1,2-Dioxetanes as New Antimalarial Agents

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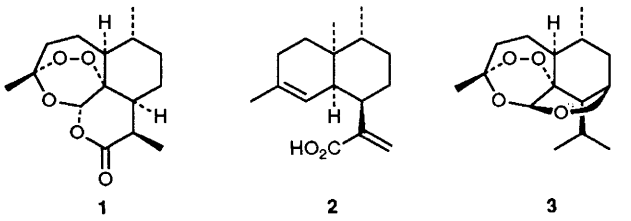
Dye-sensitized photoxygenation of cadinene derivatives **4d** and **e** has led to the isolation of 1,2-dioxetanes **5** and **9**, respectively, which exhibit moderate antimalarial activity.

Discovery of artemisinin **1**, the highly potent antimalarial drug active against the chloroquine-resistant strains of *Plasmodium falciparum*, has revived world-wide chemical interest in the area of new antimalarial agents.[1–5] During the past few years extensive efforts have been made to convert artemisinic acid **2**, the biogenetic precursor of artemisinin **1**, which is available in sufficient amounts from the plant *Artemisia annua*, into artemisinin **1** and its analogues.[6–13] However, it is only recently that Roth and Acton have been able to achieve this (with an overall yield of 21%) in a two step process using photooxygenation as the key step. At the same time, Jung *et al.*[15] following essentially the same strategy have independently synthesized a 12-deoxo-analogue of artemisinin in 18% yield from artemisinic acid **2** which is found to be eight times more active than **1**.

The only cadinene, **4a**, having close stereochemical resem-



1 2 3

blance to artemisinin **1** was first isolated by Bohlman *et al.* from *Ageratina adenophora*,[16] and its absolute stereochemistry was determined by some of us and coworkers through chemical and X-ray crystallographic studies.[17] Compound **4a** possesses functionalities suitable for conversion into derivatives of artemisinin and therefore it was originally plánned to synthesize compound **3** from **4a** in order to evaluate its antimalarial activity.

Cadinen **4a** (Scheme 1) was reduced with sodium borohydride to the diol **4b** which on acetylation furnished the diacetate **4c**. Nickel boride generated *in situ* effected the reductive removal of the allylic acetate function in **4c** to furnish the monoacetate **4d** in 60% yield.[18] A solution of the monoacetate **4d** (100 mg, 0.378 mmol) in dry dichloromethane (100 cm^3) containing Methylene Blue (2.5 mg) as sensitizer was taken in a Solidex glass-made photochemical apparatus and cooled to −78 °C and irradiated with a 125 W UV lamp while a slow stream of dry oxygen was passed through the solution. After 2 h the solvent was evaporated under reduced pressure and the residue thus obtained was purified by preparative SiO_2-TLC (hexane–ethyl acetate, 4 : 1) to furnish compounds **5** (24 mg) and **6** (15 mg) as gums.† Attempts to convert compound **5** into **3** by acid treatment (CF_3CO_2H or Dowex-50, hexane, room temp. 4 h) led instead to the isolation of **7** (35% yield) as a gum, whereas under the same reaction condition **6** gave **8** as a gum in 42% yield.

Acidic or basic hydrolysis of the acetate **4d** to prepare the corresponding alcohol **4e** gave only a complex mixture of products. However, lithium aluminium hydride reduction of **4d** furnished the alcohol **4e** in quantitative yield. Photooxygenation of **4e** (120 mg, 0.54 mmol) as described above furnished a mixture (1 : 1) of two compounds which were separated by preparative SiO_2-TLC (hexane–ethyl acetate, 4 : 1) to furnish **9** (55 mg) and **10** (46 mg) as gums. Attempts to prepare **3** from compound **10** through acid treatment (Dowex-50, hexane, room temp. 4h) led to a mixture of products whereas under the same reaction conditions **9** gave **11** as a gum in 59% yield.

Compounds **5** and **9** showed moderate antimalarial activity when tested *in vitro* against African D-6 clone and Indo-China W-2 clone of *P. falciparum*; compound **9** is five times more active then **5**. Biological evaluation of **8** is under investigation.

To our knowledge, this is the first report on the antimalarial activity of 1,2-dioxetanes.[19] Work is in progress to prepare a variety of 1,2-dioxetanes as new potential antimalarial agents.

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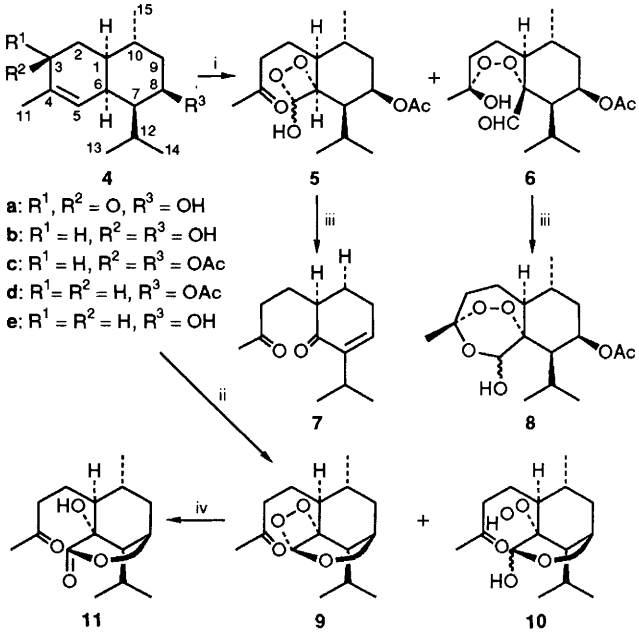

Scheme 1 i, **4d**, UV irradiation, CH_2Cl_2, O_2, −78 °C, 2h; ii, **4e**, UV irradiation, CH_2Cl_2, O_2, −78 °C, 2 h; iii, CF_3CO_2H or Dowex-50, hexane, room temp., 4 h; iv, Dowex-50, hexane, room temp., 4 h

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† *Selected spectral data*: **5**; IR ν/cm^{-1} ($CHCl_3$): 3400, 1735 and 1715; ^{1}H NMR ($CDCl_3$): δ 5.20 (br, s, H-5), 5.00 (m, H-8) and 2.00 (s, 6H); MS *m/z* 328.1870 (calc. 328.1884). **6**; IR ν/cm^{-1} ($CHCl_3$): 3430, 1735 and 1720; ^{1}H NMR ($CDCl_3$): δ 9.90 (s, 1H); 5.00 (m, H-8), 2.00 (s, 3H) and 1.40 (s, 3H, H-11); MS *m/z* 328.1864 (calc. 328.1884). **7**; IR ν/cm^{-1} ($CHCl_3$): 1715 and 1670; ^{1}H NMR ($CDCl_3$): δ 6.80 (m, H-8) and 2.00 (s, 3H, H-11). **8**; IR ν/cm^{-1} ($CHCl_3$): 3450 and 1735; ^{1}H NMR ($CDCl_3$): δ 5.25 (br s, H-5), 5.00 (m, H-8) and 1.48 (s, 3H, H-11); MS: *m/z* 328.1872 (calc. 328.1884) **9**; IR ν/cm^{-1} ($CHCl_3$): 1720; ^{1}H NMR ($CDCl_3$): δ 5.00 (br s, H-5) 4.20 (m, H-8), and 2.10 (br s, H-11); MS: *m/z* 268.1622 (calc. 268.1602). **10**; IR ν/cm^{-1} ($CHCl_3$): 3450 and 1725; ^{1}H NMR ($CDCl_3$): δ 4.40 (br s, H-5), 4.15 (m, H-8), 2.15 (s, 3H, H-11). **11**; IR ν/cm^{-1} ($CHCl_3$): 3400, 1775 and 1720, ^{1}H NMR ($CDCl_3$): δ 5.05 (m, H-8), 2.00 (s, 3H, H-11).