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# Synthesis and Antimalarial Activity of 2-Methoxyprop-2-yl peroxides derivatives.

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**Abstract**—: 2-Methoxyprop-2-yl peroxides were synthesized and evaluated *in vitro* against *Plasmodium falciparum*. These acyclic artemisinin-related peroxides revealed moderate to good activity but were devoided of alkylating property towards the synthetic model of haeme Mn<sup>II</sup> – TPP.

Malaria is the most widespread infection disease. It is worldwide aspread and affects about 300 million people causing from one to three million deaths every year. Moreover *Plasmodium* resistance to classical therapy such as choroquine has considerably increased. Artemisinin **1** and related trioxanes have received considerable attention as alternative therapy since their fast antimalarial activity was maintained against chloroquine resistant strains of *P. falciparum*.<sup>1</sup> Their antimalarial activity was dependent of endoperoxide interaction with intraparasitic haeme. Monoelectronic transfert from iron (II) to peroxide function resulted in the cleavage of endoperoxide bond with primary formation of an unstable oxygen centered radical, rearrangement and creation of a C centered radical.<sup>2</sup> Such a radical was able to alkylate the haemin as it has been experimentally shown with manganese (II) tetraphenyl porphyrin (Mn<sup>II</sup> – TPP)<sup>3</sup> or more recently with haemin.<sup>4</sup> That would be lethal for the parasite throught the accumulation of non polymerisable redox-active haeme adducts.<sup>5</sup> These radicals may also be responsible for the alkylation of proteins<sup>6,7</sup> and that could also be lethal for the *Plasmodium*.<sup>7</sup> However, the final mechanism responsible of the death of the parasite has not yet been definitely determined.<sup>8</sup>

As a part of our research on antimalarial peroxide with simple synthetic access, we focused our attention on 2-methoxyprop-2-yl peroxides **2**. These perketals have

been previously developed by Dussault as useful synthetic precursors of hydroperoxides.<sup>9</sup> We used this procedure which proved to be a far superior method compared to others for preparing our sensitive hydroperoxides.<sup>10</sup> We have also focused our attention on these simple accessed linear perketals **2** for their biological properties. We reported recently their powerful trichomonacidal activity.<sup>11,12</sup> Anaerobic *Trichomonas vaginalis* was for example ten times more sensible to 2-methoxyprop-2-yl hexadec-1-yl peroxide than to the reference compound Metronidazole.<sup>12</sup>

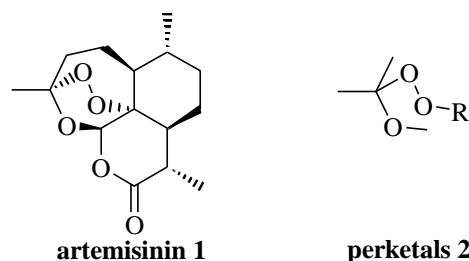


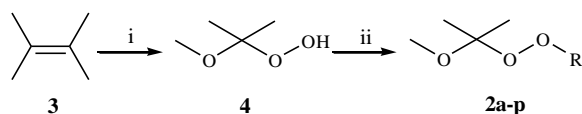
Figure 1.

Perketals **2** could also constituted acyclic analogues of artemisinin **1** and related trioxanes since they both contained an  $\alpha$ -alkoxyperoxide function essential for antimalarial activity.<sup>13</sup> We reported herein the synthesis

and antimalarial activity of a series of 2-methoxyprop-2-yl peroxides.

### Synthesis

2-methoxyprop-2-yl peroxides were prepared according to Dussault procedure, *i.e.* ozonolysis of 2,3-dimethylbutene **3** in methanol afforded 2-methoxyprop-2-yl hydroperoxide **4** that reacted with alkyl bromides **5a-p** under mild conditions to give perketals **2a-p** into moderate to good yields.<sup>11, 12</sup>



**Scheme 1.** Synthesis of perketals **2a-p**. Reagents and conditions: (i) O<sub>3</sub>, MeOH, -78°C. (ii) RBr **5a-p**, CsOH, BHT, DMF, RT.

### Antimalarial activity

Perketals **2a-p** were evaluated *in vitro* against *P. falciparum* FCR3 strain.<sup>14</sup> They all revealed antimalarial activity with IC<sub>50</sub> ranging from 10<sup>-5</sup> to 10<sup>-7</sup> M. The most active compounds (**2k**, **2m**) were about one eighth of the antimalarial potency of artemisinin on this strain, and were substituted with alkyl pinenyl group. Other perketals **2** with apolar radical chain tested herein had medium to good activities. The less active compounds had an alkyl chain substituted with a polar moiety *i.e.* a nitrile (**2h**), an ester (**2i**) or in a lesser extent an ether function (**2g**). Previously reported arachidonic acid derived Dussault perketals had an alkenyl chain, end substituted with CH<sub>2</sub>-CH<sub>2</sub>-CO<sub>2</sub>H or O-CH<sub>2</sub>-CO<sub>2</sub>H. They showed a weak activity against *P. falciparum* (respectively 36 and 14 % inhibition *in vitro* at 4.10<sup>-5</sup> M). It appeared clearly that introduction of a polar function on this alkyl chain is deleterious for a good antimalarial activity.

### Alkylating properties

Two of the most potent compounds, **2k** and **2m** were evaluated for they alkylating property of the haeme following the Meunier model.<sup>3</sup> They both were incubated with a manganese (II) complex of tetraphenylporphyrin generated *in situ* by *n*-Bu<sub>4</sub>NBH<sub>4</sub> reduction of Mn<sup>III</sup>(TPP)Cl. After demetallation, the tetraphenyl-porphyrin was recovered unchanged in both cases. These perketals **2k,m** didn't alkylated haeme model, as unlike artemisinin<sup>3</sup> and other related trioxanes.<sup>15</sup> However it was not excluded that they could interact with haeme to generate radicals that had no haeme alkylating property as it was reported for other peroxides.<sup>16</sup> They showed a different mechanism of action albeit they could be assimilated to linear trioxane analogues.

**Table 1.** Structure and *in vitro* antimalarial activities of compounds **2a-p** against FCR3 *P. falciparum* strain.

| Compound <sup>a,b</sup> | Structure | Activity <sup>c</sup><br>IC <sub>50</sub> , nM |
|-------------------------|-----------|--|
| <b>2a<sup>a</sup></b>   |           | 1 650 <sup>d</sup>                             |
| <b>2b<sup>b</sup></b>   |           | 1 550 <sup>e</sup>                             |
| <b>2c<sup>b</sup></b>   |           | 800 <sup>e</sup>                               |
| <b>2d<sup>b</sup></b>   |           | 2 600 <sup>e</sup>                             |
| <b>2e<sup>b</sup></b>   |           | 520 <sup>e</sup>                               |
| <b>2f<sup>a</sup></b>   |           | 660 <sup>e</sup>                               |
| <b>2g<sup>a</sup></b>   |           | 3 200 <sup>e</sup>                             |
| <b>2h<sup>b</sup></b>   |           | 12 800 <sup>e</sup>                            |
| <b>2i</b>               |           | 6 950 <sup>e</sup>                             |
| <b>2j<sup>b</sup></b>   |           | 870 <sup>e</sup>                               |
| <b>2k<sup>a</sup></b>   |           | 370 <sup>d</sup>                               |
| <b>2l<sup>b</sup></b>   |           | 600 <sup>e</sup>                               |
| <b>2m</b>               |           | 480 <sup>d</sup>                               |
| <b>2n<sup>b</sup></b>   |           | 670 <sup>e</sup>                               |
| <b>2o<sup>b</sup></b>   |           | 440 <sup>e</sup>                               |
| <b>2p<sup>b</sup></b>   |           | 1 330 <sup>e</sup>                             |
| <b>Chloroquine</b>      |           | 170 <sup>e</sup>                               |
| <b>Artemisinin</b>      |           | 55   |
| <b>Artemether</b>       |           | 14   |

For physicochemical data see <sup>a</sup> ref 11, <sup>b</sup> ref 12. <sup>c</sup> experiments were conducted in duplicate. <sup>d</sup> artemisinin was the reference compound. <sup>e</sup> artemether was the reference compound.

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