Journal of Natural Products
Vol. 53, No. 4, pp. 920-925, Jul-Aug 1990

DECOMPOSITION OF DIHYDROARTEMISITENE ON SILICA GEL

FAROUK S. EL-FERALY,* ABIDIN AYALP, MOHAMMED A. AL-YAHYA,

Department of Pharmacognosy and Medicinal, Aromatic and Poisonous Plants Research Center, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

DONALD R. MCPHAIL, and ANDREW T. MCPHAIL*

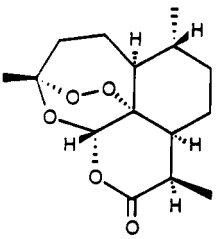
Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

ABSTRACT.—Dihydroartemisitene [**5**], obtained by reducing its hydroperoxy analogue with triphenylphosphine, was found to undergo isomerization to the keto-aldehyde **6** when chromatographed on Si gel. X-ray crystallographic analysis established the structure of each compound.

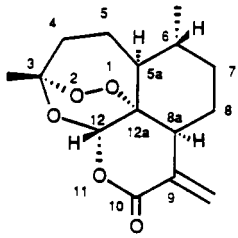
In an earlier paper, we reported (1) on the conversion of the antimalarial sesquiterpene artemisinin [**1**] to its dehydro analogue artemisitene [**2**]. The transformation was accomplished by dye-sensitized photo-oxygenation of the enol ether **3** to give the hydroperoxide intermediate **4**. In an extension of this work, reduction of **4** with polymer-bound triphenylphosphine furnished **5**, whereas **6** resulted when free triphenylphosphine was used. The structure and solid-state stereochemistry of each of these products and a rational explanation for their formation are the subjects of this paper.

RESULTS AND DISCUSSION

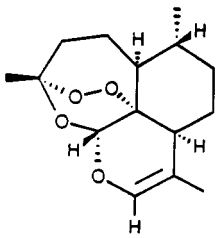
The hydroperoxide analogue **4** was reduced smoothly with polymer-bound triphenylphosphine to produce dihydroartemisitene [**5**] in 84% yield. Spectral data (see Experimental) confirmed the structure shown for **5**, which, being a hemiacetal like dihydroartemisinin [**7**] (2), was also found to occur in solution as a mixture of C-10 epimers. Single-crystal X-ray analysis of **5** not only verified its constitution but also revealed that, in common with **7**, the hemiacetal hydroxyl group again existed in the thermodynamically more stable β configuration in the solid state. Carbon and oxygen



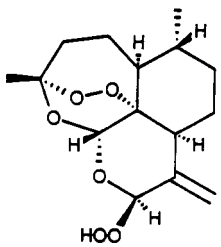
1



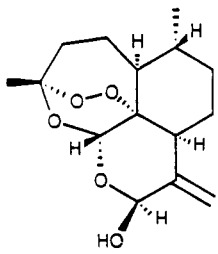
2



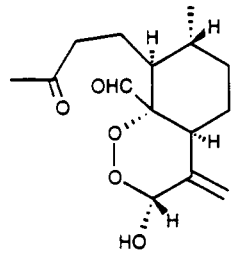
3



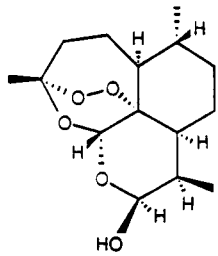
4



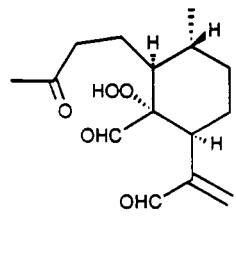
5



6



7



8

atom fractional coordinates are provided in Table 1.[1] A view of the solid-state conformation is shown in Figure 1. Bond lengths, bond angles, and torsion angles in **5** all lie close to corresponding mean values for the two crystallographically independent

TABLE 1. Fractional Coordinates and Equivalent Isotropic Thermal Parameters for the Non-hydrogen Atoms in Compound **5**, with Estimated Standard Deviations in Parentheses.

Atom	*x*	*y*	*z*	B_{eq} (Å^2)
O-1	0.4773(1)	0.4283(1)	0.5737(3)	4.80(4)
O-2	0.3933(2)	0.3811(1)	0.6234(3)	5.54(4)
C-3	0.3928(2)	0.3193(1)	0.4727(5)	5.29(6)
C-4	0.4903(2)	0.2802(1)	0.4634(6)	5.63(6)
C-5	0.5541(2)	0.3054(1)	0.2687(6)	5.24(6)
C-5a	0.5769(2)	0.3897(1)	0.2622(5)	4.17(4)
C-6	0.6193(2)	0.4113(2)	0.0283(5)	4.70(5)
C-7	0.6418(2)	0.4950(2)	0.0189(6)	5.37(6)
C-8	0.5550(2)	0.5423(2)	0.0749(5)	4.81(5)
C-8a	0.5137(2)	0.5236(1)	0.3098(4)	4.10(5)
C-9	0.4266(2)	0.5690(1)	0.3685(4)	4.46(5)
C-10	0.3356(2)	0.5472(1)	0.2489(5)	4.68(5)
O-11	0.3201(1)	0.4678(1)	0.2700(3)	4.49(3)
C-12	0.3980(2)	0.4198(1)	0.2060(4)	3.62(4)
C-12a	0.4908(2)	0.4392(1)	0.3309(4)	3.66(4)
C-13	0.3119(3)	0.2711(2)	0.5575(8)	7.91(9)
C-14	0.7090(2)	0.3658(2)	−0.0278(7)	7.15(8)
C-15	0.4254(3)	0.6238(2)	0.5221(6)	6.58(8)
O-16	0.3667(1)	0.3464(1)	0.2519(3)	4.68(4)
O-17	0.3420(1)	0.5683(1)	0.0227(3)	5.20(4)

[1]Atomic coordinates for compounds **5** and **6** have been deposited at the Cambridge Crystallographic Data Centre, and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

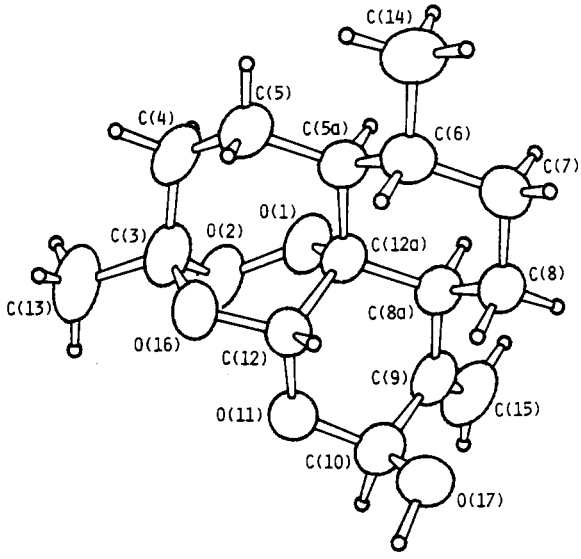


FIGURE 1. Atom numbering scheme and solid-state conformation of dihydroartemisitene [**5**]; small circles represent hydrogen atoms.

molecules of the C-10 hydroperoxide analogue **4** (1). In the solid state, molecules of **5** related by the crystallographic 2_1 screw axis along *c* are associated by an O-H . . . O hydrogen bond [O-17 . . . O-11 = 2.785 (2) Å].

Reduction of **4** with free triphenylphosphine proceeded smoothly, but it was necessary to chromatograph the resulting mixture on Si gel to remove excess reagent as well as triphenylphosphine oxide. The reaction product, obtained in 85% yield, surpris-

TABLE 2. Fractional Coordinates and Equivalent Isotropic Thermal Parameters for the Non-hydrogen Atoms in Compound **6**, with Estimated Standard Deviations in Parentheses.

Atom	*x*	*y*	*z*	B_{eq} (Å^2)
O-1	−0.0950(3)	0.3434(2)	0.0975(7)	4.0(1)
O-2	−0.1855(3)	0.3913(2)	0.1368(7)	4.8(1)
C-3	0.0528(5)	0.2006(3)	−0.4400(10)	4.5(1)
C-4	0.0664(6)	0.2238(4)	−0.2230(10)	6.8(2)
C-5	0.0645(6)	0.3078(3)	−0.1984(10)	5.4(2)
C-5a	0.0807(4)	0.3390(3)	0.0221(9)	3.4(1)
C-6	0.1849(4)	0.3801(3)	0.0511(10)	4.6(1)
C-7	0.1973(5)	0.4135(4)	0.2642(11)	5.3(2)
C-8	0.1125(4)	0.4687(3)	0.3199(10)	4.3(1)
C-8a	0.0096(4)	0.4270(3)	0.3012(9)	3.2(1)
C-9	−0.0844(4)	0.4705(3)	0.3579(9)	3.7(1)
C-10	−0.1791(4)	0.4244(3)	0.3405(10)	4.4(1)
O-11	0.0238(4)	0.5080(2)	−0.1114(8)	6.9(1)
C-12	−0.0271(5)	0.4520(3)	−0.0805(10)	4.3(1)
C-12a	−0.0062(4)	0.3926(3)	0.0858(9)	3.2(1)
C-13	−0.0529(5)	0.1929(3)	−0.5289(11)	5.2(2)
C-14	0.2749(5)	0.3247(4)	0.0051(14)	7.5(2)
C-15	−0.0903(5)	0.5440(4)	0.4089(11)	5.6(2)
O-16	0.1264(3)	0.1907(3)	−0.5488(8)	7.0(1)
O-17	−0.1796(3)	0.3680(2)	0.4919(7)	5.3(1)

ingly differed from **5**. Spectral data (see Experimental) in combination with the results of a single-crystal X-ray analysis established structure **6** for this product which also occurs as a mixture of C-10 epimers in solution but for which the hemiacetal hydroxyl group assumes an α configuration in the solid state. Final fractional coordinates for the carbon and oxygen atoms are listed in Table 2.[1] The structure and solid-state conformation of **6** are illustrated in Figure 2. Bond lengths and angles in **6** are in accord with expected values (3). In crystals of **6**, an O-H . . . O hydrogen bond [O-17 . . . O-16 = 2.761 (6) Å] links molecules related by the crystallographic 2_1 screw axis along *a*.

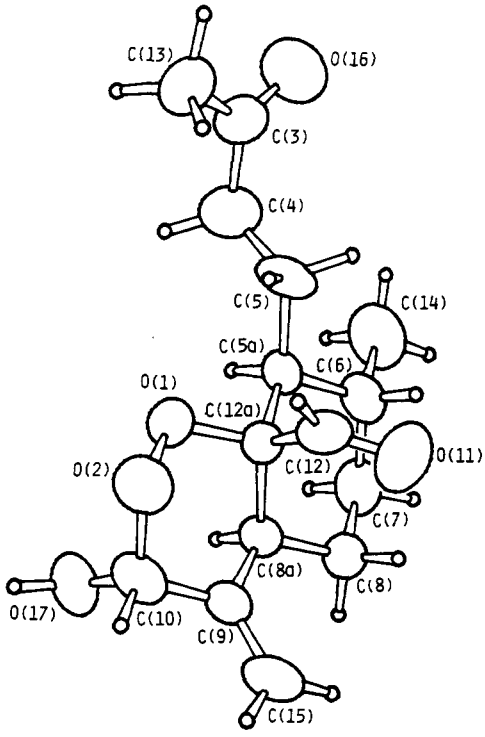


FIGURE 2. Atom numbering scheme and solid-state conformation of compound **6**; small circles represent hydrogen atoms.

Because purification on Si gel was the major difference between the two sets of reaction conditions leading to the formation of **5** and **6**, it was rationalized that reduction with free triphenylphosphine probably led to **5** which underwent isomerization when it was subjected to chromatography. Support for this notion was derived from the fact that filtration of pure **5** over a column of Si gel produced **6**. In some runs, however, the conversion was complete after only one filtration whereas in others filtration needed to be performed twice. The extent of isomerization can be monitored by tlc on Si gel G plates by use of C_6H_6-Et_2O (1:1) as solvent, giving R_f values of 0.52 and 0.48, respectively, for **5** and **6**. Tlc is apparently too rapid to promote any appreciable isomerization of **5** to **6**.

Isomerization of dihydroartemisitene [**5**] to **6** over acidic Si gel can be explained readily by assuming that **5** would undergo acid-catalyzed opening of its ketal and acetal moieties to give intermediate **8**, which recyclizes to **6**.

The foregoing transformation opens the way to a novel series of endoperoxide analogues and derivatives, the biological activities of which are yet to be studied. Work in this area is being actively pursued.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Instrumentation used and origin of artemisinin [**1**] were as described previously (1). Tlc was performed on Si gel G plates using Et_2O-C_6H_6 (1:1) as solvent and visualized by spraying with anisaldehyde spray reagent (4).

REDUCTION OF **4** TO DIHYDROARTEMISITENE [**5**].—The hydroperoxide **4** (50 mg), obtained as previously reported (1), was dissolved in CH_2Cl_2 (5 ml) and stirred for 25 min at room temperature with polymer-bound triphenylphosphine. The mixture was then filtered and the residue washed with CH_2Cl_2. Evaporation of the filtrate left a crystalline residue that was recrystallized from CH_2Cl_2-hexane to give prisms of **5** (42 mg, 84%): $C_{15}H_{22}O_5$; mp 120–121°; $[\alpha]^{25}D$ +155° (c = 0.05, $CHCl_3$); ir (KBr) (cm^{-1}) ν max 3390 (OH) and no CO bands; ^1H nmr ($CDCl_3$) showed that the compound, in solution, was a mixture of C-10 epimers whose composition was concentration-dependent: a 50 mg/ml solution exhibited major signals at δ 5.78 (s, H-10), 5.76 (s, H-12), 5.20 and 2.04 (s, 9-CH_2), 1.43 (s, 3-Me), 0.98 (d, J = 6 Hz, 6-Me); ^{13}C nmr ($CDCl_3$) major signals at δ 143.5 (C-9), 115.1 (9-CH_2), 103.9 (C-3), 95.2 (C-10), 88.3 (C-12), 81.0 (C-12a), 25.94 (3-Me), 20.1 (6-Me), three methine signals at δ 51.8, 47.8, 37.5 (C-5a, C-6, and C-8a, unassigned) and four methylene signals at δ 36.4, 34.3, 31.8, and 24.5 (C-4, C-5, C-7, and C-8, unassigned); eims m/z (rel. int.) $[M]^+$ 282 (0.5). Calcd for $C_{15}H_{22}O_5$, C 63.81, H 7.86; found C 63.71, H 7.88.

REDUCTION OF **4** TO **6**.—The hydroperoxide **4** (115 mg) was dissolved in CH_2Cl_2 (5 ml) and stirred for 5 min at room temperature with triphenylphosphine (103 mg). Evaporation left a crystalline residue that was flash chromatographed (5) on Si gel using C_6H_6-Et_2O (1:1) as solvent to yield 98 mg (85%) of **6**: $C_{15}H_{22}O_5$; mp 105–106°; $[\alpha]^{25}D$ −241° (c = 0.05, $CHCl_3$); ir (KBr) (cm^{-1}) ν max 3365 (OH), 1720 (CHO), 1700 (ketone); ^1H nmr ($CDCl_3$) showed that the compound, in solution, was a mixture of C-10 epimers whose composition was concentration-dependent: a 62.5 mg/ml solution exhibited major signals at δ 9.96 (s, H-12), 5.52 (s, H-10), a pair of broad singlets at δ 5.03 and 4.88 (9-CH_2), 2.14 (s, 3-Me) and 0.94 (d, J = 6.5 Hz, 6-Me); ^{13}C nmr ($CDCl_3$) major signals at δ 208.5 (C-3), 204.3 (C-12), 140.5 (C-9), 111.3 (9-CH_2), 100.3 (C-10), 92.0 (C-12a), 20.3 (6-Me), 30.0 (3-Me), three methine signals at δ 49.01, 42.8, and 33.8 (C-5a, C-6, and C-8a, unassigned), and 4 methylene signals at δ 43.6, 34.2, 21.7, and 21.3 (C-4, C-5, C-7, and C-8, unassigned); eims m/z (rel. int.) $[M]^+$ 282 (0.5). Calcd for $C_{15}H_{22}O_5$, C 63.81, H 7.86; found C 63.77, H 7.71.

CONVERSION OF DIHYDROARTEMISITENE [**5**] TO **6**.—Dihydroartemisitene [**5**] (100 mg), obtained as described above, was filtered on Si gel (mesh size 230–400), packed in a column 1.2 cm × 14.1 cm, using C_6H_6-Et_2O (1:1) as eluent. The eluate contained a mixture of **5** and **6** as shown by tlc, to give R_f values of 0.52 and 0.48, respectively. Repeating the filtration gave exclusively a product identical with **6** (indistinguishable ir and nmr spectra, same mp and mmp).

X-RAY CRYSTAL STRUCTURE ANALYSIS OF COMPOUNDS **5** AND **6**.—Crystal data for **5**: $C_{15}H_{22}O_5$; MW = 282.34, orthorhombic, space group $P2_12_12_1$, a = 13.967 (2), b = 17.803 (2), c = 5.891 (1) Å (from 25 orientation reflections, 45° <θ<48°), V = 1464.8 (6) Å^3, Z = 4, D_c = 1.280 g·cm^{-3}, μ (CuKα radiation, λ = 1.5418 Å) = 7.5 cm^{-1}; crystal dimensions 0.30 × 0.36 × 0.40 mm.

Crystal data for **6**: $C_{15}H_{22}O_5$, MW = 282.34, orthorhombic, space group $P2_12_12_1$, a = 13.082 (2), b = 17.428 (2), c = 6.508 (1) Å (from 25 orientation reflections, 37°<θ<41°), V = 1483.8 (6) Å^3, Z = 4, D_c = 1.264 g·cm^{-3}, μ (CuKα radiation) = 7.4 cm^{-1}; crystal dimensions 0.06 × 0.06 × 0.30 mm.

Preliminary unit-cell parameters and space group information for crystals of **5** and **6** were derived from oscillation and Weissenberg photographs. One octant of intensity data was recorded for each compound on an Enraf-Nonius CAD-4 diffractometer [CuKα radiation, incident-beam graphite monochromator; ω–2θ scans; scan width (1.10 + 0.14 tan θ)°, θ max = 75° for **5**, θ max = 67° for **6**]. From totals of 1745 and 1540 measurements for **5** and **6**, respectively, those 1410 and 739 reflections with I>3.0σ (I) were retained for the structure analyses, and the usual Lorentz and polarization corrections were applied. An empirical absorption correction (T_{max}: T_{min} = 1.00:0.93) was also made to the data for **5**. For compound **6**, which was unstable to X-irradiation, a linear decay correction (overall intensity loss = 17%) was applied to the data.

Both crystal structures were solved by direct methods (MULTAN11/82). Approximate carbon and oxygen atom coordinates were obtained in each case from an E-map. Full-matrix least-squares adjustment of positional and thermal parameters (at first isotropic and then anisotropic) to convergence was followed by evaluation of difference Fourier syntheses which revealed hydrogen atom positions. With the inclusion of

hydrogen atom positional and isotropic thermal parameters as well as an extinction correction as variables in the subsequent least-squares iterations for **5**, the refinement converged at $R = 0.034$ ($R_w = 0.047$, GOF = 1.7). For **6**, where the rather small crystal employed led to a low ratio of observations to parameters, hydrogen atoms were included at their calculated positions in the final rounds of least-squares parameter refinement which converged at $R = 0.044$ ($R_w = 0.054$, GOF = 1.3). For both compounds, $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$; $GOF = [\Sigma w(|F_o| - |F_c|)^2/(N_{observations} - N_{parameters})]^{1/2}$.

Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf-Nonius Structure Determination Package (SDP). For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were from the literature (6). In the least-squares iterations, $\Sigma w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] was minimized.

ACKNOWLEDGMENTS

The authors thank Dr. Charles D. Hufford, School of Pharmacy, University of Mississippi, for recording some of the nmr spectra.

LITERATURE CITED

1. F.S. El-Feraly, A. Ayalp, M.A. Al-Yahya, D.R. McPhail, and A.T. McPhail, *J. Nat. Prod.*, **53**, 66 (1990).
2. X.-de Luo, H.J.C. Yeh, A. Brossi, J.L. Flippen-Anderson, and R. Gilardi, *Helv. Chim. Acta*, **67**, 1515 (1984).
3. F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, S1 (1987).
4. F.S. El-Feraly and C.D. Hufford, *J. Org. Chem.*, **47**, 1527 (1982).
5. W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
6. J.A. Ibers and W.C. Hamilton, Eds., "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham, England, 1974, Vol. IV.

Received 8 January 1990