[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, STATE UNIVERSITY OF IOWA]

Antioxidants and the Autoxidation of Fats. XII. The Antioxidant Properties of Tocopherols, Hydroxychromans, Hydroxycoumarans and Related Compounds[1]

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The sterol-free unsaponifiable fraction of wheat germ, palm, and cottonseed oils and the tocopherols[2] isolated from such concentrates stabilize animal fats and oils against oxidative rancidity. The effective phenolic stabilizers of fat contain at least two hydroxyls in ortho or para positions,[3] whereas it has long been known that vitamin E (the tocopherols) contains only the hydroxyl group.[4]

The free hydroxyl of the tocopherols is essential for their antioxygenic action[5]; the heterocyclic oxygen provides the para configuration and is also essential as shown by the observations here reported on the parent hydroxy chromans and related compounds.

Their antioxygenic activity was determined on lard and other fat substrates by the oxygen absorption method.[6] The synthetic 6-hydroxychromans,[7] including α-, β-, γ-tocopherols, 5,7-dimethyltocol, 6-hydroxychromens, 5-hydroxycoumarans, 5-hydroxycoumarones and 5-hydroxyisocoumaranones (thirteen compounds were tested) are effective stabilizers for lard, the methyl and ethyl esters of lard fatty acids, highly purified unsaturated fatty acids and their esters and for 9,10-octadecene. The concentration of the antioxidants was 0.02 to 0.10%; their antioxygenic indices[8] ranged from 27 (for 6-hydroxy-2,2,4-trimethylchroman) to 3 (for α-tocopherol and 5-hydroxyisocoumaranone). The 6-hydroxycoumarins, dihydrocoumarins and methoxycoumaranones (13 substances in all were tested) are devoid of antioxygenic properties.

With one exception the desoxy forms (2,2,5,7,8-pentamethylchroman, 2-methyl- and 2,2,4,6,7-tetramethylcoumaran) were inactive, thus further establishing the indispensability of the aromatic hydroxyl. The exception was 3-phenyl-isocoumaranone (index 8). This compound exists partly in the enolized form[9]; when its labile hydrogen is replaced by a phenyl group, as in 3,3-diphenyl- or 5-hydroxy-3,3-diphenyl-isocoumaranone the antioxygenic action is lost. The unexpected antioxidant activity of the allophanates of tocopherols and phenolic inhibitors[2] may likewise be explained by enolization of one of the hydrogen atoms of the allophanyl group.

The stabilizing action of hydroquinones and benzoquinones is decreased and finally lost with progressive nuclear methylation. Trimethyl- and tetramethyl-hydroquinones, their corresponding quinones, the tocohydroquinones and tocoquinones are all inactive. In contrast, nuclear methylation of the 6-hydroxy chroman series, although it progressively lessens, does not destroy the antioxygenic action; the heterocyclic ring tends to nullify the effect of nuclear alkylation. α-Tocopherol is less effective than the dimethyltocols; the antioxygenic action of the dimethyltocols and dimethylhydroquinones varies with the position of the substituent methyl groups.

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Summary

The antioxygenic action of hydroxychromans, tocopherols and related compounds on animal fats and related ethenoid substances has been studied with reference to the molecular configuration responsible for their stabilizing action.

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(1) Presented before the Organic Division of the American Chemical Society, Detroit meeting, September, 1940.

(2) Olcott and Mattill, THIS JOURNAL, **58**, 1627 (1936); Olcott and Emerson, *ibid.*, **59**, 1008 (1937).

(3) Mattill, *J. Biol. Chem.*, **90**, 141 (1931); Olcott, THIS JOURNAL, **56**, 2492 (1934).

(4) Drummond, Singer and MacWalter, *Biochem. J.*, **29**, 456 (1935); Olcott, *J. Biol. Chem.*, **110**, 695 (1935).

(5) Olcott and Mattill, *ibid.*, **104**, 423 (1934); Isler, *Helv. Chim. Acta*, **21**, 1756 (1938).

(6) French, Olcott and Mattill, *Ind. Eng. Chem.*, **27**, 724 (1935).

(7) All of the active substances mentioned were synthesized in this Laboratory when not obtainable on the market. Desoxypentamethylchroman, desoxytetramethylcoumaran and additional samples of some of the other compounds were generously furnished by Professor L. I. Smith of the Univeristy of Minnesota, to whom the author is indebted for his friendly interest. Dr. R. L. Shriner of the University of Illinois kindly supplied samples of various coumaran-3-ones.

(8) The ratio of the induction period in hours of the stabilized fat to that of the unstabilized fat.

(9) Löwenbein and Folberth, *Ber.*, **58**, 610 (1925).