194\text{--}195^\circ\text{C}$, $[\alpha]_D^{25} + 110^\circ$ (c 0.20 in CHCl_3), λ_{max} (MeOH) $255\text{ m}\mu$ (ϵ 15 000); lit. (1) m.p. $193\text{--}194^\circ$, $[\alpha]_D^{25} + 116^\circ$.

We wish to thank the National Research Council of Canada for support of this work.

1. E. H. WHITE and R. E. K. WINTER. *Tetrahedron Lett.* **3**, 137 (1963).
2. W. HERZ and K. UEDA. *J. Am. Chem. Soc.* **83**, 1139 (1961).
3. R. E. K. WINTER. Ph.D. Thesis. The Johns Hopkins University, Baltimore, Maryland, 1963.
4. E. H. WHITE and J. N. MARX. *J. Am. Chem. Soc.* **89**, 5511 (1967).
5. E. H. WHITE, S. EGUCHI, and J. N. MARX. *Tetrahedron*, **25**, 2099 (1969).
6. J. N. MARX and E. H. WHITE. *Tetrahedron*, **25**, 2117 (1969).
7. NMR Spectra Catalog. Vol. 1. Varian Associates, Palo Alto, California. Spectrum No. 279.
8. J. T. PINHEY and S. STERNHELL. *Aust. J. Chem.* **18**, 543 (1965).
9. T. OKAMOTO and Y. KAWAZOE. *Chem. and Pharm. Bull. (Japan)*, **11**, 643 (1963).
10. R. A. BELL and E. N. C. OSAKE. *Chem. Commun.* 1093 (1968).
11. K. TORI, M. OHTSURU, I. HORIBE, and K. TAKEDA. *Chem. Commun.* 943 (1968).
12. S. J. SMOLENSKI, C. L. BELL, and L. BAUER. *Lloydia*, **30**, 144 (1967).