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RESEARCH NOTE

SINGLET OXYGEN-MEDIATED PHOTOOXIDATION OF METHYL 11-HYDRO-13-(METHYLOXY)CARBONYLARTEMISINATE

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Abstract – Singlet oxygen-mediated photooxidation and subsequent triplet oxygen insertion of 11-hydro-13-(methyloxy)carbonylartemisinate (**4**) yielded a diketo compound **5** as the major product instead of the expected 11-hydro-13-(methyloxy)carbonylartemisinin (**6**). The formation of the unexpected product was in part consistent with the mechanism proposed by Acton and Roth and is the first isolation of the diketo compound from the photooxidation of artemisinate.

INTRODUCTION

Artemisinin, **1**, a natural product isolated from *Artemisia annua*, and its derivatives are under clinical trial for antimalarial drug against quinine-resistant *Plasmodium* clones.[1,2] There have been several synthesis of this interesting compound.[2] However, the synthesis of this compound has been a challenge to introduce the unique endoperoxide-acetal-lactone functionality. Recently it was found that a simple photooxidation of artemisinic acid, a sesquiterpene occuring in the same plant, could produce artemisinin in a reasonable yield.[3,4] Acton and Roth studied the mechanism of the reaction and found that the oxidation occurs in two distinctive steps; light generated singlet oxygen adds to double bond and then triplet oxygen attacks at C6.[5] Thus, the endoperoxide moiety is derived from a triplet oxygen molecule.

In the course of the synthesis of artemisinin analogues through the light-generated singlet oxygen oxidation, we found out a product with diketo functionality was formed instead of the expected artemisinin analogue. The structure of the product and relevancy with the Acton and Roth's mechanism[5] will be presented.

MATERIALS AND METHODS

Methyl 13-cyano-11-hydroartemisinate (**3**). Methyl artemisinate (**2**, 4 mmol) was added to absolute ethanol (10 mL), followed by 4 mL of 10 *M* aqueous KCN (40 mmol) solution and 1.4 mL of glacial acetic acid (20 mmol). The reaction mixture was refluxed for 9 h. The crude reaction mixture was vacuum liquid chromatographed (hexane:ether) to give methyl 13-cyano-11-hydroartemisinate (**3**) in 60% yield. Compound **3**. ^{1}H-NMR (80 MHz, $CDCl_3$) δ 5.04 (1H, br. s, H-5), 3.76 (3H, s, MeO), 2.80 (1H, m, H-11), 2.58 (2H, d, J=10.4 Hz, H-13), 2.40 (1H, br. s, H-6), 1.55 (3H, s, 15-Me), 0.86 (3H, d, J=5.5 Hz, 14-Me); ^{13}C-NMR (50 MHz,$CDCl_3$) 173.7 (C-12), 137.4 (C-4), 117.7 (C-5), 52.0 (C-16), 44.2, 42.7, 41.4, 39.6, 36.6, 34.9, 27.3, 26.4, 25.5, 23.6 (C-15), 19.5, 18.6, 17.9; MS (EI, 70 eV) m/z (rel. int.) 275 (M^+, 3.0), 260 (1.7), 244 (2.0), 216 (25.0), 163 (15.6),162 (100), 147 (19.7), 121 (10.3), 105 (10.9), 93 (10.3), 91 (15.6), 81 (10.4), 79 (15.6).

Methyl 11-hydro-13-(methyloxy)carbonylartemisinate (**4**). A mixture of compound **3** (4 mmol), NaOH (1.5 g), ethylene glycol (1.5 mL), H_2O (2.5 mL), and methanol (5 mL) was refluxed for 75 h until no more ammonia could be detected. The mixture was cooled, dimethylformamide (15 mL) and methyl iodide (4 mL) were added, and finally the reaction mixture was stirred overnight at 25℃. After the addition of water (40 mL), the product was extracted with CH_2Cl_2 (3 × 10 mL). After workup, the reaction mixture was chromatographed on VLC (hexane: ether) to give methyl 11-hydro-13-(methyloxy)carbonylartemisinate (**4**) in 75% yield. Compound **4**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.04 (1H, s, H-5), 3.61 (3H, s,12-

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† *Abbreviations* : EI, electron impact; GC, gas chromatography; HRMS, high resolution mass spectrometry; HPLC, high performance liquid chromatography; MB, methylene blue; Me, methyl; MeOH, methanol; TfOTMS, trimethylsilyl trifluoromethanesulphonate; MS, mass spectrometry; NMR, nuclear magnetic resonance; TsOH, toluenesulphonic acid; VLC, vacuum liquid chromatography

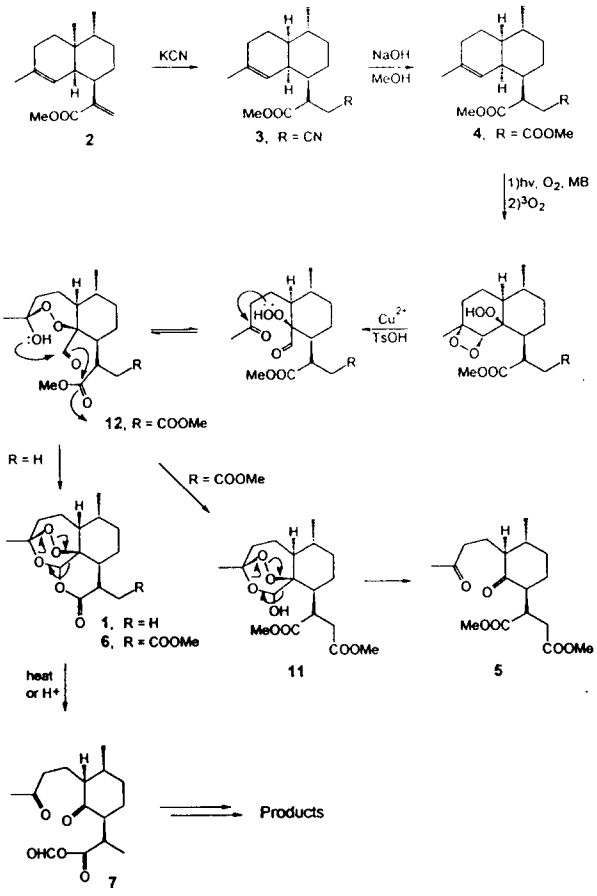
$COOCH_3$), 3.56 (3H, s, 16-$COOCH_3$), 2.87 (1H, m, H-7), 2.52 (2H, d, J=7, H-13), 2.33 (1H, br.s, H-6), 1.63 (3H, s, 15-Me), 0.87 (3H, d, J=6.5, 14-Me); ^{13}C-NMR(100 MHz, $CDCl_3$) δ 176.2 (C16), 172.7 (C12), 136.5 (C4), 118.7 (C5), 51.8 (12-$COOCH_3$), 51.6 (16-$COOCH_3$), 43.9 (C11), 43.4 (C7), 41.8 (C1), 39.2 (C6), 35.3 (C9), 34.4 (C13), 27.5 (C10), 26.9 (C3), 26.5 (C8), 25.4 (C2), 23.7 (C15), 19.6 (C14); HRMS (EI, 70 eV) (m/z) 308.1987 ($C_{18}H_{28}O_4$, calculated : 308.1988); MS (EI, 70 eV) m/z (rel. int.) 308 ([M]$^+$, 10.1), 277 ([M-OCH_3]$^+$,19.1), 249 ([M-$COOCH_3$]$^+$, 10.8), 245 (17.8), 217 (4.5), 199 (5.1), 174 (3.3), 163 (75.8), 162 (100), 161 (12.2), 148 (10.3), 147 (83.1),146 (100), 145 (5.1), 133 (12.3), 121 (11.9), 120 (14.2), 119 (17.1), 114 (38.7), 107 (15.1), 93 (14.8), 91 (17.2), 81 (18.3), 80 (2.6), 67 (6.7), 59 (5.4), 57 (2.6), 31 (8.6); IR (KBr) 1739.7 (C=O stretching), 1437.5 (C=C stretching), 1260.0 (C-O stretching), 1164.6 (C-O stretching)

Photooxidation. The compound **4** was subjected to the singlet oxygen-mediated photooxidation as described by Haynes and Vonwiller[4]. The final mixture with Cu^{2+}/TsOH catalyst was left standing for six days. The reaction mixtures were chromatographed with column chromatography(silica gel) and VLC using hexane-ether solvent system and further purified by prep. High performance liquid chromatography using the same solvents to afford a 4,6-diketo compound (**5**) in 27% yield and 13-(methyloxy)carbonylartemisinin (**6**) in 4.3% yield. Compound **5**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.62 (3H, s, 12-$COOCH_3$), 3.61 (3H, s, 15-$COOCH_3$), 3.08 (1H, m, H-11), 2.68(2H, m, H-13), 2.53 (1H, m, H-7), 2.27 (1H, dt, H-1), 2.05 (3H, s, 5-CH_3), 1.91 (1H, m, H-2_a), 1.52 (2H, m, H-9), 1.44 (1H, m, H-10), 1.32 (2H, m, H-1 and H-10), 1.01 (3H, d, J=6, 14-CH3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 211.1 (C6), 208.9 (C4), 174.39 (C15), 172.51 (C12), 56.74 (12-$COOCH_3$), 51.86 (15-$COOCH_3$), 51.20 (C1), 41.24 (C7), 41.12 (C11), 40.07 (C5), 34.28 (C13), 33.99 (C9), 31.07 (C10), 29.88 (C3), 20.49 (C8), 20.07 (C14); HRMS (CI, CH_4, 70 eV) m/z (rel. int.) 327.1817 ([M+H]$^+$, 12.79) ($C_{17}H_{27}O_6$, calculated : 327.1808); MS [CI, CH_4, 70 eV] (m/e, rel. int.) 367 ([M+C_3H_5]$^+$, 8.3), 355 ([M+C_2H_5]$^+$, 20.7), 327 ([M+H]$^+$, 27.1), 311 ([M-CH_3]$^+$, 8.7), 295 ([M-OCH_3]$^+$, 94.3), 284 ([M-CH_3CO]$^+$, 5.6), 267 (25.5), 249 (10.6), 237 (5.8), 209 (2.9), 183 (3.9); IR (KBr) 1735.5, 1702.0, 1668.5 (C=O stretching), 1171.4, 1092.4 (C-O stretching)

RESULTS AND DISCUSSION

A 4,6-diketone compound (**5**), a white plate-like crystal, was obtained as a major product of photooxidation. The isolated compound was a mixture of 11 *R,S*-stereoisomers in the ratio of 2.3 to 1 as shown by ^{1}H-, ^{13}C-NMR and GC. But the mixture resisted separation on VLC or HPLC [Lichrosorb Si 60 (7μm), 246 nm, 3 mL/min, ether gradient in n-hexane]. Literature survey quickly established that the compound has not been recognized before although related structures have been suggested[6,7] and reported.[8]

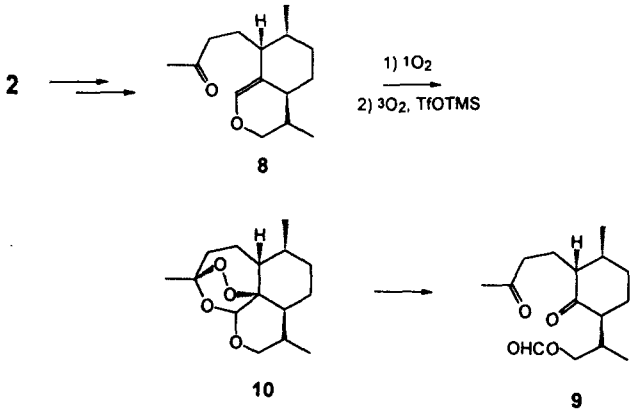
Several reports suggested the formation of a



Scheme 1. Formation of the diketo compound **5**

formyl-oxycarbonyl 4,6-diketo compound (**7**) from thermolysis[6] or acidic decomposition[7] of artemisinin as a reactive intermediate to form decomposition products (Scheme 1). Another related 4,6-diketo compound was also found in the singlet oxygen-mediated photooxidation of a cyclic enol ether (**8**) of 11, 13-dihydroartemisinic acid as a by-product as shown in Scheme 2.[8] In the former case, ring opening due to expulsion of the oxygen molecule from the endocyclic peroxide moiety from artemisinin was suggested for the reaction mechanism. Thus, formation of the diketo compound (**9**) from the cyclic enol ether in the photooxidation reaction would be easily justified by the decomposition of desoxyartemisinin (**10**) formed from photooxidation (Scheme 2), not by the parallel formation of **9** and **10** from **8** as suggested by Ye and Wu.[8]

In the process of oxygen repulsion during the thermolysis[6] and acidic decomposition,[7] a formyl group becomes attached to carboxy group as shown in Schemes 1 and 2. If the 4,6-diketo compound (**5**) was derived from an artemisinin derivative **6**, a formyl, instead of a methyloxy group, would be found in the compound. Therefore, the existence of methyloxy group on the diketo compound **5** strongly argues for



Scheme 2. Formation of the diketo compound **9**. Adopted from ref. 8.

the existence of partially closed ring system in **11** as shown in the Scheme 1. Presumably, this diketo compound **5** seemed to be derived by the acidic degradation due to the excess p-TsOH added as an acid catalyst for the ring closure. Why the extra carboxymethyl group in **12** drived the reaction toward the expulsion of oxygen molecule is yet to be answered.

Acton and Roth suggested a conserted mechanism for the ring closure of **12** leading to artemisinin.[5] This diketo compound indirectly suggests the existence of the partial closure compound **11**, hence partly confirming their mechanism. However, the question whether the ring closure proceeds concerted or step-wise manner awaits further investigation.

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