Journal of Chemistry, Vol. 47 (1), P. 122 - 126, 2009

PHOTOCHEMICAL REACTION OF DIHYDROARTEMISININ ESTERS

Received 26 December 2008

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ABSTRACT

Photochemical reaction of three dihydroartemisinin esters: acetate, benzoate and succinate under 254 nm UV light in CH_2Cl_2 have been studied. The result showed, that these artemisinin derivatives are easily decomposed forming different elimination and rearrangement compounds.

I - INTRODUCTION

Artemisinin (quinghaosu **1**) isolated for the first time by Chinese scientist from *Artemisia annua L.* [1, 2] showed antimalarial activity. Currently artemisinin and its derivatives are used for treatment of malaria. Many works on chemistry and pharmacology of artemisinin and its derivatives were reported, however the photochemistry of which is very few. We reported previously the photochemistry of some oxoalkyl aldehydes of dihydroartemisinin [3]. This work deals with photochemical reactions of three dihydroartemisinin esters, e.g. the acetate, benzoate and succinate.

II - EXPERIMENTAL

The NMR spectra were measured with a NMR-500 MHz AVANCE spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C), in $CDCl_3$ at Institute of Chemistry-Vietnam Academy of Science and Technology, Hanoi.

1. Synthesis of the starting materials, compounds 3-5

a) Synthesis of Dihydroartemisinin (DHA, 2) [3]

The synthesis of DHA is described in [3]. 5 g artemisinin was reacted with $NaBH_4$ in anhydrous MeOH at -5°C. The mixture was diluted with EtOAc, washed with NaCl 5%, and then H_2O, dried over Na_2SO_4, evaporated *in vacuo* and recrystallized in *n*-hexane/EtOAc. After filtration, the obtained product was washed with cooled n-hexane/CH_2Cl_2 mixture, and dried at room temperature over night to yield 4.88 g dihydroartemisinin (97%).

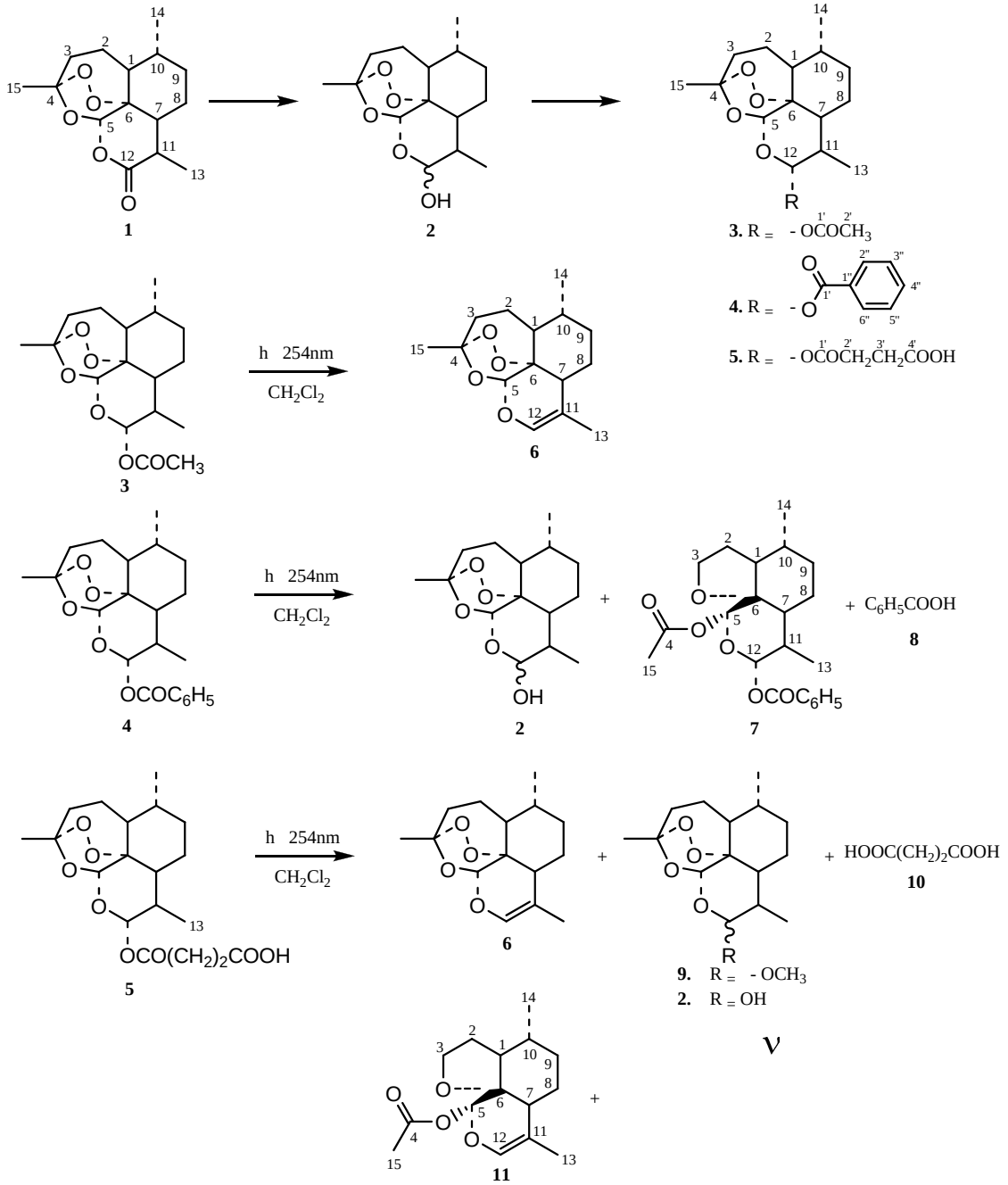
b) Synthesis of α-dihydroartemisinin acetate (3) [4]

The reaction mixture of 2.84 g dihydroartemisinin, 3 ml pyridine, 0.2 g 4-dimethylaminopyridine (DMAP) and 2 ml acetic anhydride in 70 ml anhydrous CH_2Cl_2 was stirred at room temperature about 30 hour, (checked by TLC). The reaction mixture was washed with HCl 5%; $NaHCO_3$ 5% and H_2O. The organic phase was dried over Na_2SO_4 evaporated *in vacuo* and recrystallized in *n*-hexane/CH_2Cl_2 to yield 3.12 g of **3** (95.7%).

3: ***^{1}H-NMR (500MHz, $CDCl_3$)***: δ 5,80 (d, *J* = 8.6 Hz, 1H, H12); 5.44 (s, 1H, H5); 2.60 - 2.52 (m, 1H); 2.41 - 2.35 (m, 1H); 2,13 (s, 3H, H2'); 1.44 (s, 3H, H15); 0.97 (d, *J* = 6.2 Hz, 3H, H14); 0.85 (d, *J* = 7.2 Hz, 3H, H13).

^{13}C-NMR (125MHz, $CDCl_3$): 169.74 (C1'); 104.41 (C4); 91.82 (C12); 91.46 (C5); 80.08 (C6); 51.55 (C1); 45.22 (C7); 37.24 (C10); 36.20 (C3); 34.07 (C9); 31.73 (C11); 25.94

(C15); 24.55 (C2); 21.97 (C8); 21.07 (C2'); 20.17 (C14); 12.04 (C13).



Schema 1: Photochemical reactions of three dihydroartemisinin esters

b) Synthesis of α-dihydroartemisinin benzoate (4) [5]

Solution of 2.84 g dihydroartemisinin, 3 ml pyridine, 0.2 g DMAP and 2.1 g benzoyl chloride in 100 ml CH_2Cl_2. was stirred at room temperature about 30 hours, (checked by TLC). The mixture was washed with HCl 5%;

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neutralized with $NaHCO_3$ 5% and H_2O, dried over Na_2SO_4, evaporated *in vacuo* and recrystallized in *n*-hexane/CH_2Cl_2. The crystal were filtered, washed with cooled *n*-hexane/CH_2Cl_2 solution, and dried to yield 3.66 g (94.1%) compound **4**.

4: ***^{1}H-NMR (500MHz, $CDCl_3$)***: δ 8.15 (d, *J* = 7.4 Hz, 2H, phenyl); 7.55 (t, *J* = 7.4 Hz, 1H, phenyl); 7.40 (t, *J* = 7.4 Hz, 2H, phenyl); 6.0 (d, *J* = 9.8 Hz, 1H, H12); 5.52 (s, 1H, H5); 1.43 (s, 3H, H15); 0.98 (d, *J* = 6.2 Hz, 3H, H14); 0.92 (d, *J* = 7.2 Hz, 3H, H13).

^{13}C-NMR (125MHz, $CDCl_3$): 165.24 (C1'); 133.25 (C1"); 130.07 (C2"; C6"); 129.62 (C4"); 128.26 (C3"; C5"); 104.37 (C4); 92.50 (C12); 91.55 (C5); 80.14 (C6); 51.63 (C1); 45.33 (C7); 37.24 (C10); 36.24 (C3); 34,11 (C9); 31.97 (C11); 25.92 (C15); 24.56 (C2); 22.03 (C8); 20.20 (C14); 12.20 (C13).

c) Synthesis of α-dihydroartemisinin succinate (5)

α-dihydroartemisinin succinate (**5**) was synthesized with the same procedure as for **4** with the yield of 97.6%.

5: ***^{1}H-NMR (500 MHz, $CDCl_3$)***: δ 11,15(s,br, 1H, OH); 5.81 (d, *J* = 8.7 Hz, 1H, H12); 5.44 (s, 1H, H5); 2.76 - 2.64 (m, 4H); 1,4 (s, 3H, H15); 0.96 (d, *J* = 6.9 Hz, 3H, H14); 0.85 (d, *J* = 7.1 Hz, 3H, H13).

^{13}C-NMR*: *(125 MHz, $CDCl_3$): 177,32 (C1'); 170.69 (C4'); 104.07 (C4); 91.95 (C12); 91.14 (C5); 79.74 (C6); 51.23 (C1); 44.91 (C7); 36.85 (C10); 35.90 (C3); 33.78 (C9); 31.46 (C11); 28.61 (C2'); 28.36 (C3'); 25.53 (C15); 24.25 (C2); 21.60 (C8); 19.87 (C14); 11.60 (C13).

2. Photochemical reactions of compounds 3-5

a) Photochemical reaction of **3**

Solution of 1,5 g **3** in 100 ml anhydrous CH_2Cl_2 in 250 ml quartz round flask, under N_2 was irradiated with a 254 nm fluorescent 15W lamp at room temperature for 60 minutes, checked by TLC. The reaction mixture was evaporated *in vacuo* and the residue chromatographed over silica gel with *n*-hexane:CH_2Cl_2:MeOH (40:15:1) ***as*** solvent to give 405 mg (27%) dihydroartemisinin dehydrate (**6**).

6: ***^{1}H-NMR (500MHz, $CDCl_3$)***: δ 6,18 (q, *J*=1.03 Hz, 1H, H12); 5,54 (s, 1H, H5); 1,58 (s, 3H, H13); 1,42 (s, 3H, H15); 0,98 (d, *J*=5,9 Hz, 3H, H14).

^{13}C-NMR (125MHz, $CDCl_3$): 134.97(C12); 108.10(C11); 104.52 (C4); 89.66 (C5); 78.94 (C6); 51.41 (C1); 44.42 (C7); 37.46 (C10); 36.20 (C3); 34.09 (C9); 29.96 (C8); 25.85 (C15); 24.39 (C2); 20.27 (C14); 16.17 (C13).

b) Photochemical reaction of **4**

A solution of 1.94 g dihydroartemisinin benzoate (**4**) in 100 ml anhydrous CH_2Cl_2 was irradiated with a 15W fluorescent lamp (254 nm, under N_2) for about 120 minutes. The solution was evaporated under reduced pressure, the residue was crystallized in *n*-hexane/CH_2Cl_2; it yielded after filtration 108 mg (20%) benzoic acid (**8**). The filtrate was evaporated, chromatographed over silica gel to give 170 mg (12%) dihydroartemisinin (**2**), 407 mg (21%) of dihydoartemisinin G benzoate (**7**) [6 - 8].

7: ***^{1}H-NMR (500 MHz, $CDCl_3$)***: δ 8.08 (d, *J* = 1.1 Hz, 2H, phenyl); 7.55 (t, *J* = 6.1 Hz, 1H, phenyl); 7.40 (t, *J* = 6.4 Hz, 2H, phenyl); 6.29 (s. 1H. H5); 6.07 (d, *J* = 9.6 Hz, 1H, H12); 2.08 (s, 3H, H15); 0.94 (d, *J* = 6.3 Hz, 3H, H14); 0.92 (d, *J* = 6.7 Hz, 3H, H13).

^{13}C-NMR (125 MHz, $CDCl_3$): 168.56 (C4); 164.93 (C1'); 133.29 (C1"); 130.08 (C2"; C6"); 129.42 (C4"); 128.24 (C3"; C5"); 93.71 (C12); 91.09 (C5); 80.11 (C6); 68.78 (C3); 54.96 (C1); 47.29 (C7); 35.41 (C9); 34.04 (C11); 30.39 (C10); 27.52 (C2); 22,54 (C8); 21.39 (C15); 20.44 (C14); 12.09 (C13).

c) Photochemical reaction of ***5***

With the same procedure as for compound **4**. 1.92 g dihydoartemisinin succinate (**5**) was irradiated. The irradiation mixture yielded four compounds after chromatography: dihydoartemisinin (**2**) 42.8 mg (12%), dihydroartemisinin dehydrate **6** 199 mg (15%), β-artemether (**9**) 74 mg (5%) and succinic acid (**10**) 118 mg (20%),

9: ***^{1}H-NMR (500MHz, $CDCl_3$):*** δ 5.38 (s, 1H, H5); 4.68 (d, *J* = 3.36, 1H, H12); 3.42 (s, 3H, OCH_3); 1.44 (s, 3H, H15); 0.95 (d, *J* = 6.4 Hz, 3H, H14); 0.90 (d, *J* = 7.4 Hz, 3H, H13).

^{13}C-NMR (125 MHz, $CDCl_3$): 104.05 (C4); 103.37 (C12); 87.77 (C5); 81.10 (C6); 55.93 (C1'); 52.59 (C1); 44.51 (C7); 37.40 (C10); 36.46 (C3); 34.64 (C9); 30.91 (C11); 26.18 (C15); 24.70 (C2); 24.47 (C8); 20.33 (C14); 12.94 (C13).

The ^{1}H- and ^{13}C-NMR data of **9** are in agreement with [11].

III - RESULTS AND DISCUSSION

Dihydroartemisinin (**2**) was obtained by $NaBH_4$ reduction of artemisinin (**1**) in methanol with good yield (> 95% of **1**). The dihydroartemisinin esters **3**, **4** and **5** (α-form) were prepared in very high yields by reaction between dihydroartemisinin (**2**) with acetic anhydride, benzoyl chloride and succinic anhidride, respectively. Interestingly, starting from dihydroartemisinin (α:β form ≈ 1:1) we received as reaction products only the α-dihydroartemisinin esters (≥95% yield), which were purified by crystallization. The photolysis of the esters **3**, **4** and **5** has been carried out with fluorescent 15W-lamp (254 nm), under N_2 - atmosphere at room temperature.

When irradiated in dichloromethane 60 minutes, the dihydroartemisinin acetate (**3**) afforded the elimination product **6** in 27% yields after column chromatography. The formation of compound **6** can be happened through an elimination of one molecule acetic acid maybe by the heat of the UV light. The elimination reaction of this type has also been observed before on the photolysis of an ether derivative of dihydroartemisinin [3]. Compound **6** has been obtained as a by-product in the synthesis of many dihydro-artemisinin derivatives. The ^{1}H- and ^{13}C-NMR spectra of **6** are given in Figs. 1 and 2.

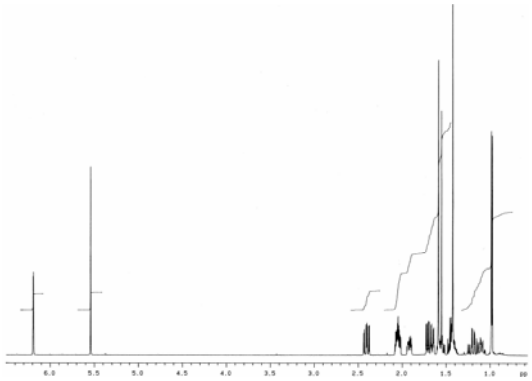

Figure 1: ^{1}H- NMR of **6**

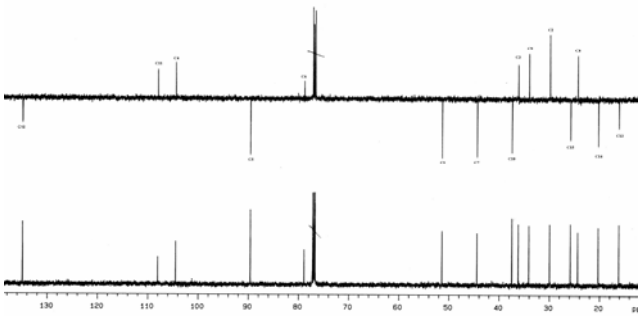

Figure 2: APT- and ^{13}C-NMR of **6**

A different, interesting result has been obtained by photolysis of dihydroartemisinin benzoate under the same condition, but with longer irradiation time. Here we received the dihydroartemisinin (**2**) (12%) as isomer mixture, the rearrangement compound **7** (21%) and benzoic acid. Compound **7** is a derivative of the naturally - occurring artemisinin G, the dihydroartemisinin G benzoate [8]. Compound **11** which is similar to **7** has been obtained on the photolysis of *β*-dihydroartemisinyl butylaldehyde (254 nm, benzene) [3]. The presence of a small amount of dihydroartemisinin is probably due to the hydrolysis of compound **4** under a trace of water in the solvent. The ^{1}H- and ^{13}C-NMR spectra of **7** are given in Figs. 3 and 4.

Under the same irradiation condition as for compound **4**, the artesunate (dihydro-artemisinin monosuccinate **5**) yielded after chromatography on silica gel the elimination product **6** (15%), dihydroartemisinin (**2**, isomer

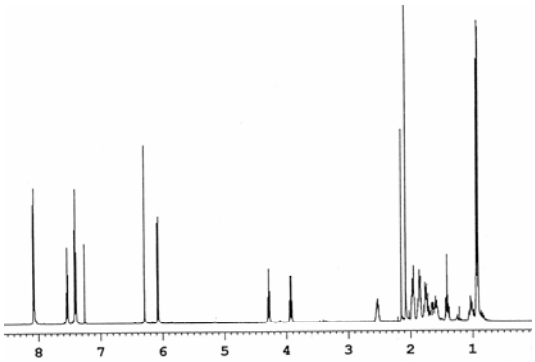

Figure 3: ^{1}H- NMR of **7**

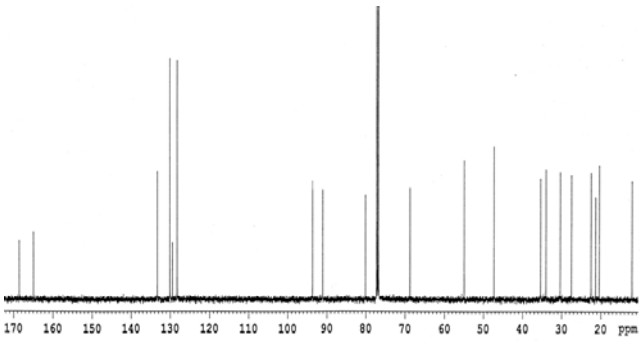

Figure 4: ^{13}C-NMR of **7**

mixture), β-artemether (**9**) and succinic acid. Similarly as for compound **4**, it maybe happened here also a hydrolysis of **5** under trace of water in the solvent to yield dihydroartemisinin, which again *insitu* reacts with a trace of methanol to give artemether. Irradiation of **5** in methanol as solvent afforded the same results.

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