We study the oxidation of clean suspended mono- and few-layer graphene in real-time by in situ environmental transmission electron microscopy. At an oxygen pressure below 0.1 mbar we observe anisotropic oxidation in which armchair-oriented hexagonal holes are formed with a sharp edge roughness below 1 nm. At a higher pressure, we observe an increasingly isotropic oxidation, eventually leading to irregular holes at a pressure of 6 mbar. In addition, we find that few-layer flakes are stable against oxidation at temperatures up to at least 1000 °C in the absence of impurities and electron beam-induced defects. These findings show first that the oxidation behavior of mono- and few-layer graphene depends critically on the intrinsic roughness, cleanliness and any imposed roughness or additional reactivity from a supporting substrate; and second, the activation energy for oxidation of pristine suspended few-layer graphene is up to 43 % higher than previously reported for graphite. In addition we have developed a cleaning scheme that results in the near complete removal of hydrocarbon residues over the entire visible sample area. These results have implications for applications of graphene where edge roughness can critically affect the performance of devices, and more generally highlights the surprising (meta)stability of the basal plane of suspended bilayer and thicker graphene towards oxidative environments at high temperature.