

Full Papers

Preparation and Characterization of a New Artemisinin-Derived Dimer

Ahmed M. Galal, M. Shamim Ahmad, and Farouk S. El-Feraly*[†]

Department of Pharmacognosy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

Andrew T. McPhail*[‡]

Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27708-0346

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A new dimer (**1**) that is likely to be a reduction metabolite of arteether (**2**), the potent antimalarial agent, was prepared from deoxydihydroartemisinin (**3**). The identity of **1** was established from spectral data and was confirmed by X-ray crystallographic analysis. In addition, the stereochemistry of the related, previously reported dimer (**4**), is now more clearly defined, based on revising its X-ray crystallographic data.

In the course of our study of the dehydrating action of BF₃ etherate^{1–3} on deoxydihydroartemisinin (**3**), it was found that the reaction could be controlled to exclusively yield either the enol ether, anhydrodeoxydihydroartemisinin (**5**), or the dimer **1** as a major product, depending on the conditions used. This paper describes the preparation and characterization of this new dimer and its stereochemical relationship to the related and previously reported dimer **4**.⁴

Results and Discussion

In the course of attempted dehydration of deoxydihydroartemisinin (**3**) to the enol ether, anhydrodeoxydihydroartemisinin (**5**), by treatment with BF₃ etherate, it was observed that this reaction could go to completion in quantitative yields only if it were run at ambient temperature in an Et₂O–*n*-hexane mixture (1:4), using a large concentration of the dehydrating agent (see Experimental Section). By reducing the amount of BF₃ etherate and using Et₂O alone as a solvent, another product was obtained, which corresponded to dimer **1** with a much reduced yield of the enol ether **5**. The two products were separated by flash chromatography to produce **1** and **5** in 30% and 5% yields, respectively.

The structure and stereochemistry of dimer **1** were established from its ¹H-NMR and ¹³C-NMR spectral data (see Table 1) as well as other spectral features (see Experimental Section). It was observed that C-13 in dimer **1** has retained its β stereochemistry. This was based on the fact that its chemical shift value was 14.8 ppm, that is, about the same as in deoxydihydroartemisinin itself,⁵ in which C-13 is reported to resonate at δ 15.0. An α stereochemistry for C-13 would have shifted⁶ its resonance to around δ 19.⁶ Stereochemical assignments at C-12 and C-12' in **1** were tentatively made by comparing *J*_{H11α,H12α} and *J*_{H11'α,H12'β} values with

Table 1. ¹³C-NMR Chemical Shift Assignments^a for Compounds **1**, **4**, and **5**

carbon	chemical shift assignments (ppm)		
	1	4	5
1,1'	47.6, 45.4 (1)	45.2 (1)	45.7 (1)
2,2'	22.1, 22.0 (2)	22.2 (2)	21.6 (2)
3,3'	34.7, 34.6 (2)	34.6 (2)	34.4 (2)
4,4'	108.1, 107.1 (0)	107.1 (0)	107.7 (0)
5,5'	94.4, 94 (1)	97.3 (1)	95.6 (1)
6,6'	84, 81.4 (0)	82.7 (0)	83.3 (0)
7,7'	41.5, 41.2 (1)	44.2 (1)	41.1 (1)
8,8'	23.9, 22.2 (2)	32.6 (2)	27.6 (2)
9,9'	34.4, 34.1 (2)	34.5 (2)	34.2 (2)
10,10'	35.2, 35.1 (1)	35.1 (1)	35.3 (1)
11,11'	31.1, 30.7 (1)	39.2 (1)	112.6 (0)
12,12'	103.3, 102.1 (1)	97.7 (1)	133.9 (1)
13,13'	14.8, 12.9 (3)	18.7 (3)	16.6 (3)
14,14'	19.1, 18.6 (3)	18.9 (3)	18.8 (3)
15,15'	24.8, 24.6 (3)	23.9 (3)	24.2 (3)

^a Numbers in parentheses designate the number of attached protons at the respective carbon.

those reported¹ for β-deoxyarteether (**6**) and α-deoxyarteether (**7**). The values for **1** were found to be 3.3 and 8.2 Hz, corresponding to the cis and trans units, respectively, as compared to coupling constants of 4.5 for **6** and 6.1 Hz for **7**.

Unequivocal determination of the complete structure and stereochemistry of **1** was accomplished by X-ray crystallographic analysis. Non-hydrogen atom fractional coordinates are listed in Table 2. A view of the solid-state conformation, with the atom numbering scheme, is provided in Figure 1. Corresponding bond lengths in each half of the molecule agree well and lie close to expected values.⁷ Torsion angles characterizing the ring conformations are presented in Table 3. Rings A and A', as well as B and B', have chairlike conformations, with the former pair being considerably more puckered than normal around O-1 and somewhat flattened around C-2. In contrast, the different stereochemistries at C-12 and C-12' have a profound effect on the shapes of the C and D rings. Ring C has a flattened chair conformation, whereas the torsion angles in ring C' depart significantly from the symmetry-related values for 1,2-diplanar (envelope), 1,3-diplanar,

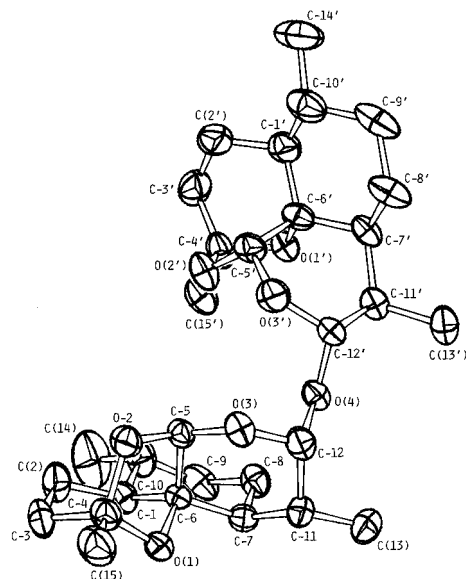
[†] Correspondence may be addressed to this author. Tel.: (966)-1-467-7256. FAX: (966)-1-467-6383. E-mail: F30H002@saksu00.bitnet@vtbit.cc.vt.edu.

[‡] Correspondence may be addressed to this author. Tel.: (919)-660-1500. FAX: (919)-660-1605. E-mail: chem@chem.duke.edu.

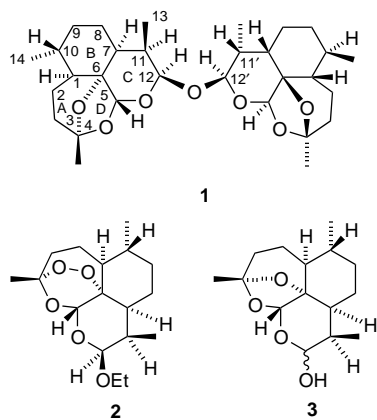
[®] Abstract published in *Advance ACS Abstracts*, August 1, 1996.

Table 2. Non-hydrogen Atom Fractional Coordinates and Equivalent Isotropic Thermal Parameters for **1**, with Estimated Standard Deviations in Parentheses

atom	x	y	z	$B_{eq}(\text{\AA}^2)$
C-1	0.4725(8)	0.0574(2)	0.4003(7)	5.5(2)
C-2	0.5676(8)	0.0622(3)	0.5173(7)	6.7(2)
C-3	0.6996(7)	0.0412(3)	0.4864(7)	5.9(2)
C-4	0.7397(7)	0.0562(2)	0.3439(7)	5.1(2)
C-5	0.6113(7)	0.1172(2)	0.2638(6)	4.2(1)
C-6	0.5368(7)	0.0697(2)	0.2653(6)	3.9(1)
C-7	0.4473(7)	0.0615(2)	0.1458(7)	4.7(1)
C-8	0.3123(7)	0.0846(3)	0.1685(7)	5.7(2)
C-9	0.2530(8)	0.0718(3)	0.3035(8)	7.2(2)
C-10	0.3428(8)	0.0843(3)	0.4196(7)	6.9(2)
C-11	0.5130(7)	0.0779(2)	0.0158(6)	5.2(2)
C-12	0.5692(7)	0.1273(2)	0.0294(6)	5.2(2)
C-13	0.4253(9)	0.0743(3)	-0.1068(7)	7.4(2)
C-14	0.2778(11)	0.0717(5)	0.5526(10)	13.3(4)
C-15	0.8738(8)	0.0415(3)	0.3055(8)	7.1(2)
O-1	0.6488(4)	0.0382(1)	0.2518(4)	4.8(1)
O-2	0.7257(5)	0.1073(1)	0.3370(5)	5.6(1)
O-3	0.6568(4)	0.1301(2)	0.1353(4)	4.8(1)
O-4	0.4659(4)	0.1608(1)	0.0395(4)	4.5(1)
C-1'	0.3861(8)	0.3395(2)	0.2288(8)	6.4(2)
C-2'	0.3872(9)	0.3360(3)	0.3836(9)	7.6(2)
C-3'	0.2959(10)	0.2981(3)	0.4353(8)	8.2(2)
C-4'	0.2986(7)	0.2532(3)	0.3498(8)	6.4(2)
C-5'	0.4897(7)	0.2579(2)	0.2322(7)	5.2(2)
C-6'	0.3851(7)	0.2892(2)	0.1693(7)	5.0(2)
C-7'	0.3850(7)	0.2876(2)	0.0178(7)	4.9(1)
C-8'	0.4983(8)	0.3174(2)	-0.0367(9)	6.9(2)
C-9'	0.4886(8)	0.3678(3)	0.0186(9)	8.1(2)
C-10'	0.4939(8)	0.3701(3)	0.1709(9)	7.7(2)
C-11'	0.3842(6)	0.2352(2)	-0.0277(6)	4.7(1)
C-12'	0.5019(6)	0.2089(2)	0.0258(6)	4.5(1)
C-13'	0.3760(8)	0.2293(3)	-0.1796(7)	6.5(2)
C-14'	0.4862(11)	0.4222(3)	0.2183(12)	10.8(3)
C-15'	0.2096(9)	0.2146(3)	0.3976(8)	7.6(2)
O-1'	0.2680(4)	0.2662(2)	0.2152(4)	5.1(1)
O-2'	0.4278(5)	0.2343(2)	0.3382(5)	6.6(1)
O-3'	0.5563(5)	0.2264(2)	0.1471(5)	6.5(1)

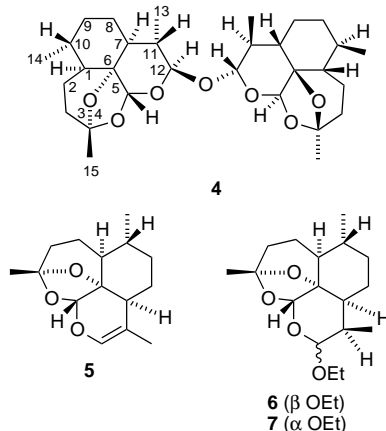
**Figure 1.** ORTEP diagram (30% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation of **1**; hydrogen atoms have been omitted for clarity.

1,4-diplanar (boat), or half-chair forms and most closely correspond to those for a very distorted 1,4-diplanar (boat) conformation. Ring D is in a half-chair form, with its C_2 -symmetry axis passing through O-2 and the midpoint of the C-6–O-1 bond, while ring D' approximates to a C_s -envelope conformation with O-1' as the out-of-plane atom.



Dimer **1** is remarkably different from the C_2 -symmetrical dimer **4**, which was suggested as a possible metabolite of arteether (**2**).⁴ The latter was prepared by treating deoxydihydroartemisinin (**3**) with *p*-toluenesulfonic acid in dry toluene. It was reported to have a symmetrical structure, with both C-13 and C-13' possessing inverted stereochemistry (α). Unfortunately,

the results of the X-ray analysis⁴ of **4** are somewhat ambiguous with regard to the overall stereochemistry, as the listed coordinates yield the mirror image of the correctly shown structure represented in Figure 1; moreover, the C15–C11–C12–O16 torsion angles should be positive not negative as stated. These inconsistencies came to light when an X-ray crystallographic analysis was performed on a sample of dimer **4** prepared in our laboratory using the reported procedure;⁴ the complete crystallographic data derived from this investigation have been deposited at the Cambridge Crystallographic Data Centre. Endocyclic torsion angles for rings A–D from the present study are included for comparison in Table 3 alongside the corresponding values in **1**. Table 1 includes the ¹³C-NMR spectral assignments for dimer **4**, which have not been previously reported.



Experimental Section

General Experimental Procedures. Mp's were recorded on an Electrothermal 9100 instrument. UV spectra were obtained in MeOH, using a Varian DMS 90 spectrophotometer, and IR spectra were obtained as KBr disks on a Perkin-Elmer 5808 spectrophotometer. The NMR spectra were recorded in $CDCl_3$ on a Varian VXR 300 instrument at 300 MHz (¹H) and 75 MHz (¹³C)

Table 3. Endocyclic Torsion Angles^a (°) for **1** and **4**, with Estimated Standard Deviations in Parentheses

	1		4^b			
	unprimed	primed	molecule A		molecule B	
			unprimed	primed	unprimed	primed
ring A						
$\omega_{C1,C2}$	-43.8(8)	-42.1(9)	-42.9(3)	-44.6(4)	-41.6(3)	-43.0(3)
$\omega_{C2,C3}$	43.7(8)	40.3(10)	42.0(4)	43.9(4)	41.1(4)	43.4(4)
$\omega_{C3,C4}$	-61.6(7)	-56.5(9)	-58.5(3)	-59.3(4)	-57.5(4)	-59.7(3)
$\omega_{C4,O1}$	76.9(6)	74.2(7)	75.1(2)	75.6(3)	74.1(3)	75.6(3)
$\omega_{O1,C6}$	-72.9(6)	-77.8(7)	-75.8(2)	-77.3(3)	-75.4(2)	-75.3(2)
$\omega_{C6,C1}$	57.0(6)	61.0(8)	60.0(3)	60.7(3)	58.8(3)	58.6(3)
ring B						
$\omega_{C1,C6}$	-54.9(7)	-51.7(9)	-51.0(3)	-52.2(3)	-51.7(3)	-52.9(3)
$\omega_{C6,C7}$	49.3(7)	53.3(8)	52.3(3)	54.7(3)	52.5(3)	54.1(3)
$\omega_{C7,C8}$	-49.7(8)	-55.7(8)	-55.6(3)	-57.5(3)	-54.8(4)	-56.3(3)
$\omega_{C8,C9}$	55.8(9)	59.8(9)	58.2(4)	58.3(4)	57.8(4)	59.1(4)
$\omega_{C9,C10}$	-58.7(8)	-56.7(9)	-53.8(4)	-52.7(4)	-54.5(4)	-56.1(4)
$\omega_{C10,C1}$	57.9(8)	50.8(9)	50.0(3)	49.0(4)	50.8(3)	52.0(4)
ring C						
$\omega_{C5,C6}$	-39.7(8)	-10.2(8)	-22.7(3)	-22.9(3)	-20.2(3)	-21.2(3)
$\omega_{C6,C7}$	41.3(7)	50.3(7)	48.9(3)	50.5(3)	49.8(3)	52.4(3)
$\omega_{C7,C11}$	-49.1(7)	-59.1(7)	-15.6(3)	-18.2(3)	-20.1(3)	-23.7(3)
$\omega_{C11,C12}$	56.5(7)	27.2(7)	-42.8(3)	-39.7(3)	-38.0(3)	-34.6(3)
$\omega_{C12,O3}$	-56.9(7)	15.7(8)	73.7(3)	72.2(3)	72.3(3)	70.8(3)
$\omega_{O3,C5}$	47.9(8)	-25.2(9)	-37.3(3)	-37.5(3)	-40.0(3)	-39.6(3)
ring D						
$\omega_{C4,O2}$	11.8(7)	30.6(7)	23.4(3)	21.7(3)	25.2(3)	23.5(3)
$\omega_{O2,C5}$	16.9(6)	-5.7(7)	2.7(3)	4.3(3)	0.7(3)	2.3(3)
$\omega_{C5,C6}$	-37.8(5)	-20.7(6)	-27.2(3)	-28.0(3)	-25.5(3)	-26.7(3)
$\omega_{C6,O1}$	45.8(5)	39.5(6)	41.9(2)	41.5(3)	41.4(3)	41.6(2)
$\omega_{O1,C4}$	-37.5(6)	-44.0(7)	-41.4(2)	-40.1(3)	-42.3(2)	-41.3(2)

^a The torsion angle A-B-C-D is defined as positive if, when viewed along the B-C bond, atom A must be rotated clockwise to eclipse atom D. ^b Two crystallographically independent C₂-symmetric molecules in the asymmetric unit.

or Varian 200 XL, using TMS as internal standard. Spectral editing (APT and DEPTGL) and 2D NMR spectra (COSY and HETCOR) were obtained using standard Varian software. CIMS were recorded on a Finnigan MAT 300 mass spectrometer, using NH₃ as ionizing gas. Optical rotations were recorded in EtOAc, at ambient temperature using a Perkin-Elmer 241 MC polarimeter. Deoxydihydroartemisinin (**3**) was prepared from dihydroartemisinin using a literature procedure.⁸ Likewise, dimer **4** was prepared by the procedure reported.⁴ TLC was performed on Si gel 60 F 254, using CH₂Cl₂-CH₃CN (60:1) as solvent, unless otherwise specified, with visualization using *p*-anisaldehyde/H₂SO₄ spray reagent.

Anhydrodeoxydihydroartemisinin (5).⁹ Deoxydihydroartemisinin (**3**) (500 mg) was dissolved by stirring in dry Et₂O-*n*-hexane mixture (1:4) (50 mL) at ambient temperature. BF₃ etherate (0.9 mL) was added, and the reaction was stirred for 50 min, then quenched by the addition of 20 mL of a 1% aqueous solution of NaHCO₃. The mixture was diluted with 200 mL of Et₂O and washed with H₂O, following which the Et₂O phase was separated and dried over anhydrous Na₂SO₄. Evaporation of Et₂O afforded a yellowish oil (500 mg) that, upon TLC, showed the presence of a single spot, *R*_f 0.75, and yielded upon crystallization (*n*-hexane) colorless prisms of **5** (480 mg, 97%): mp 105–106 °C; [α]_D +16° (*c* 0.1, MeOH); IR (KBr) ν_{\max} 1675 cm⁻¹ (-CH=C-) and no OH absorption bands; ¹H NMR δ 0.90 (3H, d, *J* = 6.4 Hz, H-14), 1.47 (3H, s, H-13), 1.62 (3H, d, *J* = 1.6 Hz, H-15), 5.48 (1H, s, H-5), 6.05 (1H, q, *J* = 1.6 Hz, H-12); for the ¹³C-NMR assignments see Table 1.

Dimer 1. Deoxydihydroartemisinin (**3**) (500 mg) was

dissolved by stirring in dry Et₂O (50 mL) at ambient temperature. BF₃ etherate (0.30 mL) was added, and the reaction was stirred for 50 min, then worked up as before (see above) to yield a yellowish oil (500 mg) that, upon TLC, showed the presence of a number of spots, with that at *R*_f 0.15 being the major component and corresponding to dimer **1**. Flash chromatography on Si gel using CH₂Cl₂-CH₃CN mixture (95:5) as a solvent provided first 27 mg of **5** (5%) then 148 mg of dimer (**1**)(30%), obtained as colorless crystals (*n*-hexane): mp 155–157 °C; [α]_D -87° (*c* 0.1, EtOAc); IR (KBr) no OH absorption bands; ¹H NMR δ 0.85 (6H, d, *J* = 6.5 Hz, H-14 and H-14'), 0.92 and 0.90 (3H each, d, *J* = 7.2 Hz, H-13 and H-13'), 1.44 and 1.50 (3H each, s, H-15 and H-15'), 2.43 (2H, m, H-11 and H-11'), 4.56 and 4.76 (1H each, d, *J* = 8.2, and 3.3 Hz, respectively, H-12 and H-12'), 5.36 and 5.60 (1H each, s, H-5 and H-5'); for the ¹³C-NMR assignments see Table 1; CIMS(NH₃) *m/z* 536 (27) [M]⁺ with the base peak at *m/z* 251.

X-ray Crystal Structure Analysis of Dimer (1): crystal data, C₃₀H₄₆O₇; MW = 518.70, orthorhombic, space group *P*2₁2₁2₁(*D*₂⁴)-No. 19, *a* = 10.272(3) Å, *b* = 28.203(9) Å, *c* = 9.979(1) Å, *V* = 2891(3) Å³, *Z* = 4, *D*_c = 1.192 g·cm⁻³, μ (Cu K α radiation, λ = 1.5418 Å) = 6.4 cm⁻¹; crystal dimensions: 0.04 × 0.22 × 0.40 mm.

Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs. Refined unit-cell parameters were derived from the diffractometer setting angles for 25 reflections (36° < θ < 40°) widely separated in reciprocal space. The space group was defined uniquely by the Laue symmetry and systematic absences: *h*00 when *h* ≠ 2*n*, 0*k*0 when *k* ≠ 2*n*, 00*l* when *l* ≠ 2*n*. One octant of intensity data was recorded on an Enraf-

Nonius CAD-4 diffractometer [CuK α radiation, incident beam graphite monochromator; $\omega - 2\theta$ scans; scanwidth $(1.20 + 0.14 \tan \theta)^\circ$, $\theta_{\max} = 65^\circ$; 2792 reflections]. The intensities of four reference reflections, monitored every 2 h during data collection, showed no significant variation (<1% overall). The data were corrected for the usual Lorentz and polarization effects; an empirical absorption correction, based on the ϕ -dependency of the intensities of several reflections with χ ca. 90° , was also applied. A total of 1334 reflections with $I > 3.0 \sigma(I)$ were retained for the analysis.

The crystal structure was solved by direct methods (MULTAN11/82). Initial coordinates for all carbon and oxygen atoms were derived from an E -map. Positional and temperature factor parameters (first isotropic and then anisotropic) of these atoms were adjusted by means of several rounds of full-matrix least-squares calculations. Hydrogen atoms were incorporated at their calculated positions during the later iterations. Parameter refinement converged at $R = 0.049$ ($R_w = 0.062$) $\{R(\Sigma|F_o| - |F_c|/\Sigma|F_o|), R_w[\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}\}$. A final difference Fourier synthesis contained no unusual features [$\Delta\rho(\text{e.}\text{\AA}^{-3}) = 0.13$ (max), -0.17 (min)]. Non-hydrogen atom coordinates are listed in Table 2. Anisotropic temperature factor parameters, hydrogen atom parameters, bond lengths, bond angles and torsion angles, and a list of observed and calculated structure amplitudes have been deposited at the Cambridge Crystallographic Data Centre.

Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf-Nonius Structure Determination Package (SDP). For structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from Ibers and Hamilton.¹⁰ In the least-squares

iterations, $\Sigma w\Delta^2[w = 1/\sigma^2(|F_o|), \Delta = (|F_o| - |F_c|)]$ was minimized.

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Supporting Information Available: Figures S1 and S2 and Tables S1–S10, containing atomic coordinates and crystallographic data for **1** and **4** (33 pages). Ordering information is given on any current masthead page.

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