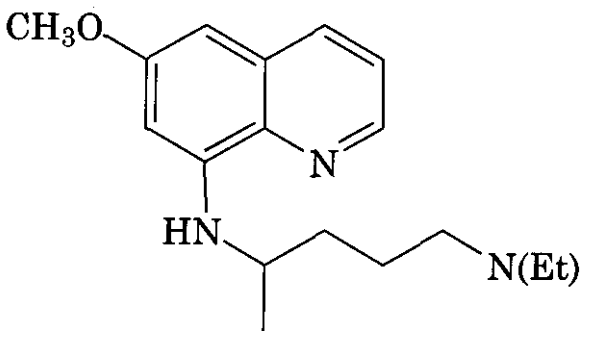
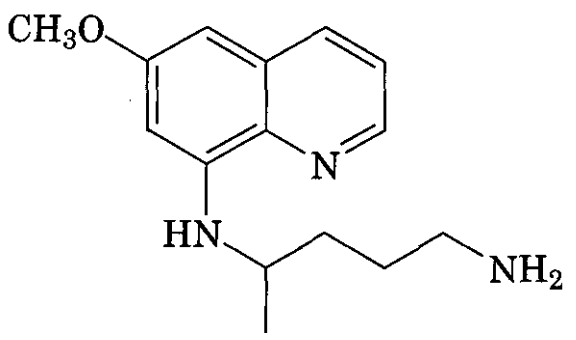
of drugs was found to have radical curative ability against the relapsing malarias. Several hundred analogs were tested during World War II and of these, primaquine **(161)** survives to the present day for short-term use as a radical curative **(215).**

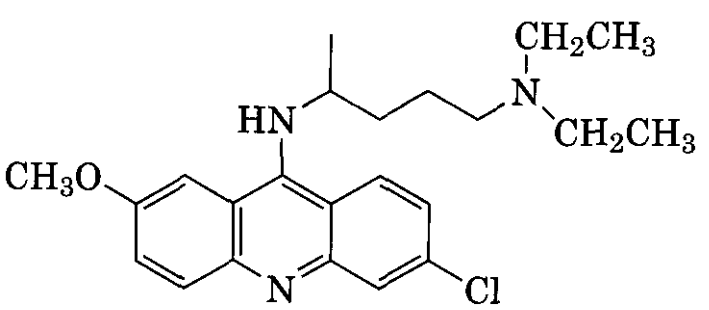


(160) pamaquine



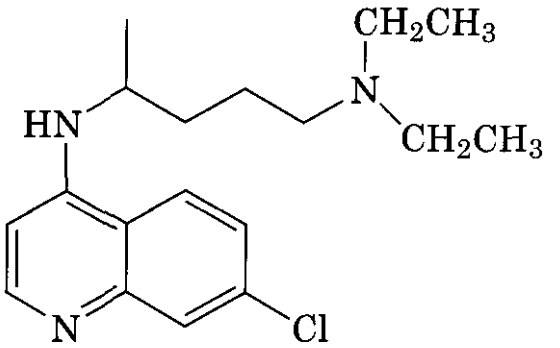
(161) primaquine

Quinacrine **(162)** is an obvious embodiment of the principle outlined above; as a derivative of both quinine and 9-aminoacridine it combined a known antimalarial with a known antimicrobial. The result was a useful, relatively nontoxic antimalarial, although it stained the skin and eyeballs yellow **(216).** Despite this side effect and a high incidence of gastrointestinal disturbance, quinacrine was widely used during World War II by European troops in East Asia. The availability of the results of medicinal chemistry research to both sides in wartime is a curious feature of antimalarial development, highlighted below.



(162) quinacrine (mepacrine)

As has been explained, the major stimulus for research into synthetic antimalarials was not so much the therapeutic inadequacy of quinine as the potential lack of availability in times of social upheaval. During World War II, the United States encouraged the planting of Cinchona in Costa Rica, Peru, and Ecuador (216). The total synthesis of quinine was too difficult in the 1940s and is unlikely to become economically viable even in the new millennium. This problem was partly overcome with quinacrine, which was used widely in World War II, although quinacrine has the defects described above. The conceptual derivation of chloroquine **(163)** from quinacrine is obvious and apparently happened twice, in Germany and the United States, the latter about **10** years after the Germans had discarded the drug as being too toxic! The story of the rediscovery of chloroquine is fascinating, as an account of human muddle and misjudgment, finally leading to an extraordinarily valuable drug **(216).**



(163) chloroquine

Over decades of sublethal exposure the resistance of **all** types of malaria has increased to a point where chloroquine no longer offers certain protection (217). With the partial exception of quinine and dihydroquinine (218), resistance to antimalarials had reached the stage at the time of the Vietnam war where more research was required. The development of mefloquine (**164**) was a continuation of the World War II effort, with a gap of about **20** years. Resistance to chloroquine had developed widely during that period, but surprisingly less so to quinine, given the obvious similarities in structure. This observation stimulated a reappraisal of quinolines, known as quinoline methanols, which bear a hydroxy group on the α-carbon of a substituent at-