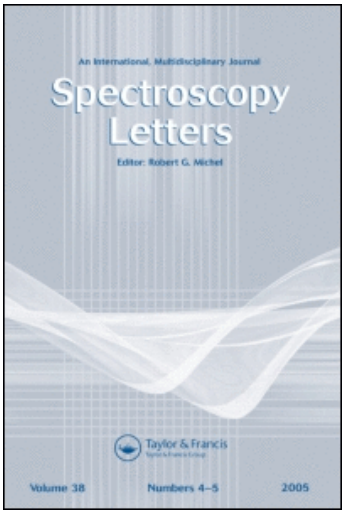

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

^{13}C NMR Assignments of Artemisinin, Desoxyartemisinin and Artemether

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To cite this Article El-feraly, Farouk S. , El-sherei, Moshera M. , Hufford, Charles D. , Croom Jr., Edward M. and Mahier, Thomas J.(1985) '^{13}C NMR Assignments of Artemisinin, Desoxyartemisinin and Artemether', Spectroscopy Letters, 18: 10, 843 — 849
To link to this Article: DOI: 10.1080/00387018508062315
URL: http://dx.doi.org/10.1080/00387018508062315

SPECTROSCOPY LETTERS, 18(10), 843-849 (1985)

^{13}C NMR ASSIGNMENTS OF ARTEMISININ, DESOXYARTEMISININ AND ARTEMETHER

Key Words: Artémisinin (Qinghasu); desoxyartemisinin; artemether; dihydroartemisinin; antimalarial activity, ^{13}C nmr assignments; selective decoupling.

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Abstract

The ^{13}C nmr assignments for all carbons except the methylene groups were made for artemisinin (1), artemether (2) and desoxyartemisinin (3). The assignments were based on chemical shift theory and confirmed by selective band decoupling experiments.

INTRODUCTION

Artemisinin (Qinghasu) (1), extracted[1] from the traditional Chinese herb Artemisia annua L., is a novel type of an antimalarial with rapid action and low toxicity. It is particularly useful against the chloroquine-resistant parasite and in cerebral malaria[1]. The structure and absolute configuration of artemi-

 0038-7010/85/1810-0843$3.50/0

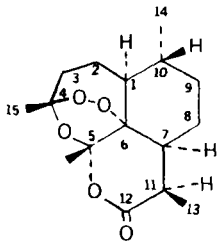
sinin (1), a sesquiterpene lactone with a peroxide bridge was firmly established by X-ray diffraction studies, and later confirmed by total synthesis[2].

Sodium borohydride reduction[1] of artemisinin (1) provides its dihydro derivative 4 which serves as the starting material for the preparation artesunate (the sodium salt of its hemisuccinate ester) and artemether[1,3] (2). Both forms are claimed to be more potent than artemisinin (1) itself[1].

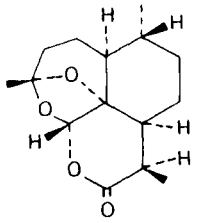
As a part of our ongoing study of the biosynthetic routes to artemisinin (1), and the structure elucidation of its metabolites along with those of artemether (2), it was deemed important to assign the carbon signals in their ^{13}C nmr spectra. This study, it was thought, should not only identify unambiguously possible biosynthetic precursors for artemisinin (1) but also help identify its metabolites and those of artemether (2).

RESULTS AND DISCUSSION

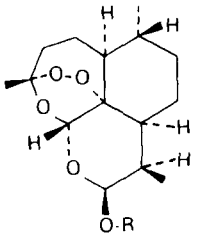
Examination of the proton-noise and off-resonance decoupled ^{13}C nmr spectra of artemisinin (1) revealed the presence of three methyl signals at δ 12.5, 19.8 and 25.2, three methylene signals at δ 33.7, 24.9, 23.4 and 35.9, five methine signals at δ 32.9, 45.0, 37.5, 50.1 and 93.8, two quaternary signals at δ 79.5 and 105.3, and a carbonyl signal at δ 171.9. This information agreed well with what was briefly reported[4] by



Artemisinin (1)



Desoxyartemisinin (3)



Artemether (2, R = CH_3)
Dihydroartemisinin (4, R = H)

the Chinese except for the signal at δ 23.4 which was inaccurately assigned to a methyl group while the signal at 24.9 was ascribed to a methylene carbon[5].

Differentiation between the methyl signals was readily accomplished by selective band decoupling at the respective

^1H nmr positions. Assignment of the C-5 and C-11 methines was similarly determined. The two quaternary oxygenated carbons at C-4 and C-6 were distinguished based on chemical shift theory.

Assignment of the remaining methine carbons at C-1, C-7 and C-10 necessitated the study of the ^{13}C nmr spectra of artemether[4] (**2**) and desoxyartemisinin[1] (**3**). The spectra for **2** retained the methine signal at δ 37.5 while that at δ 45.0 was insignificantly shifted to δ 44.6 and that at δ 50.1 now appeared at δ 52.8. This pattern permitted the assignments of C-1, C-7 and C-10 as shown in Table 1. Distinction between C-1 and C-10 was based on the difference between their chemical shift values. As expected, in the desoxy-derivative **3**, C-1, C-7 and C-10 all shifted (Table 1) since both C-1 and C-7 are alfa to the oxide bridge while C-10 is in a beta position.

While all the above carbons have now been unambiguously assigned, those of the methylene groups remained to be distinguished. However, based on chemical shift theory alone C-3 and C-9 should be the most deshielded of all methylene carbons.

Also, it should be noted that dihydroartemisinin (**4**) which is reported[3] to exist in the solid form as an epimeric mixture of **4** and its C-11 epimer was found to exhibit complex concentration-dependent ^{13}C and ^1H nmr spectra. In concentrated solutions containing 100 mg per 0.40 ml of $CDCl_3$ at least two alde-

TABLE 1

^{13}C nmr[a] Assignments of Artemisinin (1), Artemether (2) and Desoxyartemisinin (3)

Carbon Number	Artemisinin (1)	Artemether (2)	Desoxyartemisinin (3)
1	44.9 (*d*)	44.6 (*d*)	44.7 (*d*)
2	23.4[b] (*t*)	24.6[b] (*t*)	22.1[b] (*t*)
3	35.9[b] (*t*)	36.6[b] (*t*)	35.5[b] (*t*)
4	105.3 (*s*)	104.1 (*s*)	109.2 (*s*)
5	93.8 (*d*)	87.8[c] (*d*)	99.7 (*d*)
6	79.5 (*s*)	81.2 (*s*)	82.5 (*s*)
7	50.1 (*d*)	52.8 (*d*)	44.7 (*d*)
8	24.9[b] (*t*)	24.8[b] (*t*)	34.0[b] (*t*)
9	33.7[b] (*t*)	34.8[b] (*t*)	23.6[b] (*t*)
10	37.5 (*d*)	37.5 (*d*)	35.4 (*d*)
11	32.9 (*d*)	30.9 (*d*)	32.8 (*d*)
12	171.9 (*s*)	103.4[c] (*d*)	171.8 (*s*)
13	12.5 (*q*)	13.0 (*q*)	12.6 (*q*)
14	19.8 (*q*)	20.4 (*q*)	18.6 (*q*)
15	25.2 (*q*)	26.2 (*q*)	24.0 (*q*)
$O\underline{C}H_3$	----	55.9 (*q*)	----

[a]All spectra were taken in $CDCl_3$.

[b]Assignments interchangeable within the same column.

[c]Distinction between these two signals was accomplished by irradiation at δ 5.40 (C_5-H, *s*) which collapsed the doublet at δ 87.8 into a singlet.

hyde signals can be observed in the ^{1}H nmr spectrum at δ 10.20 and 10.30 with a singlet at δ 2.20 suggesting a methyl ketone. This is associated with the appearance of two aldehyde carbonyls in the ^{13}C nmr spectrum at δ 207.6 and δ 206.5 and a ketone carbonyl at δ 208.8. Dilution of the sample reduces the intensity of the signals due to the aldehyde groups in the ^{1}H nmr spectrum. It appears that **4** exists in solution as a mixture of numerous equilibrium components whose identification is now in progress.

EXPERIMENTAL

Artemisinin (1) was isolated from locally grown Artemisia annua L. and its identity was established by direct comparison with an authentic sample supplied by Dr. A. Brossi of the NIH, Bethesda, Maryland. Artemether[3], desoxyartemisinin[1] and dihydroartemisinin[3] were prepared by literature methods. The ^{13}C nmr spectra were obtained at 15.03 MHz on a JeolFX60 FT NMR Spectrometer, using TMS as internal standard and $CDCl_3$ as solvent. The proton-noise decoupled spectra were obtained using a 45° pulse, 5-s repitition and 8,192 datum points. Single frequency off-resonance spectra were conducted by centering the decoupling frequency 1100 Hz downfield from the signal for TMS. The abbreviations *s* , *d* , *t* , and *q* denote singlet, doublet, triplet and quartet, respectively.

ACKNOWLEDGEMENT

This investigation received the financial support of the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases.

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Received: 06/14/85

Accepted: 07/31/85