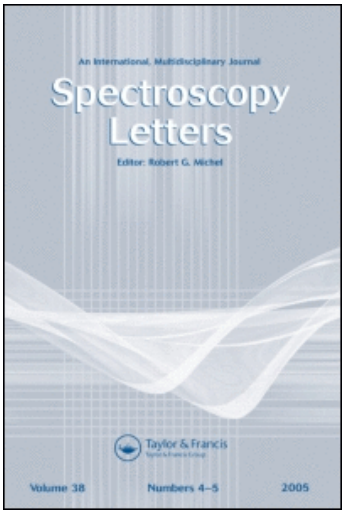

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^{1}H AND ^{13}C NMR ASSIGNMENTS OF ARTEETHERS

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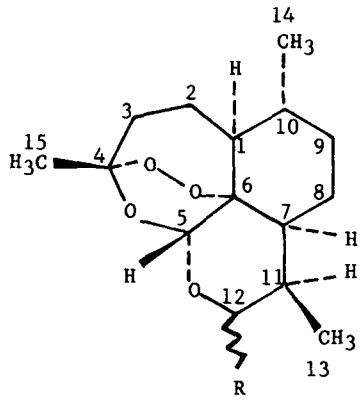
Abstract

The ^{1}H and ^{13}C nmr assignments for all hydrogen and carbon atoms were made for β and α arteethers (5 and 6) based on chemical shift theory and 2D-nmr techniques (COSY and HETCOR).

INTRODUCTION

Artemisinin (1), a novel type of antimalarial drug, is receiving considerable attention in the treatment of the chloroquine resistant and cerebral malaria.[1] Sodium borohydride reduction of 1 yields dihydroartemisinin (2).[2] Compound 2 is converted into either the hemisuccinate ester (artesunate 3), or the methyl- and ethyl ether derivatives (artemether 4 and arteether 5).[3,4] These ethers, 4 and 5, are reported to be more potent than artemisinin.[1,5] The World Health Organization has chosen β-arteether (5), for clinical investigation and development.[6]

As part of ongoing studies of the metabolism of new antimalarial drugs, it was deemed important to report here the complete ^{1}H and ^{13}C-nmr assignments for β and α -arteether (5,6) since this information is invaluable for the structure elucidation of key metabolites.



RESULTS AND DISCUSSION

The ^{1}H and ^{13}C-nmr assignments for artemisinin (1) have been reported[7,8] as well as some partial ^{13}C-nmr assignments for artemether.[8] Reduction of the lactone carbonyl of artemisinin, followed by conversion to the ethyl ether derivatives **5** and **6** results in significant shifts of the proton and carbon signals in the immediate vicinity of carbon 12 when compared with artemisinin.

The ^{1}H and ^{13}C-nmr assignments for the arteethers (**5** and **6**) are summarized in Table 1. The 300 MHz spectrum of β-arteether (**5**) showed well resolved multiplets (Fig. 1) for almost every signal greatly facilitating the proton assignments. The proton-proton connectivities were established from the COSY spectrum. The assignment of the signal at β 4.77 to H-12 was straight-forward which then allows assignments for H-11, CH_3-13, H-7 and H-8. The assignment of the other methyl doublet at δ 0.93 to CH_3-14 then allows assignments for H-10, H-1, and H-9. The assignment of H-3 to the signal at δ 2.35 follows by comparison to that of artemisinin (1)[7] which further verifies the H-2 signals. The ^{1}H nmr for α-arteether (**6**) was not as well resolved as for **5** but the assignments could be made from connectivities shown in the COSY spectrum and by analogy with the data for **5**.

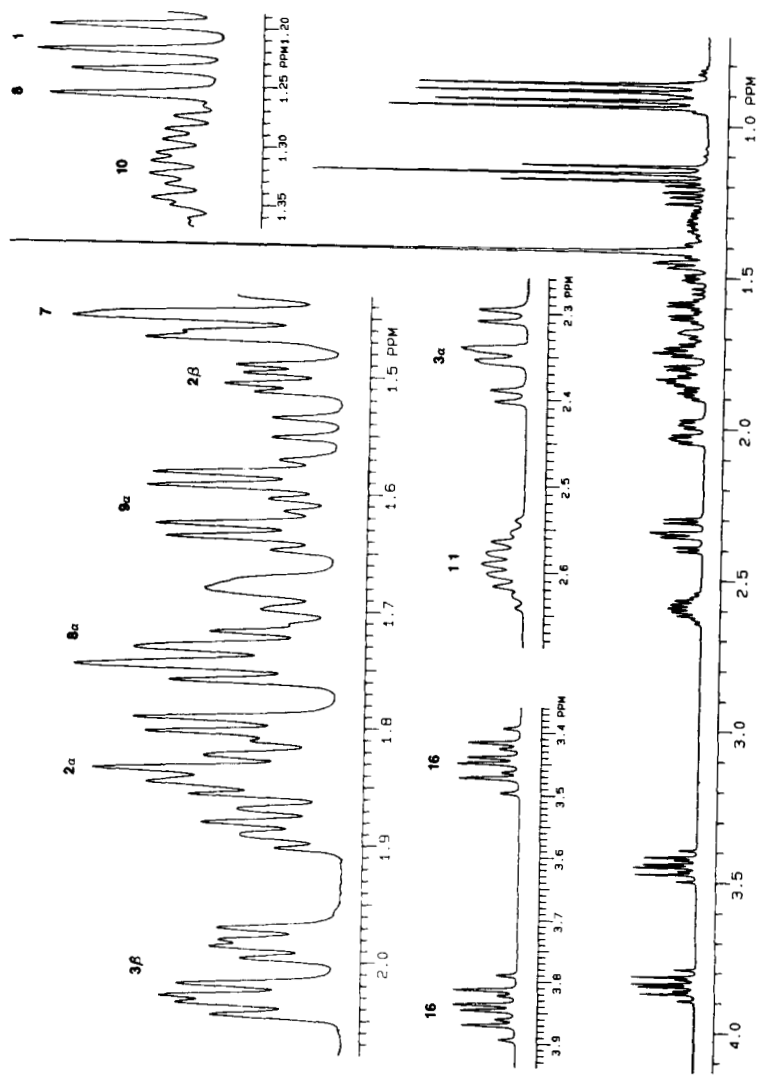


FIG. 1. 300 MHz ^{1}H nmr spectrum of β-arteether (5).

Table 1

^{1}H and ^{13}C nmr Assignments for
β-Arteether (5) and α-Arteether (6)

	β-Arteether (5)		α-Arteether (6)	
	H[a]	C[b]	H[a]	C[b]
1	1.2 m	52.8 (1)	1.28 m	51.7 (1)
2	α1.84 m; β1.6 m	24.8 (2)	α1.86 m; β1.5 m	24.7 (2)
3	α2.35 ddd (4.2,14.7,14.7); β2.00 ddd (3.0,4.5,14.7)	36.6 (2)	α2.36 ddd (3.9,14.0,14.0); β1.99 ddd (3.3,4.8,14.0)	36.4 (2)
4	-	104.0 (0)	-	101.2 (0)
5	5.39 s	87.9 (1)	5.31 s	91.2 (1)
6	-	81.2 (0)	-	80.3 (0)
7	1.46 m	44.7 (1)	1.5 m	45.4 (1)
8	α1.74 m; β1.24 m	24.6 (2)	α1.7 m; β1.3 m	22.2 (2)
9	α1.61 dddd (3.3,3.3,3.3, 13.2); β0.9 m	34.8 (2)	α1.7 m; β1.0 m	34.3 (2)
10	1.33 m	37.6 (1)	1.25 m	37.4 (1)
11	2.59 ddq (3.6,7.8,7.8)	31.0 (1)	2.40 m	32.5 (1)
12	4.77 d (3.6)	101.7 (1)	4.42 d (9.0)	99.8 (1)
13	0.88 d (7.8)	13.1 (3)	0.86 d (7.2)	12.6 (3)
14	0.93 d (6.0)	20.4 (3)	0.94 (5.7)	20.3 (3)
15	1.42 s	26.3 (3)	1.42 s	26.1 (3)
16	3.84 dq (7.5,9.6); 3.45 dq (7.5,9.6)	63.8 (2)	3.98 dq (6.0,9.0); 3.49 (6.0,9.0)	64.4 (2)
17	1.16 t (7.5)	15.3 (3)	1.19 t (6.0)	15.1 (3)

[a]The numbers in parenthesis represent J values and are in Hz. Abbreviations s,d,t,q and m denote singlet, doublet, triplet, quartet and multiplet, respectively.
[b]The number in parenthesis represents the number of attached protons.

The multiplicity in the ^{13}C nmr spectrum (75 MHz) for arteethers **5** and **6** were unambiguously established using the DEPTGL pulse sequence. The ^{13}C nmr assignments were established by the one bond ^{1}H-^{13}C correlation experiment (HETCOR). These assignments for **5** and **6** then allow the previously ambiguous carbon assignments for artemether (**4**) to also be established.[8]

EXPERIMENTAL

The ^{1}H and ^{13}C nmr data were obtained in $CDCl_3$ (75 mg/0.5 ml) on a Varian VXR-300 nmr spectrometer. The DEPTGL[9], COSY (90°)[10], and HETCOR[11] experiments were performed using the standard Varian software.

Artemisinin (**1**) was isolated from Artemisia annua grown in the Medicinal Plant Garden, School of Pharmacy, University of Mississippi. Its identity was established by direct comparison with an authentic sample supplied by Dr. Brossi of the NIH, Bethesda, Maryland. Dihydroartemisinin (**2**), β-arteether (**5**) and α-arteether (**6**) were prepared according to literature procedures.[2-4] The β-arteether (**5**) prepared was identical to an authentic sample.

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