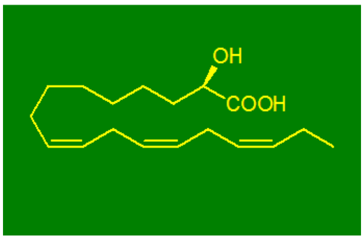
Lipid of the Month: March 2009

2-Hydroxylinolenic acid



Smith and Wolff in 1969 reported the presence of a new hydroxy acid in seeds of Common thyme (*Thymus vulgaris* L.) (1). Chemical degradation studies and NMR spectroscopy demonstrated the identity of the compound as 2-hydroxy-9(*Z*),12(*Z*),15(*Z*)-octadecatrienoic acid (2-hydroxylinolenic acid), and optical rotation data indicated that the chiral carbon had the "*R*" configuration. The mode of formation of 2-hydroxylinolenic acid in thyme seeds was not clarified, however, the presence of low levels of the odd-chain fatty acid 8(*Z*),11(*Z*),14(*Z*)-heptadecatrienoic acid (norlinolenic acid) suggested that the plant α-oxidation pathway was involved.

The α-oxidation pathway in plants was characterized by Stumpf, who showed that preparations of peanut cotelydons catalyzed the oxidation of palmitic acid into a long-chain fatty aldehyde with concomitant liberation of CO_2 (2). In subsequent work, α-oxidation of various C_n fatty acids into C_{n-1} aldehydes together with varying amounts of C_n 2-hydroxy acids and C_{n-1} fatty acids has been studied in preparations from higher plants and algae. The α-oxidation enzymes appear to operate together with aldehyde dehydrogenases and in this way provide a pathway for stepwise degradation of fatty acids into lower homologs. The involvement of 2-hydroperoxy fatty acids as intermediates in α-oxidation was suggested by experiments by Shine and Stumpf, in which inclusion of a hydroperoxide reductant (glutathione/glutathione peroxidase) to an α-oxidation system led to decreased formation of aldehydes and CO_2 but increased formation of 2-hydroxy acids (3). Conclusive evidence for 2-hydroperoxy fatty acids serving as intermediates in α-oxidation was provided ten years ago by the actual isolation of 2-hydroperoxy fatty acids by two research groups. Thus, Akakabe and coworkers obtained 2(*R*)-hydroperoxypalmitic acid in incubations of palmitic acid with the α-oxidation system of the green alga *Ulva pertusa* (4), and Hamberg *et al.* obtained 2(*R*)-hydroxylinolenic acid in incubations of linolenic acid with α-oxidation enzymes in cucumber and with a new plant-derived recombinant oxygenase (5). This enzyme was a heme-containing fatty acid dioxygenase and was given the name "α-dioxygenase". Interestingly, α-dioxygenase from germinating pea was isolated as a dual function enzyme having a 70-kD subunit of α-dioxygenase-peroxidase and a 50-kD subunit of an NAD^+-dependent oxidoreductase (6).

On the basis of these findings the complete sequence of α-oxidation in plants can be formulated as:

C_n fatty acid → C_n 2(*R*)-hydroperoxy-fatty acid → C_{n-1} fatty aldehyde → C_{n-1} fatty acid

The first step is catalyzed by α-dioxygenase whereas the second step can take place spontaneously because of the inherent chemical instability of the 2-hydroperoxides (*cf.* ref. 7). The third step is catalyzed by aldehyde dehydrogenases. It is thus clear that 2-hydroxy fatty acids are not intermediates in α-oxidation but can be formed from the 2-hydroperoxy acids in a side reaction promoted by reductase or peroxidase enzymes.

Interestingly, α-dioxygenases are not only involved in the plant α-oxidation pathway but also appear to provide products involved in plant physiology and plant pathology. Thus, the α-oxidation pathway was activated when tobacco plants are infected with microbial pathogens, and 2-hydroxy fatty acids exerted a tissue-protective effect in bacterially infected leaves (8). Additionally, a role of α-dioxygenase in plants during drought and salt-stress has been proposed (9).

2(*R*)-Hydroxy-9(*Z*),12(*Z*),15(*Z*)-octadecatrienoic acid (O-1803-17a) is isolated by Lipidox from a natural source. Other α-oxidation products such as 8,11,14-heptadecatrienal and norlinolenic acid are also available.

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