124. The Deoxygenation and Isomerization of Artemisinin and Artemether and Their Relevance to Antimalarial Action

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Dedicated to the memory of our late colleague Professor *Wolfgang von Oppolzer*

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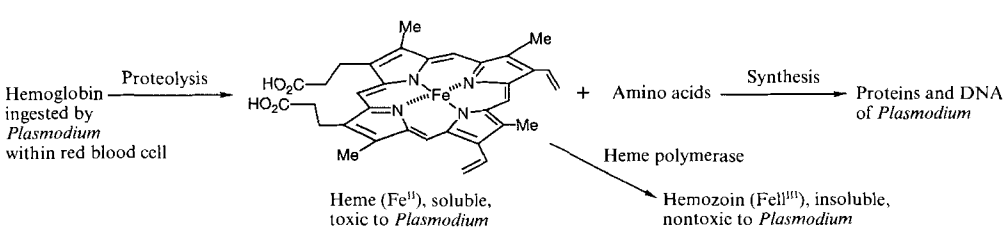
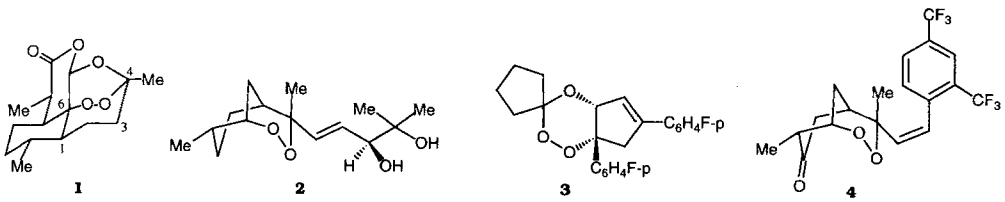
The treatment of artemisinin (**1**) and β-artemether (**6**) with Zn dissolving in AcOH for a few hours results in mono-deoxygenation giving deoxyartemisinin (**5**) and deoxy-β-artemether (**7**), respectively, as the sole product. In contrast, submission of **1** to $FeCl_2 \cdot 4\ H_2O$ in MeCN at room temperature for 15 min causes only isomerization, (3a*S*,4*R*,6a*S*,7*R*,10*S*,10a*R*)-octahydro-4,7-dimethyl-8-oxo-2*H*,10*H*-furo[3,2-*i*]benzopyran-10-yl acetate (**8**) and (3*R*)-3-hydroxydeoxyartemisinin (**9**) being produced in 78 and 17% yield, respectively. The action of $FeCl_2 \cdot 4\ H_2O$ in MeCN on **6** is similar. Under the same conditions, **6** gives products analogous to **8** and **9** accompanied by an epimeric mixture of 2-[4-methyl-2-oxo-3-(3-oxobutyl)cyclohexyl]propanaldehyde in yields of 32, 23, and 16%, respectively. No epoxide is formed on repeating the last two experiments in the presence of cyclohexene. The deoxygenation of **1** and **6** by Zn is rationalized in terms of its oxophilic nature. The catalyzed isomerization of **1** and **6** by Fe^{2+} is attributed to the redox properties of the Fe^{2+}/Fe^{3+} system.

The discovery that two natural products of Chinese origin, qinghaosu or artemisinin (**1**) and yingzhaosu (**2**), possess potent antimalarial properties has led to the development of synthetically more accessible compounds of enhanced activity such as the bis(4-fluorophenyl)cyclopenta-1,2,4-trioxane **3** and arteflene (**4**) [1] [2]. It is apparent from their chemical structure that these entities share a common mode of action which will be different from that of the traditional quinoline-based antimalarials [3]. Nonetheless, like chloroquine and quinine, these peroxidic antimalarials act as blood schizonticides [4]. *Plasmodium*, in the intraerythrocytic stage, multiplies by digesting hemoglobin, which on proteolysis discards the prosthetic group, ferroprotoporphyrin IX, or heme. Since heme is toxic to the parasite, it is normally eliminated by oxidative polymerization to hemozoin, an insoluble pigment (*Scheme 1*) [5] [6]. Evidence has accumulated indicating that

Scheme 1



the aforementioned antimalarials interrupt the detoxification process either by potentiating heme *in situ* or by interacting with it to produce a toxic species which kills the parasite [7]. Artemisinin is reported to form an adduct with hemin [8] or heme [9] after first generating an unidentified oxy radical which on rearrangement can alkylate malarial proteins [10]. The treatment of cultures of *Plasmodium falciparum* infected red blood cells with samples of radio-labelled arteether, dihydroartemisinin, or arteflene followed by incubation revealed that label was transferred to certain proteins associated with the membrane of the parasite [11]. No transfer was observed on repeating the incubation with a radio-labelled inactive derivative, *e.g.* deoxyartemisinin (**5**). Further evidence gleaned from model studies with artemisinin-like tricyclic trioxanes has suggested that they react with heme to produce a parasiticidal, C-centered radical [12].



1 **2** **3** **4**

As a counterpoint to these conclusions, the view has endured that active trioxanes, probably on account of their peroxidic nature, are capable in some way of behaving as oxidizing agents. In fact, the formation of **5** as a metabolite from **1** in a biological context was adduced as a sign that an O-atom had been transferred to a receptor implicated in the parasiticidal event [3b] [13]. We recently reported that **3** and its non-fluorinated analogue display different reaction courses depending on whether they were treated with Zn of $FeCl_2$ [14a]. The action of Zn dissolving in AcOH was taken as a dehydrogenase equivalent and resulted in deoxygenation, whereas $FeCl_2$ in MeCN, a model for heme, brought about unravelling of the trioxane and spirocyclic rings[1]). Significantly, the addition of cyclohexene in the latter experiment was inconsequential; no epoxide being formed. As a logical continuation, we now fully describe the application of the above reagents to artemisinin (**1**) and β-artemether (**6**) with the aim of gaining further insights into their mechanism of antimalarial action[2]).

Results. – The addition of 1 equiv. of Zn powder to a solution of **1** in AcOH, after a few hours of stirring at room temperature, resulted in a nearly quantitative conversion to deoxyartemisinin (**5**). The same experiment carried out with **6** gave deoxy-β-artemether (**7**) as the sole product in 68% yield (*Scheme 2*).

Exposure of **1** to 1 equiv. of $FeCl_2 \cdot 4\ H_2O$ in MeCN with stirring for no more than 15 min at room temperature brought about complete reaction. Just two products were

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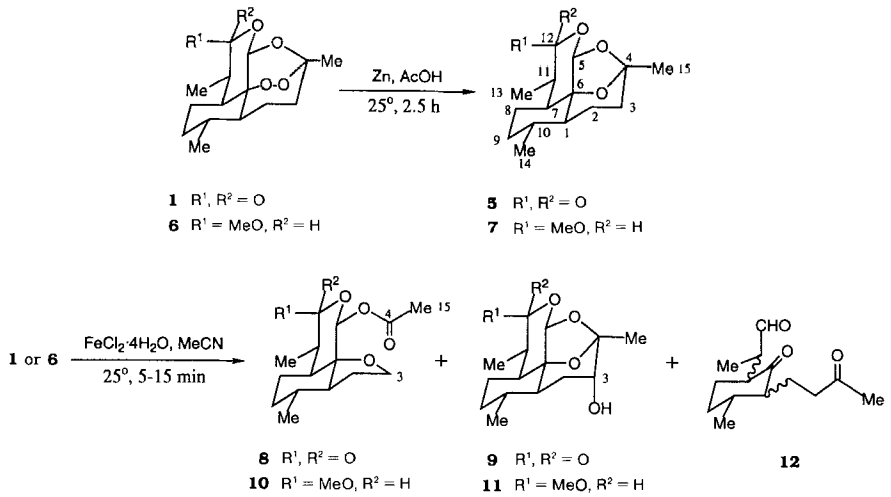
[1]) The chief products of the $FeCl_2$-induced reaction were originally incorrectly described as the 'dimeric' ethers derived from the 5-hydroxy-3,5-diarylcyclopent-2-enyl 5-hydroxypentanoates. Re-examination of these products revealed that they are in fact the 5-hydroxy-3,5-diarylcyclopent-2-enyl 5-chloropentanoates. The proposed mechanistic scheme, in which Fe^{2+} initially generates a C-centered radical, remains unchanged [14b].

[2]) A report on the $FeCl_2$-induced isomerization of artemisinin was presented by one of us (*C. W. J.*) in an invited lecture at the 4th Tohwa University International Symposium on the Chemistry of Biologically and Physiologically Active Natural Products, Fukuoka, Japan, November 19–22, 1994.

Scheme 2[a])



[a]) Arbitrary numbering.

cleanly formed, the furano acetate **8** and 3α-hydroxydeoxyartemisinin (**9**), in yields of 78 and 17%, respectively (*Scheme 2*). β-Artemether (**6**) subjected to the same conditions for only 5 min under an inert atmosphere gave three products. The first two were the 12β-methoxy-furano acetate **10** and 3α-hydroxydeoxy-β-artemether (**11**), invariably formed in 32 and 23% yield, respectively. The third product (16%) was not an artefact of the workup procedure and was found to consist of an inseparable epimer mixture of at least two aldehydes, the gross structure of which was identified as the 2,3,6-trisubstituted cyclohexanone **12**.

The last two experiments were repeated and conducted in the presence of slightly more than 1 equiv. of cyclohexene. The reaction of **1** gave the furano acetate **8** in somewhat higher yields than hitherto (84%) and on a single occasion in 99% yield. The minor product was the same as before, namely **9**, usually obtained in 1–8% yield. There was no trace of cyclohexene epoxide. A similar reaction of β-artemether (**6**), when admixed with cyclohexene, was equally devoid of any epoxidation. The yield of the products so obtained, **10**–**12**, improved somewhat (36, 30, and 19%, resp.), but the composition remained essentially the same as that previously observed.

The identification of products was facilitated by the fact that **5**, **8**, **9**, and **12** have been reported before. Deoxyartemisinin (**5**) has been synthesized from artemisinic acid [15] and (+)-(*R*)-citronellal [16] and prepared from **1** by catalytic hydrogenation [17]. Thermolysis of **1** at 190° gave **8** and **9** in yields of 12 and 10%, respectively [18a]. Heating dihydroartemisinin afforded **5** and **12** in yields of 30 and 50%, respectively [18b]. Deoxy-β-artemether (**7**), unlike is ethyl analogue [17], to our knowledge, has not been previously described. To be sure of the structures, complete NMR analyses of **5**–**8** and **9** were undertaken. To this end, the extended H-spin systems were identified and connectivities assigned by phase-sensitive COSY-45 experiments at 9.4 Tesla [19] [20]. Standard ^{13}C-NMR spectroscopy, supported by DEPT, gave for all compounds the correct number and CH_x-multiplicities of C-resonances. Their full assignment was based on C,H correla-

tion spectroscopy (HETCOR) [21]. More complicated configurational questions were resolved by NOESY experiments [22].

The tetracyclic compounds **5**, **7**, and **9**, and the tricyclic acetate **8** showed significant correlation peaks arising from dipolar cross-relaxation between the pairs H–C(5)/H–C(10) and H–C(1)/H–C(7). The data found for **5** and **9** were in agreement with those reported for samples obtained by microbial fermentation [23]. The data for **8** accorded with those of the natural product [24]. It so happened that the configuration of the OH group in **9** could not be determined in $CDCl_3$, since the crucial H–C(3) resonance was unresolved and featureless, probably owing to second-order effects and unfavorable exchange dynamics of the OH group. Therefore, **9** was examined in (D_8)THF solution, which enabled the values of the vicinal coupling constants of H–C(3) to be clearly discerned. They were found to be 1.7, 4.3, and 7.8 Hz. As this last value arose from coupling with the OH group, the other ^3J values are compatible with an equatorial configuration for H–C(3), thereby indicating that the OH group is axial with respect to the tetrahydropyran ring.

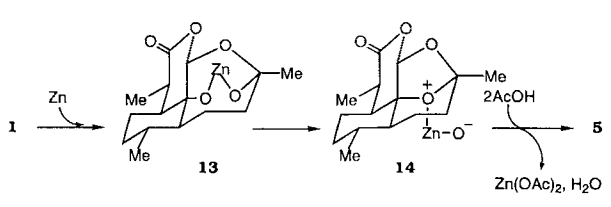
While their ethoxy analogues have been obtained in minuscule amounts by submission of β-arteether to a rat-liver microsome preparation and identified by thermospray liquid chromatography [25], 12β-methoxyfurano acetate **10** and 3α-hydroxydeoxy-β-artemether (**11**) have not been reported so far. The structures of **10** and **11** as well as **12** were elucidated by the same set of NMR experiments as that performed for **5** and **7**–**9**. The configuration of **11** was the same as that of **9**.

Measurement of the ^{1}H-NMR spectrum of **11** in (D_8)THF afforded coupling constants of 1.5, 4.1, and 8.8 Hz for H–C(3), thereby confirming that the attached OH group was in the axial position. The gross structure of the 4:1 diastereoisomer mixture **12** was more difficult to elucidate. However, by gradient-selected HMQC spectroscopy at 14.1 Tesla, the pertinent H,C-correlation spectra were obtained [26]. The NMR data listed in the *Exper. Part* refer only to the major constituent.

Discussion. – The deoxygenation of artemisinin (**1**) and β-artemether (**6**) clearly follows the same course and is conveniently rationalized in terms of the oxophilic nature of Zn [27]. The reaction is initiated by the donation of a pair of electrons to the peroxide bond, illustrated by that of **1**, which breaks to create the bidentate species **13** (*Scheme 3*). Contraction of the seven-membered metallacycle then extrudes one of the coordinated O-atoms to give the transient dipolar intermediate **14** which excises a molecule of ZnO thereby liberating deoxyartemisinin (**5**). The discarded ZnO dissolves by combination with two molecules of AcOH giving $Zn(OAc)_2$. This behavior parallels that already observed with *cis*-fused bicyclic 1,2,4-trioxanes [28]. It is the chemical equivalent of reduction by a Zn-containing NADH dehydrogenase [29]. In other words, it can be reasonably supposed that the origin of **5** and **7**, when formed in a biological context, is simply due to adventitious enzymatic deoxygenation. Support for this idea stems from a study of the *in vitro* metabolism of β-arteether in rat-liver cytosol. Deoxy-β-arteether was formed directly under the influence of an NADH-dependent cytosolic enzyme [30].

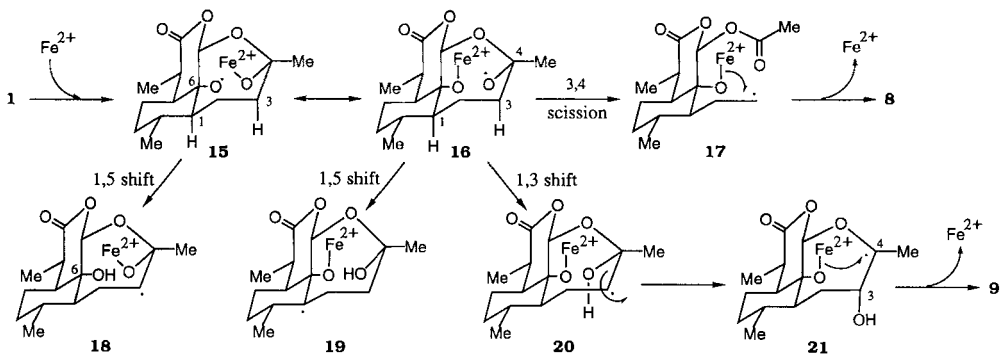
The action of $FeCl_2$ in MeCN was altogether different. There was no sign of deoxygenation. It simply behaves as a *catalyst* towards artemisinin (**1**) and β-artemether (**6**) by

Scheme 3



bringing about isomerization. Again, the peroxide bond is the primary site of attack by the Fe^{2+} ion. This time, Fe^{2+}, because of its reductive properties, immediately after or even during coordination, transfers a single electron to the O–O σ^* orbital. As a result, the trioxane ring of **1**, *e.g.*, breaks apart to the radical anion which stays closely bound to the newly created Fe^{3+} ion (*Scheme 4*). The ensuing complex, for heuristic purposes, may be depicted as a pair of ferric oxy radicals **15** and **16**. Even if formed as discrete entities, they would be freely interconvertible. In any event, the complex is now set up for profound skeletal change. The major course, shown as arising from **16**, is isomerization of the acetal to the acetate function by scission of the C(3)–C(4) bond, which simultaneously generates the pendent ethyl radical. At first sight, the primary radical **17** appears to be a high-energy species. However, it is probably complexed and thus stabilized by the adjacent ferric ion[3]). Finally, the catalytic cycle is completed by elimination of Fe^{2+} from **17** so engendering two nascent, neighboring radical centers which combine to form the tetrahydropyran moiety in **8**.

Scheme 4[a])



[a]) Arbitrary numbering.

The minor course is more convoluted. The oxy-radical character which is inherent in the complex invites H-atom migration. The obvious candidates are the axially disposed H–C(1) and H–C(3) atoms in **15** and **16** (*Scheme 4*). Normally, [1,5]-H shifts would be favored [32]. Thus, **15** would be expected to abstract H–C(3) and **16** H–C(1), generating radicals **18** and **19**, respectively. However, there is no experimental evidence for **19**, and **18** may well be unattainable in view of the boat transition structure required to produce it [33]. Indeed, the pertinent interatomic distances, both calculated[4]) and measured [35] [36], in artemisinin (**1**) taken as a model for the Fe^{3+}-bound complex, appear too great for a [1,5]-H shift (*Table*, *Entries 1* and *2*). There is little chance that H–C(1) could reach the O-atom located at C(4) in **16** (*Entry 1*). The space to be traversed by H–C(3) to get to O–C(6) in **15** is smaller (*Entry 2*), but still exceeds the critical distance of 2.1 Å above which migration is thought not to occur [37]. The gap between 1,3-disposed H- and

[3]) For a discussion on the binding of Fe cations with C-radicals in non-heme iron-containing enzymes, see [31].

[4]) More detailed studies on the geometric parameters of artemisinin calculated by semi-empirical and *ab initio* methods and their comparison with the experimental values have been reported in [34].

Table. *Selected Interatomic Distances in Artemisinin* (**1**)

Entry	Interatomic distance	Calculated value[a]) [Å]	Measured value[b]) [Å]
1	C(1)–H···O–C(4)	3.589	3.646
2	C(3)–H···O–C(6)	2.803	2.478
3	C(1)–H···O–C(6)	2.463	2.465
4	C(3)–H···O–C(4)	2.560	2.467

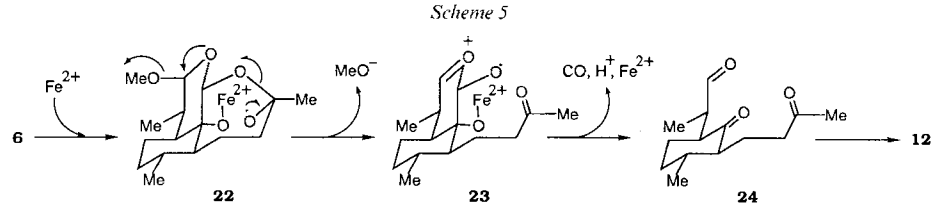
[a]) According to PM3 calculations (this work). [b]) Obtained from X-ray [35].

O-atoms is somewhat narrower (*Entries 3* and *4*), but still greater than 2.1 Å. On the basis of **1**, no clear-cut geometrical preference for [1,5]-H over [1,3]-H shift emerges. It might be argued that radical **15** could reduce the gap further by conformational adjustment. However, the desired collinear arrangement of the H–C(3) and O-atoms appears unrealizable. Therefore, we believe that the conformationally fixed oxy radical **16**, unlike flexible trioxanes [38], is denied the option of a [1,5]-H shift and instead undergoes a [1,3] migration of H–C(3). The secondary radical **20** so produced, then undergoes a suprafacial [1,2] shift by the new OH group which slides into the vacant C(3) position. The resultant tertiary radical **21** is stabilized by the substituents and, more importantly, is able to close the catalytic cycle by splitting off Fe^{2+} to form tetrahydropyran **9**. A variant of this pathway is to allow **15** to undergo a [1,5]-H shift to **18**. Tautomeric rearrangement of **18** to **20** then affords **21** and finally **9** in the usual way. Clearly, the $FeCl_2$-catalyzed rearrangement of β-artemether (**6**) to **10** and **11** proceeds by similar radical intermediates.

The foregoing chemically induced isomerizations find a precedent in the behavior of β-arteether when incubated in rat-liver cytosol [30]. The ethoxy analogue of **9** was isolated from the cytosolic compartment and was thought to have arisen by a chemical, rather than an enzymatic reaction.

Despite the parallels in reactivity between artemisinin (**1**) and β-artemether (**6**), the latter, under the conditions of rearrangement, consistently gave, as a minor component, the aldehyde mixture **12**, which corresponds, formally at least, to the loss of a molecule of methyl formate. It seems that this alternative avenue of scission is attributable to the MeO group in **6**. The actual mechanism is open to conjecture, but the adjunction of Fe^{2+} to the peroxide bond of **6** followed by rupture to the ferric oxy radical **22** provides a suitable starting point (*Scheme 5*). Subsequent cleavage and loss of methoxide ion yields the radical cation **23**, which on deprotonation, decarbonylation, and detachment of Fe^{2+} affords the diketo aldehyde **24** as the penultimate product. As H_2O is present in the reaction mixture, hydration of **23** is possible, which means that HCOOH instead of CO would be excised as a preferable option. H_2O could also account for the epimerization of **24**, thereby giving rise to the final mixture **12**.

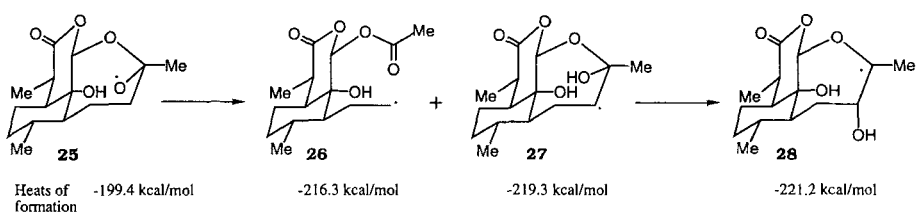
Scheme 5



It must be mentioned that **12** has not been identified so far as a metabolite among the products obtained by incubating β-arteether with rat-liver cytosol or microsome preparations [30] [25]. However, as it has now been characterized, it should be easier to detect in future experiments.

The fundamental finding is that Fe^{2+} does not reduce artemisinin (**1**) or β-artemether (**6**), but catalyses their isomerization *via* an initial acetal radical which is mainly driven to a C-centered radical thanks to the acquisition of greater thermodynamic stability through formation of the ester function. Justification for this sequence was provided by examining model structures such as the artemisinin radical **25** and its scission product, the primary radical **26** (*Scheme 6*). In these structures, the proton takes the place of the ferric ion (*cf. Scheme 4*). The minor pathway was evaluated by considering the secondary and tertiary radicals **27** and **28** taken as models for the corresponding iron-bound radicals (*Scheme 6*). The geometries of **25**–**28** were optimized and their heats of formation computed by performing semi-empirical PM3 [39] molecular-orbital calculations by using the MOPAC 6.0 program [40] [41]. As the restricted *Hartree-Fock* method implemented in the MOPAC program artificially suppresses the spin polarization for radicals owing to the 'half spin' approximation [42], the more reliable unrestricted *Hartree-Fock* method was used instead. The heats of formation (ΔH_f) for **25** and **26** were found to be −199.4 and −216.3 kcal/mol, respectively, and confirm that, although a primary radical is formed, scission of **25** is exothermic. Rearrangement of **25** to **27** is more exothermic as evidenced by the ΔH_f of the latter (−219.3 kcal/mol). It is seen that the incremental heat of formation due to a secondary radical ($\Delta\Delta H_f = -19.9$ kcal/mol) exceeds that of the ester grouping ($\Delta\Delta H_f = -16.9$ kcal/mol). As expected, the final tertiary radical **28** is the most stable.

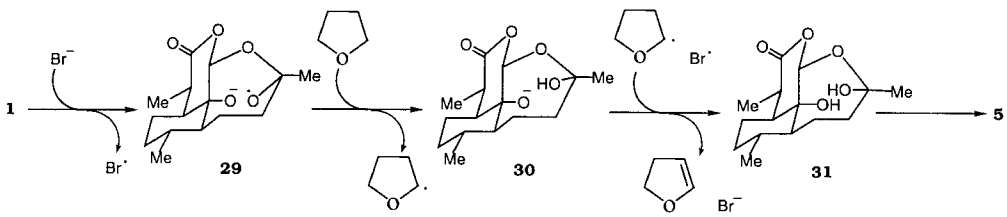
Scheme 6



The experiments conducted in the presence of cyclohexene further show that there are no products arising by an oxidative or O-atom transfer pathway. Epoxidation did not occur. If anything, it appears that cyclohexene may have slightly suppressed the subsidiary formation of the hydroxylated isomer **9**. Our results taken as a whole stand in sharp contrast to those recently reported for the reaction of **1** with $FeBr_2$ in tetrahydrofuran at 0° for 45 min [43]: Rearrangement *and* deoxygenation occurred concomitantly to give **8**, **9**, and **5** in high yield (98%) and in a ratio of 3:1:6. Under these conditions, deoxygenation was the main event. The mechanistic pathway proposed by the authors entails abstraction of an O-atom from the peroxide bond by Fe^{2+} to give deoxyartemisinin (**5**) and $O{=}Fe^{2+}$. The latter potent oxidant then formally inserts an O-atom into the H–C(3) bond of **5**, through the agency of various intermediates, to give **9**. The mechanism for forming **8** was not given.

We believe that the authors' results [43] can be accommodated by the dual behavior of the $FeBr_2$/THF couple. On the one hand, Fe^{2+} isomerizes **1** to **8** and **9** in the way we have suggested. On the other hand, bromide ion is a reducing species [44]. It could transfer an electron to the peroxide bond of **1** to give the radical anion **29**. The latter then captures H–C(2) of THF giving the anion **30** (*Scheme 7*). The resulting tetrahydrofuranyl radical and bromine radical together regenerate bromide ion and protonate **30**. The derived diol **31** finally closes to **5** by dehydration. Although this scheme is entirely speculative, it is reinforced by the finding that the proportion of **5** increased substantially when the $FeBr_2$/THF mixture contained 1,4-cyclohexadiene as an addend. Aromatization of the latter and transfer of a molecule of H_2 to the peroxide bond of **1** would furnish the diol **31** directly and thereafter **5** by loss of a H_2O molecule. A further indication that $FeBr_2$/THF behaves as a H-transfer agent is the recent observation that substantial amounts of diol were isolated from simple bicyclic endoperoxides [45].

Scheme 7

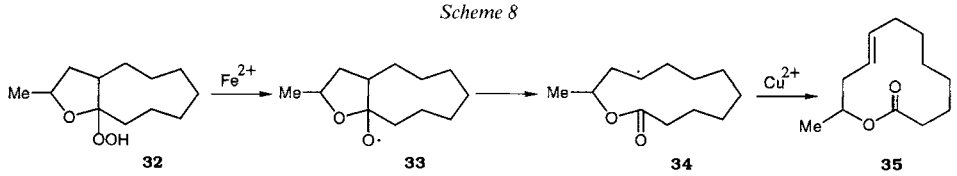


The circumstantial evidence for the involvement of $O{=}Fe^{2+}$, namely, the aromatization of hexamethyl *Dewar* benzene when added to the reaction mixture and the oxidation of easily oxidizable addends such a methyl phenyl sulfide and tetrahydronaphthalene [43], are probably either artefacts of workup or due to adventitious oxidation.

A contrasting result is the report that $Fe(ClO_4)_2 \cdot 6\ H_2O$ in MeCN was without effect on **1**, but that $FeCl_2$ in MeCN and in the presence of 1*H*-imidazole rapidly produced **8** and **9** together with a hydrolysis product of **5** in a ratio of 78:16:6 [46]. However, the action of various Fe^{III} reagents, including hemin, with or without added thiols in different solvents, usually required long reaction times and afforded variable yields of **8** and **9** together with sundry hydrolysis products [46]. In view of the diversity of the results and experimental conditions used, it is difficult to draw firm mechanistic conclusions. It is also possible that thiols may reduce the peroxide bond of artemisinin as we have intimated above. *E.g.*, it is known that L-glutathione and L-cysteine are very efficient at reducing 1,2-dioxetanes and cyclic peroxides to the corresponding diols [47].

Our results are unambiguous. They demonstrate that deoxygenation and isomerization follow two separate, unrelated reaction courses and that the latter depends crucially on the redox properties of the Fe^{2+}/Fe^{3+} system. It is worth mentioning at this juncture that ample precedent exists for such redox behavior towards peroxides [48]. A fitting example is the treatment of the bicyclic hydroperoxide **32** with $FeSO_4$ in MeOH saturated with $Cu(OAc)_2$ (*Scheme 8*) [49]. Fe^{2+}-Induced scission gave the acetal radical **33** which instantaneously rearranged to the lactone-stabilized C-centered radical **34**. Subsequent oxidation by Cu^{2+} and deprotonation afforded recifeiolide (**35**) in 96% yield.

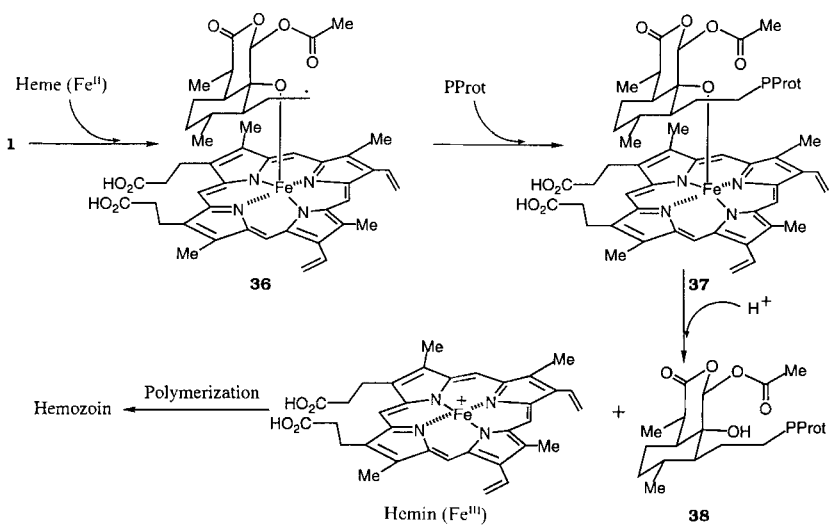
Scheme 8



Lastly, it should be remembered that $FeCl_2 \cdot 4\,H_2O$ in MeCN is not the same as heme inside the parasite. Both entities certainly display the same redox properties. The first acts as a catalyst towards artemisinin (**1**) and artemether (**6**) as already demonstrated, but intraparasitic heme can exercise the option of acting as a reagent. This subtle distinction accords well with recent findings on the effect of chloroquine and **1** on the production of hemozoin by trophozoites of *P. falciparum* [50]. Chloroquine inhibited hemozoin production to a certain extent, possibly by chelating with heme and preventing its oxidative polymerization. In contrast, hemozoin content was undiminished by **1**. This result is entirely compatible with the mechanism of action of heme. Like Fe^{2+}, it will initially bind to one of the peroxide atoms to set in motion the creation of the pendent C-centered radical **36**, but once the latter has alkylated the parasite protein (PProt), the labile O–Fe bond holding heme in the resulting complex **37** will break heterolytically, probably by protonation, releasing hemin which is ready for polymerization to hemozoin (*Scheme 9*). The parasite is thus disabled by the alkylation of specific proteins as exemplified by the formation of **38**.

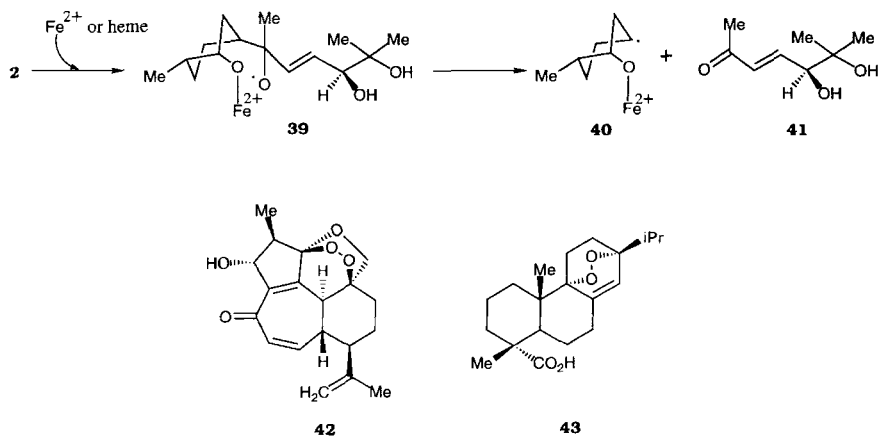
Conclusion. – The mechanistic principles proposed for the Fe^{2+}-induced isomerization of artemisinin (**1**) and artemether (**6**), namely coordination with the peroxide bond, donation of a single electron to unravel the trioxane ring to an acetal radical which is

Scheme 9



thermodynamically driven to the ester bearing a primary C-centered radical, will be applicable to many other peroxidic antimalarials. It is expected that $FeCl_2$ in MeCN will cleave yingzhaosu A (**2**), yingzhaosu C [51], and arteflene (**4**) by unmasking a ketone function as the driving force. For example, the α,β-unsaturated ketone **41** and the cyclohexyl radical **40** would be generated from **2** *via* the oxy radical **39** (*Scheme 10*). Certain 3,3,6,6-tetrasubstituted 1,2,4,5-tetroxanes [52] should behave like 1,2,4-trioxanes and rearrange to ester derivatives. Finally, naturally occurring diterpene peroxides such as caniojane (**42**) [53], and 9α,13α-epidioxyabiet-8(14)-en-18-oic acid (**43**) [54], entities as yet untested, should fulfill the aforementioned mechanistic criteria for Fe^{2+}-promoted rearrangement and consequently display antimalarial activity.

Scheme 10



Experimental Part

General. See [1]. NMR Spectra: at 9.4 and 14.1 Tesla in $CDCl_3$, except where noted, on *Bruker-AMX-400* and *-AMX-II-600* spectrometers. MS: electron-impact, high-resolution (HR), and electro-spray (ES), MS on *Finnigan-SSQ-7000* and *VG-70-70E* spectrometers.

1. *Deoxyartemisinin* (**5**). Zn Powder (38 mg, 0.59 mol) was added in one portion to artemisinin (**1**; 0.161 g, 0.57 mol) in AcOH (5 ml). The mixture was stirred at r.t. for 2.5 h and filtered over *Celite*. The latter was washed with CH_2Cl_2 and AcOEt. The filtrate and washings were evaporated. The residue was purified by column chromatography (CC) (SiO_2, 230–400 mesh, petroleum ether/AcOEt 4:1): **5** (0.149 g, 98%). Recrystallization (hexane) gave colorless platelets. M.p. 119°. $[\alpha]_D^{20} = -141.3$ ($c = 0.4$, $CHCl_3$). IR ($CHCl_3$): 3024, 2955, 2877, 1742, 1447, 1389, 1226, 1137, 1106, 1018, 868. ^{1}H-NMR (400 MHz): 5.63 (*s*, 1 H); 3.12 (*dq*, $J = 7.2, 4.6$, 1 H); 1.96–1.67 (*m*, 5 H); 1.61–1.51 (*m*, 1 H); 1.46 (*s*, 3 H); 1.22–1.15 (*m*, 3 H); 1.13 (*d*, $J = 8.0$, 3 H); 1.11–0.9 (*m*, 2 H); 0.87 (*d*, $J = 6.0$, 3 H). ^{13}C-NMR (100 MHz): 170.7 (CO); 108.2 (C); 98.7 (CH); 81.5 (C); 41.5 (CH); 34.4 (CH); 33.1 (CH_2); 32.6 (CH_2); 31.8 (CH); 23.0 (Me); 22.16 (CH_2); 21.1 (CH_2); 17.6 (Me); 11.6 (Me). MS: 266 (8, M^+), 224 (32), 222 (20), 210 (10), 195 (15), 165 (100), 163 (71), 151 (54), 149 (29), 124 (21), 107 (17), 93 (14), 81 (12), 67 (9), 55 (16). HR-MS: 266.1508 ($C_{15}H_{22}O_4^+$; calc. 266.1518).

2. *Deoxy-β-artemether* (**7**). *Exper. 1* was repeated with β-artemether (**6**; 0.153 g, 0.513 mmol) and Zn (0.336 g, 5.13 mmol) in AcOH (5 ml; reaction time 1 h). Workup (*cf. Exper. 1*) gave a whitish solid (0.144 g), which on flash chromatography (FC; SiO_2, petroleum ether/AcOEt 10:1) and recrystallization (hexane) gave **7** (0.104 g, 72%). Colorless hexagonal crystals. M.p. 74.5–76.5°. $[\alpha]_D^{20} = +10.2$ ($c = 1.1$, $CHCl_3$). IR ($CDCl_3$): 3014, 2947, 2874, 1450, 1385, 1207, 1137, 1099, 1078, 1030, 867. ^{1}H-NMR (C_6D_6): 5.39 (*s*, 1 H); 4.80 (*d*, $J = 4.8$, 1 H); 3.34 (*s*, 3 H);

2.63 (*m*, 1 H); 1.82 (*m*, 1 H); 1.72 (*m*, 2 H); 1.63–1.53 (*m*, 2 H); 1.61 (*s*, 3 H); 1.51–1.43 (*m*, 2 H); 1.24 (*m*, 1 H); 1.05 (*ddd*, *J* = 10.8, 10.8, 4.8, 1 H); 0.98 (*d*, *J* = 7.6, 3 H); 0.90 (*m*, 1 H); 0.77 (*m*, 1 H); 0.71 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR (C_6D_6): 107.8 (C); 100.7 (CH); 95.2 (CH); 83.3 (C); 55.8 (Me); 46.8 (CH); 41.5 (CH); 35.2 (CH); 35.1 (CH_2); 35.0 (CH_2); 31.1 (CH); 25.4 (CH_2); 24.7 (Me); 22.6 (CH_2); 19.1 (Me); 12.3 (Me). MS: 282 (3, M^+), 251 (34), 164 (46), 98 (55), 72 (100). HR-MS: 282.1826 ($C_{16}H_{26}O_4^+$; calc. 282.1831).

3. *Isomerization of Artemisinin* (**1**). *3.1.* Freshly purchased $FeCl_2 \cdot 4\ H_2O$ (77 mg, 0.39 mmol) was added to **1** (0.112 g, 0.4 mmol) in MeCN (5 ml). The mixture was stirred for 15 min at r.t. and then filtered over *Celite*. The latter was washed with CH_2Cl_2 and AcOEt. The filtrate and washings were evaporated. The residue was purified by CC (SiO_2, 230–400 mesh, petroleum ether/AcOEt 5:1) to give *(3aS,4R,6aS,7R,10S,10aR)-3,3a,4,5,6,6a,7,8-octahydro-4,7-dimethyl-8-oxo-2*H,*10*H-*furo[3,2-*i*]benzopyran-10-yl acetate* (**8**; 87 mg, 78%) and *3α-hydroxydeoxyartemisinin* (= *(3R,3aS,6R,6aS,8R,9R,10aS,10bR)-3a,4,5,6,6a,7,8,9-octahydro-8-hydroxy-3,6,9-trimethyl-10a*H-*9,10b-epoxypyrano[4,3,2-*jk*][2]benzoxepin-2(3*H*)-one*; **9**; 19 mg, 17%), both of which were recrystallized (CH_2Cl_2/hexane).

8: Colorless needles. M.p. 88–89°. $[\alpha]_D^{20} = +93.8$ (*c* = 0.42, $CHCl_3$). IR ($CHCl_3$): 3031, 2958, 2899, 1759, 1458, 1382, 1226, 1167, 1073, 1009, 947, 915. ^{1}H-NMR (400 MHz): 6.57 (*s*, 1 H); 4.14 (*ddd*, *J* = 9.2, 8.1, 1.7, 1 H); 3.88 (*ddd*, *J* = 9.0, 8.1, 7.2, 1 H); 3.09 (*dq*, *J* = 7.4, 4.8, 1 H); 2.09 (*s*, 3 H); 2.10–1.78 (*m*, 4 H); 1.75–1.35 (*m*, 3 H); 1.14 (*d*, *J* = 7.2, 3 H); 1.15–0.95 (*m*, 2 H); 0.91 (*d*, *J* = 6.0, 3 H). ^{13}C-NMR (100 MHz): 170.6 (CO); 167.4 (CO); 92.0 (CH); 78.4 (C); 68.2 (CH_2); 53.8 (CH); 45.7 (CH); 34.0 (CH); 33.6 (CH_2); 29.9 (CH); 26.7 (CH_2); 23.3 (CH_2); 20.2 (Me); 19.4 (Me); 11.5 (Me). MS: 282 (6, M^+), 239 (2), 223 (2), 211 (8), 195 (2), 167 (11), 166 (100), 151 (55), 139 (4), 138 (42), 137 (67), 123 (6), 96 (14), 81 (6), 69 (10), 55 (14). HR-MS: 282.1435 ($C_{15}H_{22}O_5^+$; calc. 282.1467).

9: Colorless crystals. M.p. 195–196°. $[\alpha]_D^{20} = -112.2$ (*c* = 0.41, $CHCl_3$). IR ($CHCl_3$): 3581, 3024, 2953, 2930, 1744, 1449, 1389, 1240, 1165, 1137, 1086, 1019, 974, 925, 869. ^{1}H-NMR (400 MHz): 5.57 (*s*, 1 H); 3.56 (br. *s*, 1 H); 3.14 (*dq*, *J* = 7.4, 4.8, 1 H); 2.03–1.73 (*m*, 4 H); 1.51 (*s*, 3 H); 1.54–1.42 (*m*, 2 H); 1.28–1.18 (*m*, 1 H); 1.14 (*d*, *J* = 7.2, 3 H); 1.1–0.90 (*m*, 2 H); 0.87 (*d*, *J* = 6.4, 3 H); OH not visible. ^{13}C-NMR (100 MHz): 170.3 (CO); 107.9 (C); 97.9 (CH); 82.0 (C); 68.1 (CH); 41.1 (CH); 39.6 (CH); 34.1 (CH); 32.4 (CH_2); 31.7 (CH); 29.3 (CH_2); 22.5 (CH_2); 19.5 (Me); 17.4 (Me); 11.6 (Me). MS: 282 (1, M^+), 254 (0.4), 238 (0.6), 222 (100), 204 (25), 179 (19), 166 (28), 151 (24), 150 (47), 137 (27), 123 (19), 107 (20), 93 (33), 81 (21), 67 (14), 55 (29).

3.2. Repetition of *Exper. 3.1* in the presence of cyclohexene (1.18 equiv.) resulted in the formation of **8** and **9**, usually in yields of 84 and 1–8%. On one occasion, only **8** was obtained (99%). Comparisons with a sample of cyclohexene epoxide showed that none was formed.

4. *Isomerization of β-Artemether* (**6**). *4.1.* Freshly purchased $FeCl_2 \cdot 4\ H_2O$ (0.319 g, 1.6 mmol) was added portionwise during 2 min to a soln. of **1** (0.477 g, 1.6 mmol) in MeCN (37 ml) at r.t. under Ar. The mixture was stirred for 2 more min and then filtered over neutral Al_2O_3; the latter was subsequently rinsed with MeCN, both operations being conducted under Ar. The combined washings and filtrate were concentrated *in vacuo* to *ca.* 0.5 ml and then submitted to FC (neutral Al_2O_3, progressive elution with petroleum ether/AcOEt 57:3, 55:5, and 50:10): *(3aS,4R,6aS,7R,8S,10R,10aR)-3,3a,4,5,6,6a,7,8-octahydro-8-methoxy-4,7-dimethyl-2*H,*10*H-*furo[3,2-*i*]benzopyran-10-yl acetate* (**10**; 0.158 g, 32%), *3α-hydroxydeoxy-β-artemether* (= *(2S,3R,3aS,6R,6aS,8R,9R,10aR,10bR)-2,3,3a,4,5,6,6a,7,8,9-decahydro-2-methoxy-3,6,9-trimethyl-10a*H-*9,10b-epoxypyrano[4,3,2-*jk*][2]benzoxepin-8-ol*; **11**; 0.114 g, 23%) and *2-[4-methyl-2-oxo-3-(3-oxobutyl)cyclohexyl]propanaldehyde* (**12**; 82 mg, 16%).

10: Colorless solid. M.p. 97–99°. $[\alpha]_D^{20} = +102.2$ (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): 3016, 2954, 2889, 1755, 1456, 1368, 1236, 1087, 1016, 932. ^{1}H-NMR (C_6D_6, 400 MHz): 6.54 (*s*, 1 H); 4.61 (*d*, *J* = 4.0, 1 H); 4.32 (*ddd*, *J* = 9.6, 8.4, 2.0, 1 H); 3.90 (*ddd*, *J* = 8.4, 8.4, 8.4, 1 H); 3.47 (*s*, 3 H); 2.66 (*m*, 1 H); 2.13 (*dddd*, *J* = 15.0, 13.0, 13.0, 5.0, 1 H); 1.90–1.55 (*m*, 5 H); 1.66 (*s*, 3 H); 1.49 (*m*, 1 H); 1.16 (*ddd*, *J* = 13.0, 12.0, 7.7, 1 H); 0.87 (*d*, *J* = 7.2, 3 H); 0.79 (*d*, *J* = 6.4, 3 H); 0.71 (*m*, 1 H). ^{13}C-NMR (C_6D_6, 100 MHz): 168.9 (CO); 103.7 (CH); 88.7 (CH); 80.4 (C); 68.3 (CH_2); 56.2 (CH); 55.8 (Me); 47.7 (CH); 36.3 (CH_2); 33.7 (CH); 30.9 (CH); 28.1 (CH_2); 25.2 (CH_2); 21.0 (Me); 20.6 (Me); 12.6 (Me). MS: 267 (2, $[M - 31]^+$), 209 (9), 165 (8), 138 (100), 96 (29). ES-MS: 321 (100, $[M + 23]^+$). HR-MS: 298.1781 ($C_{16}H_{26}O_5^+$; calc. 298.1780), 267.1603 ($[C_{16}H_{26}O_5 - MeO]^+$; calc. 267.1596).

11: Colorless, sticky solid. M.p. 73–75°. $[\alpha]_D^{20} = +4.4$ (*c* = 0.2, $CHCl_3$). IR ($CHCl_3$): 3575, 3008, 2932, 2878, 1709, 1600, 1447, 1387, 1022. ^{1}H-NMR ((D_8)THF, 400 MHz): 5.18 (*s*, 1 H); 4.62 (*d*, *J* = 4.5, 1 H); 3.69 (*d*, *J* = 8.8, 1 H); 3.34 (*ddd*, *J* = 8.8, 4.1, 1.5, 1 H); 3.31 (*s*, 3 H); 2.40 (*m*, 1 H); 1.90–1.60 (*m*, 5 H); 1.60–1.40 (*m*, 2 H); 1.42 (*s*, 3 H); 1.20 (*m*, 1 H); 0.96 (*m*, 1 H); 0.88 (*d*, *J* = 7.5, 3 H); 0.85 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR ((D_8)THF, 100 MHz): 108.7 (C); 101.2 (CH); 94.6 (CH); 84.0 (C); 70.0 (CH); 55.8 (Me); 43.0 (CH); 42.0 (CH); 35.9 (CH_2); 35.7 (CH); 31.7 (CH_2); 31.5 (CH); 25.9 (CH_2); 21.1 (Me); 19.1 (Me); 12.3 (Me). MS: 298 (0.4, M^+), 267 (3), 238 (20), 72 (100). HR-MS: 267.1597 ($C_{15}H_{23}O_4^+$; calc. 267.1596).

12: Colorless oil. $[\alpha]_D^{20} = -34.0$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 2965, 2931, 1703, 1458, 1360, 1218, 1164. ^{1}H-NMR (C_6D_6, 600 MHz): 9.57 (*m*, 1 H); 2.48 (*qd*, $J = 7.5, 7.5, 1$ H); 2.33 (*m*, 2 H); 2.19 (*m*, 1 H); 1.87 (*m*, 1 H); 1.83–1.70 (*m*, 2 H); 1.73 (*s*, 3 H); 1.53 (*m*, 1 H); 1.37 (*m*, 1 H); 1.15 (*m*, 1 H); 1.01 (*m*, 1 H); 0.95 (*m*, 1 H); 0.85 (*d*, $J = 6.5$, 3 H); 0.74 (*d*, $J = 7.5$, 3 H). ^{13}C-NMR (C_6D_6, 150 MHz): 211.0 (CH); 206.8 (CO); 202.5 (CO); 56.3 (CH); 51.4 (CH); 45.3 (CH); 40.9 (CH_2); 40.1 (CH); 34.4 (CH_2); 30.1 (CH_2); 29.4 (Me); 20.4 (CH_2); 20.4 (Me); 10.8 (Me). GC-MS: 238 (2, M^+), 210 (8), 209 (21), 162 (18), 152 (28), 138 (58), 137 (29), 55 (57), 43 (100), 41 (59).

4.2. Repetition of *Exper. 4.1* in the presence of cyclohexene (1.16 equiv.) resulted in the formation of **10**, **11**, and **12** in yields of 36, 30, and 19%, resp. No cyclohexene epoxide was formed.

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REFERENCES

[1] C. W. Jefford, S. Kohmoto, D. Jaggi, G. Timári, J. C. Rossier, M. Rudaz, O. Barbuzzi, D. Gérard, U. Burger, P. Kamalaprija, J. Mareda, G. Bernardinelli, I. Manzanares, C. J. Canfield, S. L. Fleck, B. L. Robinson, W. Peters, *Helv. Chim. Acta* **1995,** *78,* 647; C. W. Jefford, J. A. Velarde, G. Bernardinelli, D. H. Bray, D. C. Warhurst, W. K. Milhous, *ibid.* **1993,** *76,* 1775.

[2] W. Hofheinz, H. Bürgin, E. Gocke, C. Jaquet, R. Masciadri, G. Schmid, H. Stohler, H. Urwyler, *Trop. Med. Parasitol.* **1994,** *45,* 261; C. Jaquet, H. R. Stohler, J. Chollet, W. Peters, *ibid.* **1994,** *45,* 266.

[3] a) S. R. Meshnick, C. W. Jefford, G. H. Posner, M. A. Avery, W. Peters, *Parasitology Today* **1996,** *12,* 79; b) C. W. Jefford, D. Misra, J. C. Rossier, P. Kamalaprija, U. Burger, J. Mareda, G. Bernardinelli, W. Peters, B. L. Robinson, W. K. Milhous, F. Zhang, D. K. Gosser, S. R. Meshnick, in 'Perspectives in Medicinal Chemistry', Eds. B. Testa, E. Kyburz, W. Fuhrer, and R. Giger, Verlag Helvetica Chimica Acta, Basel, 1993, Chapt. 29.

[4] W. Peters, B. L. Robinson, J. C. Rossier, D. Misra, C. W. Jefford, *Ann. Trop. Med. Parasitol.* **1993,** *87,* 9.

[5] A. F. G. Slater, A. Cerami, *Nature (London)* **1992,** *355,* 167.

[6] A. F. G. Slater, W. J. Swiggard, B. R. Orton, W. D. Flitter, D. E. Goldberg, A. Cerami, G. B. Henderson, *Proc. Natl. Acad. Sci. U.S.A.* **1991,** *88,* 325.

[7] D. C. Warhurst, *Trans. R. Soc. Trop. Med. Hyg.* **1981,** *75,* 606.

[8] S. R. Meshnick, A. Thomas, A. Ranz, C. Xu, H. Pan, *Mol. Biochem. Parasitol.* **1991,** *49,* 181.

[9] Y. Hong, Y. Zang, S. R. Meshnick, *Mol. Biochem. Parasitol.* **1994,** *63,* 121; F. Zhang, D. Gosser, Jr., S. R. Meshnick, *Biochem. Pharmacol.* **1992,** *43,* 1805.

[10] S. R. Meshnick, Y. Yang, V. Lima, F. Kuypers, S. Kamchonwongpaisan, Y. Yuthavong, *Antimicrob. Agents Chemother.* **1993,** *37,* 1108.

[11] W. Asawamahasakda, I. Ittarat, Y. Pu, H. Ziffer, S. R. Meshnick, *Antimicrob. Agents Chemother.* **1994,** *38,* 1854.

[12] G. H. Posner, C. H. Oh, D. Wang, L. Gerena, W. K. Milhous, S. R. Meshnick, W. Asawamahasakda, *J. Med. Chem.* **1994,** *37,* 1256; G. H. Posner, C. H. Oh, *J. Am. Chem. Soc.* **1992,** *114,* 8328; G. H. Posner, C. H. Oh, D. Wang, L. Gerena, W. K. Milhous, S. R. Meshnick, W. Asawamahasakda, *J. Med. Chem.* **1995,** *38,* 607.

[13] D. Zhu, B. Huang, Z. Chen, M. Yin, *Yaoxue Xuebo* **1980,** *15,* 509; China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials, *J. Tradit. Chin. Med.* **1982,** *2,* 25.

[14] a) C. W. Jefford, F. Favarger, M. G. H. Vicente, Y. Jacquier, *Helv. Chim. Acta* **1995,** *78,* 452; b) C. W. Jefford, G. Brunner, U. Burger, in preparation.

[15] M. Jung, H. N. ElSohly, E. M. Croom, A. T. McPhail, D. R. McPhail, *J. Org. Chem.* **1986,** *51,* 5417.

[16] X. Xu, J. Zhu, D. Huang, W. Zhou, *Tetrahedron* **1986,** *42,* 819.

[17] A. Brossi, B. Venugopalan, L. Dominguez Gerpe, H. J. C. Yeh, J. L. Flippen-Anderson, P. Buchs, X. D. Luo, W. K. Milhous, W. Peters, *J. Med. Chem.* **1988,** *31,* 645.

[18] a) X. Luo, H. J. C. Yeh, A. Brossi, *Heterocycles* **1985,** *23,* 881; A. J. Lin, D. L. Klayman, J. M. Hoch, J. V. Silverton, C. F. George, *J. Org. Chem.* **1985,** *50,* 4504; b) A. J. Lin, A. D. Theoharides, D. L. Klayman, *Tetrahedron* **1986,** *42,* 2181.

[19] A. Bax, R. Freeman, *J. Magn. Reson.* **1981,** *44,* 542.
[20] W. E. Hull, in 'Two-Dimensional NMR Spectroscopy', 2nd edn., Eds. W. R. Croasmun and R. M. K. Carlson, VCH, Weinheim, 1994, p. 301.
[21] G. E. Martin, A. S. Zektzer, 'Two-Dimensional NMR Methods for Establishing Molecular Connectivity', VCH, Weinheim, 1988, Chapt. 3.
[22] D. Neuhaus, M. Williamson, 'The Nuclear Overhauser Effect in Structural and Conformational Analysis', VCH, Weinheim, 1989, pp. 253–305.
[23] I. Lee, H. N. ElSohly, E. M. Croom, C. D. Hufford, *J. Nat. Prod.* **1989,** *52,* 337.
[24] Z. Wei, J. Pan, Y. Li, *Planta Med.* **1992,** *58,* 300.
[25] J. K. Baker, R. H. Yarber, C. D. Hufford, I. Lee, H. N. ElSohly, J. D. McChesney, *Biomed. Environ. Mass. Spectrom.* **1988,** *18,* 337.
[26] W. Wilker, D. Leibfritz, R. Kerrsebaum, W. Bermel, *Magn. Reson. Chem.* **1993,** *31,* 287.
[27] J. Drenth, *Recl. Trav. Chim. Pays-Bas* **1980,** *99,* 185.
[28] C. W. Jefford, J. C. Rossier, J. Boukouvalas, *Heterocycles* **1989,** *28,* 673.
[29] M. J. Adams, in 'Enzyme Mechanisms', Eds. M. I. Page and A. Williams, Royal Society of Chemistry, London, 1987, Chapt. 24.
[30] V. Leskovac, A. D. Theoharides, *Comp. Biochem. Physiol., C: Comp. Pharmacol. Toxicol.* **1991,** *99,* 391.
[31] C. W. Jefford, in 'Advances in Detailed Reaction Mechanisms', Vol. 2, 'Mechanisms of Biological Importance', Ed. J. M. Coxon, JAI Press, Inc., Greenwich, CT, USA, 1992, pp. 149–187.
[32] C. Wentrup, 'Reactive Molecules', J. Wiley and Sons, New York, 1984, p. 90.
[33] A. E. Dorigo, M. A. McCarrick, R. J. Loncharich, K. N. Houk, *J. Am. Chem. Soc.* **1990,** *112,* 7508.
[34] C. Thomson, M. Cory, M. Zerner, *Int. J. Quantum Chem.* **1991,** *18,* 231; G. Bernardinelli, C. W. Jefford, D. Maric, C. Thomson, J. Weber, *ibid.* **1994,** *21,* 117; C. W. Jefford, J. Weber, M. Grigorov, C. Thomson, H. U. Suter, D. Maric, unpublished.
[35] Qinghaosu Research Group, *Sci. Sin.* **1980,** *23,* 380.
[36] I. Leban, L. Golic, M. Japelj, *Acta Pharm. Jugosl.* **1988,** *38,* 71.
[37] P. Brun, B. Waegell, in 'Reactive Intermediates', Plenum Press, New York, 1983, Vol. 3, p. 367, and ref. cit. therein.
[38] A. J. Bloodworth, A. Shah, *Tetrahedron Lett.* **1995,** *36,* 7551.
[39] J. J. P. Stewart, *Comput. Chem.* **1989,** *10,* 209.
[40] J. J. P. Stewart, *Comput. Chem.* **1989,** *10,* 221.
[41] J. J. P. Stewart, QCPE 455.
[42] M. J. S. Dewar, N. Trinajstic, *J. Am. Chem. Soc.* **1968,** *90,* 1953; M. J. S. Dewar, N. Trinajstic, *J. Chem. Soc., Chem. Commun.* **1970,** 646.
[43] G. H. Posner, J. N. Cumming, P. Ploypradith, C. H. Ho, *J. Am. Chem. Soc.* **1995,** *117,* 5885.
[44] H. R. Snyder, R. E. Heckert, *J. Am. Chem. Soc.* **1952,** *74,* 2006.
[45] G. H. Posner, D. Wang, L. González, X. Tao, J. N. Cumming, D. Klinedinst, T. A. Shapiro, *Tetrahedron Lett.* **1996,** *37,* 815.
[46] R. K. Haynes, S. C. Vonwiller, *Tetrahedron Lett.* **1996,** *37,* 253, 257.
[47] W. Adam, B. Epe, D. Schiffmann, F. Vargas, D. Wild, *Angew. Chem. Int. Ed.* **1988,** *27,* 429.
[48] J. K. Kochi, 'Free Radicals', Wiley-Interscience, New York, 1973, Vol. I, Chapt. 11, Vol. II, Chapt. 23; G. Sosnovsky, D. J. Rawlinson, in 'Organic Peroxides', Ed. S. Swern, Wiley-Interscience, New York, 1970, Vol. I; W. Herz, R. C. Ligon, J. A. Turner, J. F. Blount, *J. Org. Chem.* **1977,** *42,* 1885; J. A. Turner, W. Herz, *ibid.* **1977,** *42,* 1900.
[49] S. L. Schreiber, *J. Am. Chem. Soc.* **1980,** *102,* 6163.
[50] W. Asawamahasakda, I. Ittarat, C. Chang, P. McElroy, S. R. Meshnick, *Mol. Biochem. Parasitol.* **1994,** *67,* 183.
[51] L. Zhang, W. Zhou, X. Xu, *J. Chem. Soc., Chem. Commun.* **1988,** 523.
[52] C. W. Jefford, W. K. Milhous, unpublished; J. Vennerstrom, H. Fu, W. Y. Ellis, A. L. Ager, Jr., J. K. Wood, S. L. Anderson, L. Gerena, W. K. Milhous, *J. Med. Chem.* **1992,** *35,* 3023.
[53] J. Jakupovic, M. Grenz, G. Schmeda-Hirschmann, *Phytochemistry* **1988,** *27,* 2997.
[54] T. V. Leibyuk, S. A. Shevtsov, V. A. Raldugin, *Khim. Prir. Soedin.* **1990,** *4,* 556.