Artemisinin (Qinghaosu): A New Type of Antimalarial Drug

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1 Introduction

Malaria is probably older than mankind. Intermittent fevers with enlargement of the spleen have been described in medical writings from many civilizations since earliest times. In Britain the word 'ague' was used to describe the condition until the nineteenth century. The Hippocratic writings give one of the first descriptions, noting the different periods of onset – subtertian, tertian, and quartan – and calling attention to the enlarged spleen. It is possible that malaria contributed to the decline of Greek civilization. Certainly malaria was a serious problem around the city of Rome, in the Roman Campagna, and near the Pontine marshes. Within the British Isles even Scotland was affected and the English fen country was badly infected. London was plagued until 1864 when the Thames embankment was built and flooding controlled. Information about the incidence of malaria outside Europe until the sixteenth century is scanty but it has been widespread during recent times. Coastal Africa, both east and west, was malarial but a natural immunity to the especially virulent form of the malarial parasite, *Plasmodium falciparum*, exists in some 10—30% of the indigenous populations of central and western areas of Africa who carry the sickle cell trait in their red blood cells. However, European explorers, missionaries, and traders were, and still are, badly affected by this type of malaria. Malaria occurred extensively in India during colonial times. In ancient Chinese books it was recorded that malaria was widespread in areas south of the Yangtze River, especially amongst those newly immigrated from North China. It remained common in these areas, including the coastal cities of Shanghai and Kwangchow, until the beginning of the twentieth century. Now malaria is no longer a problem except on Hanan Island and in some districts along the southern border. For centuries malaria was a major problem in Central and South America, and in the rural south of the USA it was not eradicated until 1960.

2 Malarial Parasite and the Mosquito as Vector

Various writers had noted the connection between marshes with stagnant, smelly pools and malaria. Indeed, the word malaria comes from the Italian *mal'aria* or 'bad air' and the ancient Chinese term *zhangqi* means much the same thing. The reason for the connection became clear only at the end of the nineteenth century. A French army surgeon working in Algeria, Alphonse Laveran, discovered that the condition is due to members of a family of protozoal parasites named *Plasmodium* which enter red blood corpuscles when in the human blood stream. Sir Patrick Manson, while working in China, found evidence that this parasite was carried by mosquitoes and that people became infected when bitten. These ideas were confirmed by Ronald Ross, a doctor in the Indian Medical Service, and announced in 1898.

Further studies by a number of workers showed that humans are affected by four species of *Plasmodium*, three of which produce the mild forms of malaria by destroying red blood cells in peripheral capillaries and thus causing anaemia. The bouts of fever correspond to the reproductive cycle of the parasite. However, the most dangerous is the fourth species, *Plasmodium falciparum*. In this case the infected red blood cells become sticky and form clumps in the capillaries of the deep organs of the body and cause microcirculatory arrest. If this happens in the brain delirium, coma, convulsions, and death may ensue. Cerebral malaria is by far the most serious form of the infection.

Immunity to all four types of malaria is eventually acquired over a number of years as a result of frequent attacks of the condition and is maintained whilst the individual remains in the malarious area. Small children and those newly resident are therefore particularly vulnerable to attacks until their immunity is functional.

3 Eradication of Malaria

Once the role of the mosquito had been established its eradication became the key factor in the control of malaria. The draining of marshes to remove the mosquitoes' habitat is highly effective but too expensive to implement in poor countries. The use of DDT to kill mosquitoes was, at one time, widely practised but the toxic properties of DDT, its increased cost following the oil crisis of 1974, and the appearance of DDT-resistant mosquitoes have led to the re-emergence of malaria as a major world health problem. To make matters worse, strains of *P. falciparum* resistant to the principal antimalarial drug chloroquine and to some of the prophylactics have been detected in mosquitoes. Thus drugs can no longer treat all forms of malaria and it now seems unlikely that it will be possible, on a worldwide scale, to eliminate all the habitats of the mosquito by ecologically acceptable means. The size of the resulting problem can be seen from the statistics of malarial incidence in India: as a result of the eradication programme by 1961 there were fewer than 100 000 cases, by 1971 the number had risen to 1 400 000 but by 1977 this had increased catastrophically to 50 million, many cases due to infection by *P. falciparum*. There were similar increases in other parts of the world and the overall total must be at least 200 million. In the absence of an effective vaccine the only answer seems to be improved drugs for the destruction of the malarial parasite, particularly *P. falciparum*, while in the human host. In the early 1980s the need for a new antimalarial drug became a matter of great urgency as malaria is, once again, the most important of all tropical diseases.

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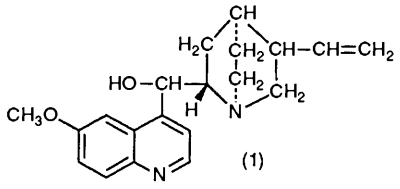
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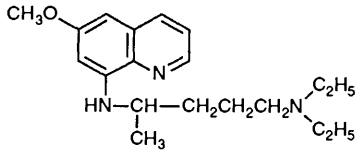
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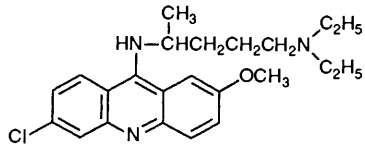
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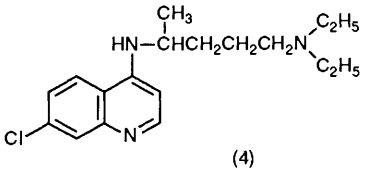
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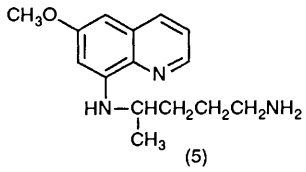
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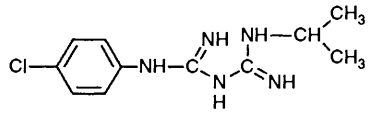
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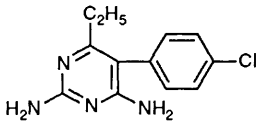
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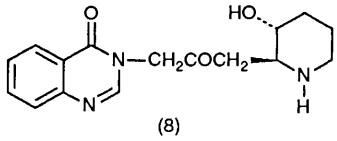
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4 Quinine as an Antimalarial Drug

The bark of the cinchona tree was used in South America by the indigenous people for the control of fevers. It was introduced into Europe by an Augustinian monk who had lived in Peru, Father Antonio de la Calancha, in the seventeenth century and proved very successful in the treatment of malaria. As it was distributed by Jesuits it became known as 'Jesuits' bark'. Cinchona bark must be one of the most successful of all herbal remedies and illustrates the value of folk medicine. The active principle, quinine, was isolated by Pelletier and Caventou in 1820 and found to be more palatable than the nauseating powdered cinchona bark. The chemical structure of quinine (1) was elucidated in 1908 and key steps in its total synthesis were achieved by Woodward and Doering in 1944.

5 Synthetic Antimalarial Drugs

During the 1920s a synthetic quinoline derivative, pamaquin (2), was found to be more effective than quinine in killing malarial parasites lodged in the liver. Also mepacrine (3) was developed as a synthetic alternative to quinine. During World War II there was a desperate need for alternatives to quinine as the Japanese cut off the supply of cinchona bark from Java and so the production of mepacrine was greatly increased. Further research led to the production of chloroquine (4) which has fewer side effects and does not turn the patient yellow. Primaquine (5) is another quinoline derivative with antimalarial properties particularly effective against *P. viva*, the cause of benign tertian fever. A biguanidine compound proguanil (6) also has powerful antimalarial properties but is more generally used as a prophylactic. A pyrimidine derivative (7), pyrimethamine, by itself is used for suppression only. For treatment it is used in combination.

Most drugs for the *treatment* of malaria are derivatives of quinoline and acridine and, until recently, there was no alternative chemotherapy. Unfortunately none of the drugs mentioned above is particularly effective against *P. falciparum*, the form of malaria now making a comeback on the world scene. There is an additional problem facing the health authorities in the countries affected: malaria is an orphan disease. It occurs in countries too poor to pay the enormous development costs of a commercial drug. Fortunately a new lead compound has appeared and early prospects are very promising.

6 Treatment of Malaria in Traditional Chinese Medicine

An important part of traditional medicine in China is the use of herbs for the treatment of disease. In this, of course, it does not differ from the medicine of medieval Europe. Collections of Chinese herbal remedies or *bencao* have been published over the centuries. The first *bencao, Shen Nong Bencao Jing*, was published in the late Han (100—200 AD) and many others appeared at intervals up to modern times. The most comprehensive is probably the *Bencao Gangmu* or 'Systematic Materia Medica' by Li Shizhen published in 1596 AD. The first pharmacopoeia (*i.e.* a volume regulating the use of drugs or *yaodian*) in Chinese was published in 1930 AD and in it the authors dismissed the *bencao* as 'nothing but waste paper'. Fortunately, since then traditional Chinese medicine has been restored to something like its former status – not instead of Western medicine but complementary – and the *bencao* seen as valuable sources of information on traditional cures tested over several thousand years. In view of the uniqueness of Chinese flora and the early invention of printing in China (*ca.* 700 AD), which means that the *bencao* are less prone to copying errors than European herbals, it is not surprising that a number of interesting new lead compounds have been obtained.

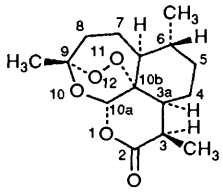
The classical remedy for malaria in traditional Chinese medicine is the root of *Dichroa febrifuga* Loureiro (*changshan* in Chinese). This material was investigated as part of the effort during World War II to find alternatives to quinine. An alkaloid, febrifugine (8), was extracted from the root and found to be 100 times more effective against *P. cynomolgi* than quinine. However, even at subtoxic levels, febrifugine is a powerful emetic and this has effectively precluded its general clinical use in the treatment of malaria.

Another traditional cure for fever, first mentioned in the *bencao* nearly 2000 years ago and many times subsequently, is the herb *qinghao* or *caohao*, *Artemisia annua* L. (sweet wormwood or annual wormwood), a weedlike plant growing over large parts of China. In the *Bencao Gangmu* it is stated rather concisely that *qinghao* 'can cure malaria, fever, and cold'. The use of *qinghao* for the treatment of malaria is also described in 'The Barefoot Doctor's Manual', a manual which did so much to improve primary health care in China. It was to this traditional herbal remedy that Chinese scientists turned in an effort to fight the resurgence of malaria.

7 Isolation of Artemisinin

Extraction of the dried leaves of *qinghao* with petroleum ether at low temperature and chromatography on silica gel with subsequent recrystallization gave fine, colourless crystals, named

qinghaosu (extract of *qinghao*) in Chinese but also given the Western name artemisinin. The yield was variable ranging from negligible quantities to almost 1% depending on the area from which the plant was collected. The formula $C_{15}H_{22}O_5$ suggested the compound to be a sesquiterpene and reaction with triphenylphosphine to give the phosphine oxide was consistent with the presence of a peroxide group. The structure of artemisinin, as well as its absolute configuration, was determined by *X*-ray diffraction as (9).[1] The lactone ring has a *trans* configuration. The most unusual feature of the chemical structure is the 1,2,4-trioxane ring which may also be viewed as a bridging peroxide group. Artemisinin is the only known 1,2,4-trioxane occurring in nature, although compounds with peroxide bridges are common, particularly in marine organisms. In extensive clinical trials in China[2] artemisinin showed promise in the treatment of otherwise drug-resistent forms of malaria, notably *P. falciparum*. This discovery has occasioned a considerable amount of research, in both China and the West, into the synthesis, biosynthesis, and biological action of artemisinin and related compounds. The rest of this review will attempt to give an account of some of that work.



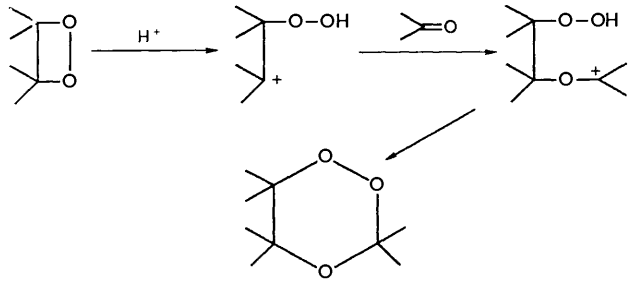
(9)

8 Nomenclature

Although the Chinese name qinghaosu, meaning extract of green plant, is attractive it is frequently misspelt. In a recent edition of a popular textbook on tropical medicine it is referred to as *Quing Hao Hsu*; in the modern *pinyin* romanization of Chinese 'q' is not followed by 'u' and 'hs' is quite different from 's'. In *qinghaosu* the 'q' is pronounced like 'ch' in 'cheat'. The systematic name is 3,6,9-trimethyl-9,10b-epidioxyperhydropyrano[4,3,2-*jk*]benzoxepin-2-one but this is hardly convenient for regular use. The name adopted by *Chemical Abstracts* is artemisinin, derived from the plant which is its source, and artemisinin will be used in this review. The systematic numbering is shown in (9), but other systems have been used.

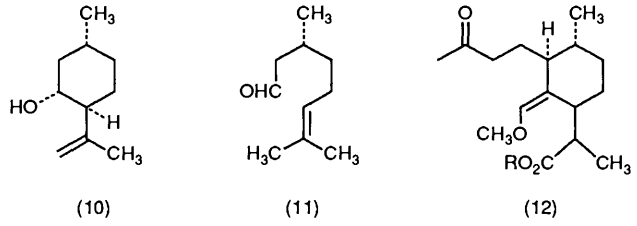
9 Total Synthesis of Artemisinin

The rather unusual structure of artemisinin has meant that the molecule constitutes a stimulating synthetic challenge and a number of successful total syntheses have been reported. In most cases the trioxane ring has been formed by addition of singlet oxygen to an olefin in the presence of a photosensitizer followed by protonation and reaction with a carbonyl compound (Scheme 1). This approach to the synthesis of trioxanes has been fully explored by Jefford and his co-workers.[3]



Scheme 1

For the application of this procedure to the synthesis of artemisinin Schmid and Hofheinz[4] started with (−)-isopulegol (10) and the synthesis was completed in ten steps. The key intermediate was a benzyloxymenthone and the photosensitizer was Methylene Blue. Zhou and co-workers[5] started with (+)-citronellal (11) and the intermediate (12) was prepared in 19 steps. Photooxidation using Rose Bengal and acidification gave artemisinin in 28% yield from (12). Avery and co-workers[6] used the cyclohexane (13) as the starting material and the peroxide bridge was introduced by the abnormal course of reaction of a vinylsilane with ozone at −78 °C. A formal stereoselective synthesis starting with (+)-car-3-ene (14) has been devised by Ravindranathan and co-workers.[7] One of the key steps was an intramolecular Diels–Alder reaction for the conversion of (15) into an epimeric mixture of ethers (16). Treatment of the mixture with MCPBA gave a single epoxide, reduction of which with LAH produced a single tertiary alcohol. The synthesis proceeded without stereochemical problems to give (17), the conversion of which into artemisinin had been accomplished in the synthetic route of Zhou *et al.*[5] mentioned above.



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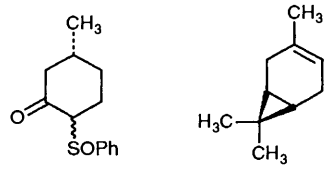

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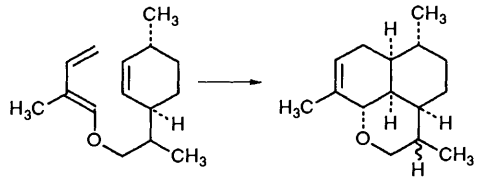

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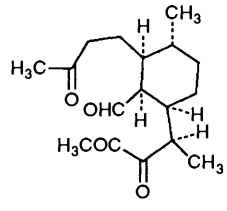


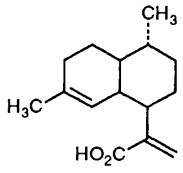
(17)

Although not a total synthesis there is an important procedure, described by Wu and Ye,[8] for the conversion of artemisinic acid (18), which is a relatively abundant constituent of *Artemisia annua*, into artemisinin by photooxidation of a cyclic enol ether in the presence of Methylene Blue followed by treatment with trimethylsilyltrifluoromethanesulfonate and regeneration of the carbonyl group at the 2-position by oxidation with ruthenium chloride–sodium periodate.

10 Chemical Reactions of Artemisinin

The most interesting aspect of artemisinin's chemistry is the stability of the peroxide bridge. Indeed, artemisinin can be

recovered unchanged from neutral solvents after several days at temperature up to 150 °C. At higher temperatures the peroxide bridge is destroyed and (19), (20), and (21) are formed, albeit in low yields.[9] A different range of products is obtained on dry heating.



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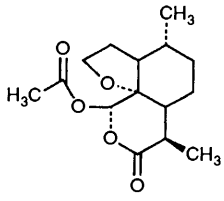

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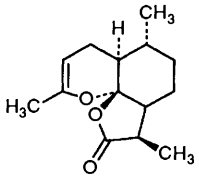

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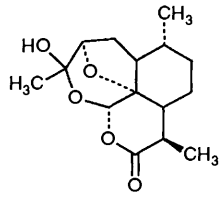

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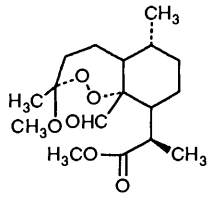
Reaction of artemisinin with acid in methanol produces mainly (22), which is converted by more concentrated acid into the diketone (23), a useful intermediate for the relay synthesis of artemisinin and its analogue. Compound (22) can be recyclized into artemisinin by TFA.[10] Artemisinin is quite sensitive to alkali and reaction with potassium carbonate results in substantial reorganization of the molecule to give, eventually, (24) as one product.[11] In terms of the medicinal uses of artemisinin the most important reaction is its reduction. Lithium aluminium hydride exhaustive reduction gives a tetrahydroxy compound (25). Reaction with hydrogen over palladium results in loss of the peroxide bridge to give 11-deoxyartemisinin (26). However, reduction with borohydride leaves the peroxide bridge intact, giving the lactol 2-hydroxy-2-deoxoartemisinin (27a).[12] This is an important intermediate in the synthesis of artemisinin analogues.



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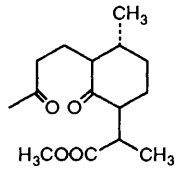

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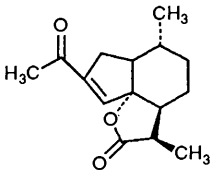

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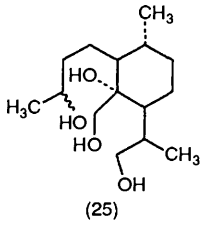

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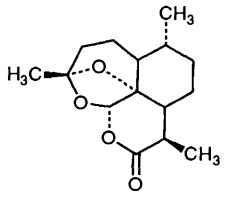
11 Derivatives and Analogues of Artemisinin

The naming of the derivatives of artemisinin is a matter of some confusion. In this review we have used the systematic numbering shown above but this may differ from that used in the original paper. The lactol (27a) has been used to prepare[13] nearly 50 derivatives [ethers (27b), esters (27c), and carbonates (27d)] of



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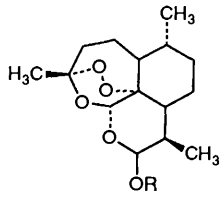
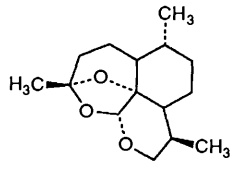


(27) (a) R = H
(b) R = alkyl
(c) R = COR′
(d) R = COOR′
(e) R = $OCOCH_2CH_2COOH$
(f) R = $OCH_2C_6H_4COOH$

artemisinin as part of a screening programme of antimalarial activity. Two other interesting derivatives of the lactol with water-solubilizing groups are artesunic acid (27e) and artelinic acid (27f).[14] The antimalarial activity of all these compounds will be discussed later. 2-Deoxo-11-deoxyartemisinin (28) has been prepared from artemisinin[15] and 11-deoxyartemisinin (26) from artemisinic acid (18) by singlet oxygenation in the presence of Methylene Blue at room temperature.[16] There has been a total synthesis of 3,6-didemethylartemisinin (29) from pyrrolidinocyclohexene and 1,4-dichloro-2-butene in 8 steps. The peroxide bridge was introduced by ozonolysis at − 78 °C with subsequent acid treatment using Amberlite 15. Similarly, 3,3a-secoartemisinin (30) has been prepared.[18]



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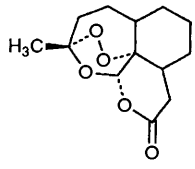

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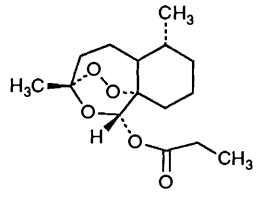
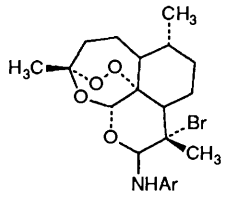


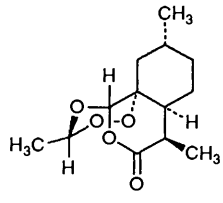
(30)

A number of amino derivatives (31) have been prepared from the lactol (27a) by elimination of the elements of water, addition of bromine to give the 2,3-dibromo compound, and subsequent reaction with the appropriate amine, both benzenoid and heteroaromatic.[19] An important derivative in attempts to understand the mechanism of artemisinin's antimalarial activity is desethanoartemisinin (32) in which the trioxane structure is retained but one of the rings has been lost. It was prepared from citronellal (11) and the sensitizer for photooxidation was Rose Bengal.[20]

Three carba-analogues of artemisinin, [(33)—(35)], have been prepared. Artemisinic acid (18) was converted into a cyclic enol ether in four steps. Reaction of this with paraformaldehyde in the presence of boron trifluoride etherate afforded (33), and oxidation of (33) with ruthenium oxide gave (34) and (35).[21]



(31)



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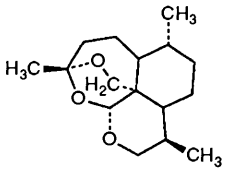

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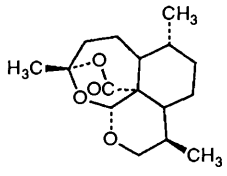

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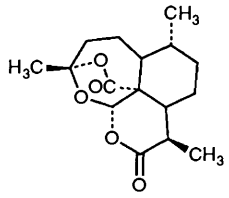
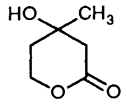


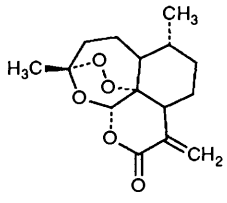
(35)

12 Biosynthesis of Artemisinin

Artemisinin appears to be unique to *Artemisia annua* and is at a maximum in the upper leaves at the beginning of budding. Labelling experiments have identified two intermediates *en route* to artemisinin: mevalonic acid lactone (36) and artemisinic acid (18).[22] It has also been established[23] that isopentenyl pyrophosphate is incorporated in artemisinin obtained from cell cultures of *A. annua*. Otherwise, little appears to be known about the biosynthetic pathway. The conversion of artemisinic acid (18) and dihydroartemisinic acid into artemisitene (37) may be significant in delineating the biosynthetic pathway.[24]



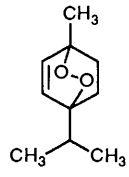
(36)



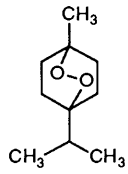
(37)

13 Antimalarial Activity of Artemisinin

It is almost certain that the crucial structure in artemisinin which gives it its antimalarial activity is the peroxide bridge. Other parts of the molecule may be modified without loss of antimalarial activity. Removal of one or two of the methyl groups at positions 3 and 6, as in (29), leaves a molecule which is still active against *P. falciparum*.[17] The lactol (27a) obtained by reduction of artemisinin, although chemically unstable, is a better antimalarial agent than artemisinin itself, indicating clearly that the carbonyl group is not the essential structure.[15] On the other hand, 11-deoxyartemisinin (26)[16] and 2-deoxo-11-deoxyartemisinin (28)[15] are not active against the malarial parasite, as neither are the carba-analogues (33), (34), and (35).[20] All these compounds lack the peroxide bridge. The converse appears also to be true. Many compounds not obviously related to artemisinin but which contain a peroxide group are antimalarial agents. Vennerstrom and co-workers[25] have examined 23 peroxides of diverse chemical structures, including di-t-butyl peroxide, ascaridole (38), and dihydroascaridole (39). Several are active *in vitro* against *P. falciparum*, although none is active *in vivo*. This suggests that the remainder of the artemisinin molecule is responsible for the delivery of the drug to the infected erythrocyte in a still active form where it can exercise its toxicity towards the parasite. However, even in compounds closely related to artemisinin the possession of a peroxide bridge is not of itself sufficient condition for antimalarial activity.[10] In this regard information on the antimalarial activity of desethanoartemisinin (32), in which the peroxide bridge has been retained but one of the rings has been lost, is awaited with interest.[20]



(38)



(39)

Although the peroxide bridge may be the crucial structure in artemisinin, the rest of the molecule has a profound effect on the *in vitro* and *in vivo* antimalarial activity of artemisinin and related compounds. The ether derivative of 2-hydroxy-2-deoxoartemisinin (27b, R = Et) is a better antimalarial agent than artemisinin itself[26] and is the form of artemisinin which is currently under commercial development; it is generally called arte-ether. Esters (27c, R′ = alkyl) are generally as effective as artemisinin but the corresponding acids (27c, R′ = H) are much less so. This may be a consequence of their lower solubility in lipids. Carbonates (27d, R′ = alkyl) are the least effective of this group of compounds.[13] Sodium artelinate [the sodium salt of (27f)] is only slightly less effective than artemisinin *in vitro* and has the advantage of water solubility and can be administered orally.[27] A number of highly effective antimalarial agents have been obtained by replacing the carbonyl group of artemisinin by a substituted amino-group (31).[18] The most potent is that with Ar = 3-fluorophenyl; the presence of bromine does not seem to have any deleterious effect.

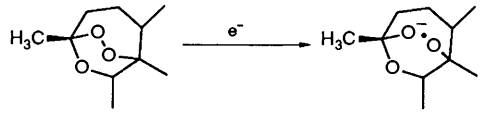
Quantum mechanical calculations give excellent correlation between calculation and experiment in cases where the structure has been determined by *X*-ray crystallography.[28] Thus it may be possible to use quantum pharmacology to explore as yet unsynthesized compounds in the search for an even better antimalarial drug.

14 Mode of Action

Artemisinin and related compounds are normally administered as a solution or suspension in oil by intramuscular injection. From studies of artemisinin it was found that absorption is rapid with a peak serum level after two hours, an elimination half life of 1.6 hours, and a mean retention time of 3.3 hours. None was detected in plasma after rectal or oral administration.[29] The action of artemisinin on the malarial parasite appears to be completely different from that of chloroquine and this may well be why artemisinin is effective against parasites which have become chloroquine-resistant.

Most research suggests that artemisinin acts by an oxidative mechanism and it effects changes in both red blood cells and in the limiting and other membranes of the malarial parasite. At concentrations much higher than those used clinically, artemisinin affects red blood cell deformability in a manner which suggests that it is acting as an efficient prooxidant.[30] At even higher concentrations artemisinin brings about complete lysis of the red blood cells.[31] The effect of artemisinin on parasite membranes after even a single dose to a mouse host is quite substantial within half an hour. There are alterations in ribosomal organization and endoplasmic reticulum. Nuclear membrane blebbing develops after one hour and segregation of the nucleoplasm after three hours. Further degenerative changes, with disorganization and death, occur from 8 hours onwards. The morphological changes in ribosomes and endoplasmic reticulum correlate in time with the *in vitro* depression of protein synthesis observed in *P. falciparum*. Similarly, the onset of nucleoplasmic segregation correlates with the development of nucleic acid synthesis inhibition. Some evidence suggests that the drug may be localized in the membranes so that changes in membrane integrity might precede the early depression of protein synthesis.[32] Changes in the phosphorus, potassium, and sodium contents of infected red blood cells occur on treatment with artemisinin consistent with alterations in the membrane.[33]

At a molecular level it is possible that the oxygen–oxygen bond of the peroxide bridge is broken due to an electron transfer with the generation of an oxygen-centred radical (Scheme 2). This radical species could be responsible for the destruction of the membranes of *Plasmodium*. Quantum mechanical calculations have shown that transfer of an electron to the peroxide moiety of artemisinin results in considerable lengthening of the oxygen–oxygen bond.[28]



Scheme 2

15 Future Prospects

It seems probable that artemisinin and its derivatives will play a substantial part in the fight against the resurgence of malaria, particularly falciparum malaria, throughout the world. In the absence of a vaccine the situation now is rather like that in Europe before the introduction of quinine. Clinical trials of arte-ether (27b, R = Et) are almost complete. Although artemether (27b, R = Me) is equally potent and both are soluble in oil, which is the normal mode of administration, arte-ether was selected for development for commercial reasons and also because metabolism in the body gives ethanol rather than the more toxic methanol. For commercial production artemisinin is obtained by extraction from cultivated *A. annua* and converted into arte-ether by reduction with sodium borohydride in methanol and subsequent reaction with ethanol and boron trifluoride etherate.[34] The more active form is the β-epimer and this can be separated from the mixture of epimers either by column chromatography or fractional crystallization. The latter is more suitable for commercial production. The Kunming Pharmaceutical Company in Southern China is already in commercial production, while the Guilin Pharmaceutical Company produces sodium artesunate (27e), another effective antimalarial agent which has the advantage of water-solubility.

But artemisinin and its derivatives have shortcomings as antimalarial agents. Although partially solved, low solubility in both oil and water is still a problem. Efficacy by oral administration is very poor and administration by injection is a problem in countries where there are inadequate medical facilities. There is also a high rate of recrudesence in treated patients. Thus there is much work still to be done in providing the world with a really successful new antimalarial drug.

In 1692 the Chinese Emperor Kangxi was cured of malaria by visiting Jesuits using cinchona bark. Today the tables have been reversed and China has provided the world with new hope in the fight against this most widespread of tropical diseases.

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16 References

The order of Chinese authors' names has been changed to that of western custom. The names of most Chinese journals are given in romanized Chinese rather than in the latinized version; *Huaxue Xuebao* is *Acta Chimica Sinica*, *Yaoxue Xuebao* is *Acta Pharm. Sinica*, and *Zhongguo Yaoli Xuebao* is *Acta Pharmacol. Sinica*. Most references to Chinese journals are to the English language editions.

1 Qinghao Research Group, *Kexue Tongbao*, 1977, **22**, 142.
2 Qinghao Antimalarial Coordinating Research Group, *Chinese Med. J.*, 1979, **92**, 811.
3 C. W. Jefford, F. Favarger, S. Ferro, D. Chambaz, A. Bringhen, G. Bernardinelli, and J. Boukouvalas, *Helv. Chim. Acta*, 1986, **69**, 1778.
4 G. Schmid and W. Hofheinz, *J. Am. Chem. Soc.*, 1983, **105**, 624.
5 Xing-xiang Xu, Jie Zhu, Da-zhong Huang, and Wei-shan Zhou, *Tetrahedron*, 1986, **42**, 819.
6 M. A. Avery, C. Jennings-White, and W. K. M. Chong, *Tetrahedron Lett.*, 1987, **28**, 4629.
7 T. Ravindranathan, M. A. Kumar, R. B. Menon, and S. V. Hiremath, *Tetrahedron Lett.*, 1990, **31**, 755.
8 Bin Ye and Yu-lin Wu, *J. Chem. Soc., Chem. Commun.*, 1990, 726.
9 X. D. Luo, H. J. C. Yeh, A. Brossi, J. L. Flippen-Anderson, and R. Gilardi, *Heterocycles*, 1985, **23**, 881; A. J. Lin, D. L. Klayman, J. M. Hoch, J. V. Silverton, and C. F. George, *J. Org. Chem.*, 1985, **50**, 4504.
10 Ying Li, Pei-lin Yu, Yi-xin Chen, Jing-li Zhang, and Yu-lin Wu, *Kexue Tongbao*, 1986, **31**, 1038.
11 Mei-yi Zeng, Lan-na Li, Shu-feng Chen, Guang-yi Li, Xiao-tian Liang, M. Chen, and J. Clardy, *Tetrahedron*, 1983, **39**, 2941.
12 Jing-ming Liu, Mu-yun Ni, Ju-fen Fen, You-you Tu, Zhao-hua Wu, Yu-lin Wu, and Wei-shan Chou, *Huaxue Xuebao*, 1979, **37**, 129
13 Ying Li, Pei-lin Yu, Yi-xin Chen, Liang-quan Li, Yuan-zhu Gai, Desheng Wang, and Ya-ping Zheng, *Yaoxue Xuebao*, 1981, **16**, 429.
14 A. J. Lin, M. Lee, and D. L. Klayman, *J. Med. Chem.*, 1989, **32**, 1249.
15 M. Jung, X. Li, D. A. Bustos, H. N. ElSohly, J. D. McChesney, and W. K. Milhous, *J. Med. Chem.*, 1990, **33**, 1516.
16 M. Jung, H. N. ElSohly, E. M. Croom, A. T. McPhail, and D. R. McPhail, *J. Org. Chem.*, 1986, **51**, 5417.
17 M. A. Avery, C. Jennings-White, and W. K. M. Chong, *J. Org. Chem.*, 1989, **54**, 1792.
18 M. A. Avery, W. K. M. Chong, and G. Detre, *Tetrahedron Lett.*, 1990, **31**, 1799.
19 A. J. Lin, Liang-quan Li, D. L. Klayman, C. F. George, and J. L. Flippen-Anderson, *J. Med. Chem.*, 1990, **33**, 2610.
20 Y. Imakura, T. Yokoi, T. Yamagishi, J. Koyama, H. Hu, D. R. McPhail, A. T. McPhail, and K. H. Lee, *J. Chem. Soc., Chem. Commun.*, 1988, 372.
21 Bin Ye and Yu-lin Wu, *Tetrahedron*, 1989, **45**, 7287.
22 Jing-jian Huang, Feng-yi Zhou, Lian-fen Wu, and Gui-hui Zhen, *Huaxue Xuebao*, 1988, 383.
23 G. J. Kudakasseril, L. Lam, and E. J. Staba, *Planta Med.*, 1987, **53**, 280.
24 R. K. Haynes and S. C. Vonwiller, *J. Chem. Soc., Chem. Commun.* 1990, 451.
25 J. L. Vennerstrom, N. Acton, A. J. Lin, and D. L. Klayman, *Drug Design Delivery*, 1989, **4**, 45.
26 Hao-ming Gu, Bao-feng Lü, and Zhi-xiang Qu, *Yaoxue Xuebao*, 1980, **1**, 48.
27 P. H. van Vianen, D. L. Klayman, A. J. Lin, C. B. Lugt, A. L. Engen, H. J. van der Laay, and B. Mons, *Exp. Parasitol.*, 1990, **70**, 115.
28 A. R. Butler and C. Thomson, unpublished observations.
29 Kai-cun Zhao, Qi-ming Chen, and Zhen-yu Song, *Yaoxue Xuebao*, 1986, **21**, 736.
30 M. D. Scott, S. R. Meshnick, R. A. Williams, D. T. Y. Chiu, H. C. Pan, B. H. Lubin and F. A. Kuypers, *J. Lab. Clin. Med.*, 1989, **114**, 401.
31 Gu Haoming, D. C. Warhurst, and W. Peters, *Zhongguo Yaoli Xuebao*, 1986, **7**, 269.
32 D. S. Ellis, Z. Li, H. M. Gu, W. Peters, B. L. Robinson, G. Tovey, and D. C. Warhurst, *Ann. Trop. Med. Parasitol.*, 1985, **79**, 367.
33 P. Lee, Z. Ye, K. van Dyke, and R. G. Kirk, *Am. J. Trop. Med. Hyg.*, 1988, **39**, 157.
34 A. Brossi, B. Venugopalan, G. L. Dominguez, H. J. C. Yeh, J. L. Flippen-Anderson, P. Buchs, X. D. Luo, W. Milhous, and W. Peters *J. Med. Chem.*, 1988, **31**, 645.