line drugs for the treatment of cerebral malaria caused by P. falciparum (197), which is otherwise fatal.

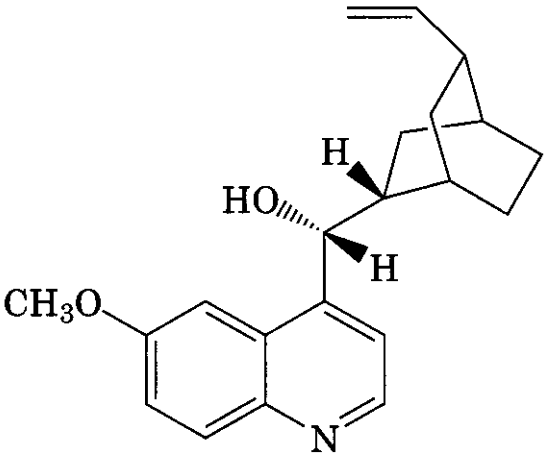
It seems highly likely (205) that most of the artemisinin found in dried plant material is formed by autoxidation after the death of the plant. From the medicinal chemist's point of view this is unimportant, but some plant biochemists might have doubts about the description of artemisinin as a "natural product." In our view, air drying in sunlight is a natural, although not a botanical, process. It is probable that many other plant-derived peroxides are formed in a similar way.

Whole plant extracts often show promising activity that may not be traceable to single components. This is obviously not true of *Artemisia annua* extracts, but it is interesting to note that other constituents, notably methoxylated flavones, have potentiating effects on the antimalarial activity of artemisinin (206).

The reported effect of artemisinin on systemic lupus erythematosus (196) is intriguing, given the history of use of quinine-type antimalarials in this disease.

8.2 Quinine, Chloroquine, and Mefloquine

The use of Cinchona bark (e.g., Cinchona *succirubra*) by South American indians to treat fevers and the subsequent importation of the bark into Europe by Jesuit priests in the 17th century is well known (207). At that time malaria was widespread, even as far north as eastern Scotland, and there was no effective treatment for "the ague." Although quinine (**159**) is not very potent or long acting, a good sample of Cinchona bark contains about 5% of the alkaloid (208). This high concentration permitted genuinely therapeutic doses of bark to be given and allowed the pure alkaloid to be isolated (209) as early as 1820. During the next 100 years quinine was the only effective treatment for malaria known to Europeans. Without quinine, life in the tropics was impossible for those without natural immunity to malaria. "One thing that was compulsory was the taking of five grains of quinine a day. . . . And if you didn't take it and got ill your salary was liable to be stopped" (210). Supplies of quinine to Europe were threatened during World War I, stimulating a major program of research into synthetic analogs.



(159) quinine

The chemical techniques available to chemists in the period 1820–1920, although improving rapidly, did not allow a structure to be proposed for quinine with any confidence: the first completely correct proposal (211) came in 1922 and was finally confirmed by total synthesis (212) as late as 1945. However, part structures were known, such as the 6-methoxyquinoline moiety, from long before, and were sufficient to allow the synthesis of mimics. The first clinically successful mimics were the 8-aminoquinolines.

In the early years of the 20th century, synthetic organic chemistry was a young discipline, largely governed by empirical rules. Progress toward synthetic analogs of complex natural structures was governed as much by synthetic feasibility as by a desire for close mimicry. The first quinine analogs were, therefore, a combination of the accessible 6-methoxyquinoline part of the quinine structure, with elements of the first successful antimicrobial agents, such as 9-aminoacridine. Nitration followed by reduction could be used to generate a number of new molecules from a variety of parent heterocycles. It is recorded (213) that 4-, 6-, and 8-aminoquinolines have antimalarial properties and, quite extraordinarily, two of these chemical classes are still used today, have quite different uses as antimalarials, and quite possibly have different modes of action.

The first of the 8-aminoquinolines to be introduced into medicine was pamaquine (**160**), not long after World War I (214). Despite greater toxicity than that of quinine, this class