Catalysed Oxygenation of Allylic Hydroperoxides Derived from Qinghao (Artemisinic) Acid. Conversion of Qinghao Acid into Dehydroqinghaosu (Artemisitene) and Qinghaosu (Artemisinin)†

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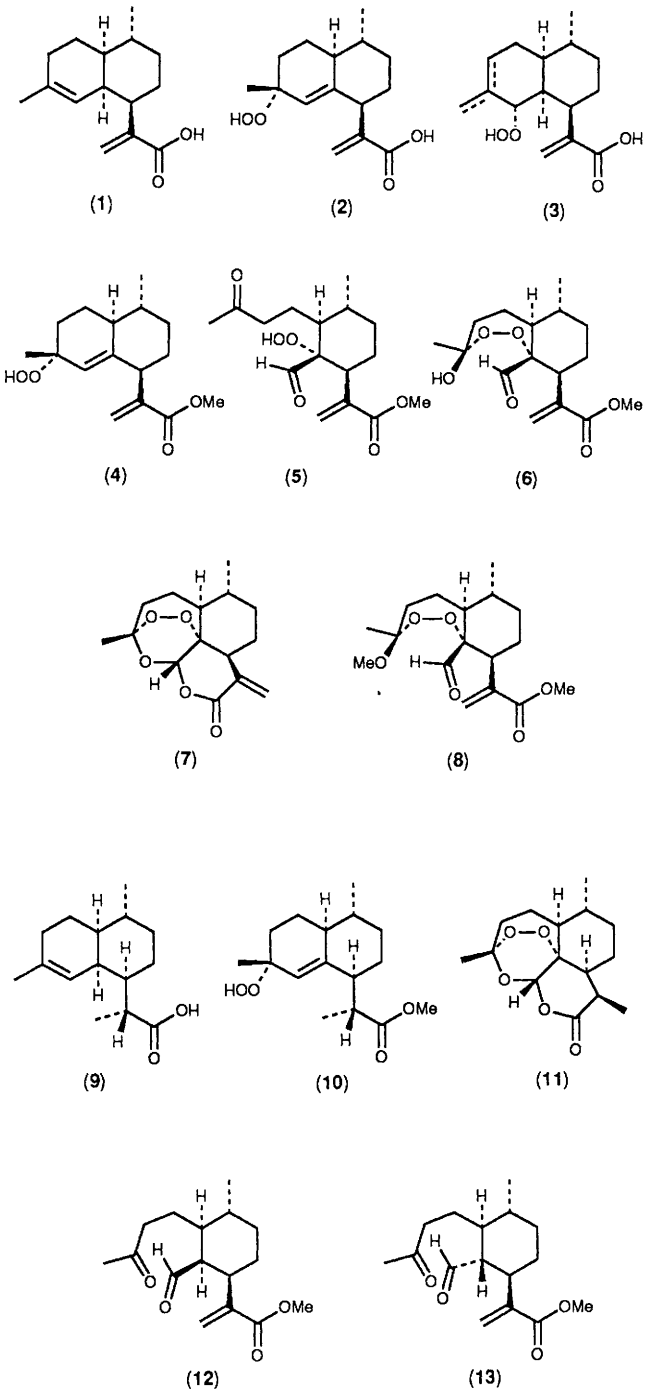
Photo-oxygenation of qinghao acid and its dihydro analogue provides allylic hydroperoxides which are converted either indirectly *via* the corresponding esters, or directly into dehydroqinghaosu (artemisitene) and the antimalarial qinghaosu (artemisinin), by treatment with a catalytic amount of copper(II) trifluoromethanesulphonate with or without an iron(III) co-catalyst in dichloromethane-acetonitrile under oxygen.

We have described how cyclic allylic hydroperoxides are cleaved by oxidizing metal catalysts into dicarbonyl compounds.[1] The possibility that these reactions may involve redox reactions of the metal ion and radical intermediates derived from the hydroperoxide has led us to examine the effect of conducting the reactions in an atmosphere of oxygen. Of particular interest in this regard is the behaviour of the allylic hydroperoxides derived from qinghao (artemisinic) acid (**1**).‡ There is considerable incentive to develop an efficient laboratory method for converting the acid, a relatively abundant constituent of *Artemisia annua*, into a relatively minor but far more important constituent of the same plant, qinghaosu (**11**), which is a clinically valuable antimalarial compound.[2] We describe here how this actual conversion, which must involve interception by oxygen of a radical intermediate derived from the allylic hydroperoxide and an oxidising metal ion, can be easily carried out.

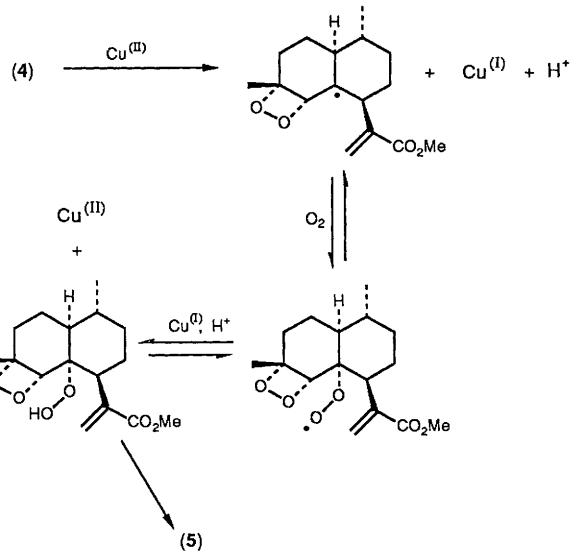
Qinghao acid (**1**) (0.144 mmol) in acetonitrile at −30 °C was quantitatively converted by photo-oxygenation (Rose Bengal, tungsten lamp 500 W) into a 4.5:1 mixture of the allylic hydroperoxide (**2**) and regioisomers (**3**). The mixture was esterified (CH_2N_2, ether, 0 °C) and the major isomer (**4**) isolated by flash chromatography (71% from qinghao acid). The hydroperoxide (**4**) (0.378 mmol) in acetonitrile (5 ml) under oxygen at 0 °C was treated with Fe(phenanthroline)$_3$(PF_6)$_3$ (0.03 equiv.) and immediately thereafter with

† Patents pending.

‡ Because of the overly subtle and often confusing differences between the names of the various chemical constituents of *Artemisia* species, we prefer usage of the pinyin *qinghao* as the basis for the colloquial naming of compounds (**1**), (**7**), (**9**), and (**11**) to indicate their derivation from the Chinese herb *qinghao* (*Artemisia annua*).



$Cu(OSO_2CF_3)_2$ (0.1 equiv.). After 30 min, the mixture was quenched to give an equilibrating mixture of the dicarbonyl hydroperoxide (**5**) and the peroxy hemiacetal (**6**) [53% overall after chromatography, from the hydroperoxide (**4**)]. Next, the crude mixture of oxygenation products (0.392 mmol) in dichloromethane (5 ml) was treated with toluene-*p*-sulphonic acid monohydrate (0.3 equiv.) during 4 h at room temperature to convert it into dehydroqinghaosu (artemisitene) (**7**)[3] [43% isolated yield from the hydroperoxide (**4**), or 30% yield from qinghao acid]. Also formed was the methyl peroxyacetal (**8**) (14%); this arises by a competing acid-catalysed acetalization of the mixture of the oxygenation products by the methanol liberated during the ring closure reaction.



Scheme 1

That an acid catalyst was required for the ring closure leading to dehydroqinghaosu suggested that oxygenation of the free carboxylic acid hydroperoxide (**2**) may lead directly to dehydroqinghaosu. This indeed turned out to be the case. Photo-oxygenation of qinghao acid (0.15 mmol) in acetonitrile (1.5 ml) as described above gave the mixture of hydroperoxides (**2**) and (**3**). The reaction mixture was diluted with dichloromethane (5 ml), and at −20 °C, the resulting solution, still under oxygen, was then treated with the iron (0.002 equiv.) and copper (0.1 equiv.) catalysts. The mixture was warmed to room temperature, to give after 12 h dehydroqinghaosu (**7**)[3] (38% after chromatography, from qinghao acid). The regioisomeric hydroperoxides (**3**) did not interfere in the conversion; they underwent a slow degradation to give uncharacterized polar products.

Both the indirect and direct conversions could be applied to dihydroqinghao acid (dihydroartemisinic acid), obtained as a 4 : 1 mixture of the (11*R*)-(**9**) and (11*S*)-epimers by reduction of qinghao acid according to a method used to reduce the conjugated double bond in the ester.[4] The hydroperoxide (**10**),[5] was obtained as described above (70% from the 11*R*-epimer). Treatment with $Cu(OSO_2CF_3)_2$ (0.1 equiv.) in the absence of the iron catalyst in acetonitrile gave after 30 min the crude mixture of hydroperoxide and peroxyhemiacetal corresponding to compounds (**5**) and (**6**). Treatment of the mixture with toluene-*p*-sulphonic acid as described above gave qinghaosu (**11**)[2] [28% after chromatography from the hydroperoxide (**1**)]. The direct method also succeeded here. Thus the mixture of hydroperoxides obtained from photooxygenation of dihydroqinghao acid with Rose Bengal in acetonitrile according to the foregoing conditions was diluted with dichloromethane and treated with the copper catalyst (0.1 equiv.). After 12 h, qinghaosu (29%) was isolated from the reaction mixture.

Several features of these new reactions are worthy of comment. As shown in the preceding communication, both the copper and iron catalysts cause rapid cleavage of allylic peroxides under nitrogen into dicarbonyl compounds to occur. Under oxygen, it is the former catalyst which induces oxygenation of the qinghao acid and ester hydroperoxides to occur, although the presence of smaller amounts of iron co-catalyst induces a more rapid reaction. The iron catalyst alone under oxygen is an ineffective catalyst; the ester hydroperoxide (**4**) is converted into the cleavage products (**12**)

and (**13**) and other products. The cleavage products are unaffected on exposure to oxygen in the presence of the copper catalyst. Mechanistically, the observations are compatible with the reversible reaction of oxygen with a dioxetanyl-alkyl free radical intermediate arising from the hydroperoxide as previously described[1] (Scheme 1). The derived peroxy radical, or its metal-bound equivalent is reduced to the dioxetan hydroperoxide, which then cleaves to the dicarbonyl hydroperoxide (**5**). The ineffectiveness of the iron catalyst may be attributed to a competing facile reduction of the dioxetanalkyl radical by iron(II)[1] to generate the precursor of the cleavage products.

The straightforward conversions of the qinghao acid into both the dehydroqinghaosu and qinghaosu are noteworthy, and are obviously related to the biosynthetic conversions in *Artemisia annua*.[6] The facile generation of the dehydroqinghaosu in particular is of obvious importance, as this compound occurs in only trace amounts in *Artemisia annua*,[3] and it possesses a functionality which renders it suitable for conversion into derivatives of qinghaosu which may possess enhanced antimalarial activity. Finally, it must be noted that Roth and Acton have also recently converted dihydroqinghao acid into qinghaosu, but the conversion apparently does not involve an allylic hydroperoxide.[7] Current work focuses on improving the yields of the reaction and applying the reaction to model substrates.

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