VITAMIN E OXIDATION WITH FREE RADICAL INITIATORS. AZOBIS-ISOBUTYRONITRILE

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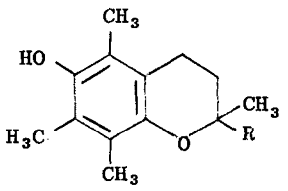
Oxidation of dl-α-tocopherol (Skinner, 1963), with various inorganic oxidizing agents such as silver nitrate, ferric chloride, gold chloride and alkaline ferricyanide has been shown to produce a variety of products. The free radical initiated oxidation of α-tocopherol has been investigated by Inglett and Mattill using benzoyl peroxide and bis(m-chlorobenzoyl)peroxide (Inglett, 1955), and more recently by Dürkheimer and Cohen (Dürkheimer, 1962), using tri-t-butylphenoxyl radicals.

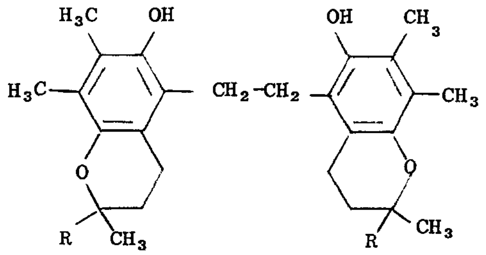
The possibility of a free radical initiated oxidation of vitamin E in the body and the likelihood of free radical initiated oxidation being of importance in its role as a naturally-occurring antioxidant in vegetable oils led us to study the effect of free radicals on both dl-α-tocopherol and its model, 6-hydroxy-2,2,5,7,8-pentamethylchroman (Ia).

Previously (Skinner, 1963), the reaction of Ia with azobisisobutyronitrile in refluxing benzene or dioxane was shown to yield the dihydroxy-dimer (IIa). We have isolated and identified the other major product of treatment of Ia with azobisisobutyronitrile. This product was shown to be the cross coupling product (IIIa) between isobutyronitrile radicals and the 6-chromanoxy radical from Ia. The product was detected by the use of silica gel G thin layer chromatography using chloroform as the developing solvent and ferric chloride--ferricyanide spray (blue color) for spotting (R_f; Ia, 0.44; R_f, IIIa 0.54; R_f, IIa, 0.34). Isolation



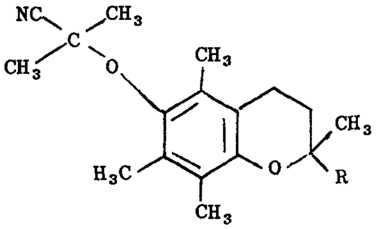
Ia, R = CH_3

Ib, R = $C_{16}H_{33}$



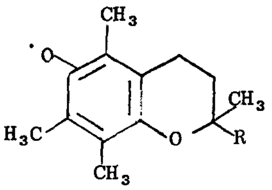
IIa, R = CH_3

IIb, R = $C_{16}H_{33}$



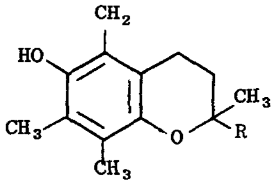
IIIa, R = CH_3

IIIb, R = $C_{16}H_{33}$



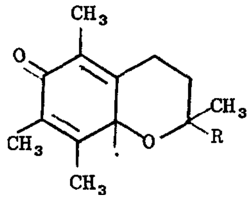
IVa, R = CH_3

IVb, R = $C_{16}H_{33}$



Va, R = CH_3

Vb, R = $C_{16}H_{33}$



VIa, R = CH_3

VIb, R = $C_{16}H_{33}$

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of IIIa was accomplished by chromatographing a petroleum ether (b.p. 30-60°) solution of the reaction mixture on a Schlesinger silica gel column and eluting with benzene. Recrystallization of IIIa from methanol-water afforded an analytically pure sample, m.p., 68-69°, absence of C=O and OH in the infrared absorption spectrum; calculated for $C_{18}H_{25}NO_2$: C, 75.3; H, 8.72; N, 4.89, molecular weight, 287; found: C, 75.6; H, 8.79; N, 5.00; molecular weight, 296 in benzene by osmometry.

When 1.0 g. of Ia in 200 ml. of benzene was refluxed with 0.5 g. of azobisisobutyronitrile for 17 hours, the yield of IIIa was 46%. A considerable amount of the starting chroman was recovered unchanged and much of the catalyst coupled after decomposition to yield tetramethylsuccinodinitrile. Small quantitites of a slowly moving material (R_f, 0.10) having C=O absorption (5.80, 5.90 μ) in the infrared were also obtained but sufficient quantities could not be purified for structural studies.

When dl-α-tocopherol (Ib) was used in place of Ia in the reaction and the products were chromatographed on a column of Schlesinger silica gel, the corresponding vitamin E derivatives (Ib) and (IIIb) were isolated. Refluxing 2.0 g. of dl-α-tocopherol in 200 ml. of benzene with 1.0 g. of azobisisobutyronitrile for 16 hours yielded a thick sirup after removal of tetramethylsuccinodinitrile which was insoluble in petroleum ether (b.p. 30-60°). Column chromatography of this sirup, on silica gel, yielded 500 mg. of compound IIIb and 100 mg. of IIb. Considerable unreacted dl-α-tocopherol was recovered. An analytical sample of IIIb was obtained by elution of the chromatographic column with petroleum ether-benzene (1:1); infrared absorption spectrum showed the absence of OH and C=O; thin layer chromatography using silica gel G and petroleum ether-$CHCl_3$ (2:1); R_f, 0.56; dl-α-tocopherol; R_f, 0.33; dihydroxydimer, R_f, 0.12; calculated for $C_{33}H_{55}NO_2$; C, 79.6; H, 11.1; n, 2.82. Found: C. 79.6; H, 11.4; N, 2.83.

The dihydroxydimer (IIb) was identified by comparison of its infrared absorption and silica gel thin layer behavior with an authentic sample (1) using benzene or petroleum ether-$CHCl_3$ (2:1) as developing solvents.

Both the chromanoxy radical (IV) and the isomeric 5-benzylic radical (V) are of importance in free radical induced reactions of vitamin E and model 6-hydroxy-chromans. Work currently under way in these laboratories using other free radical initiators has confirmed this fact and also implicated the isomeric radical VI.

It is interesting that under the conditions of reaction used here that no dl-α-tocopherylquinone is produced. Dürkheimer and Cohen (Dürkheimer, 1962) also found no α-tocopherylquinone in their products from the free radical oxidation of α-tocopherol using tri-t-butylphenoxyl radicals. However, Inglett and Mattill (Inglett, 1955) reported the production of α-tocopherylquinone from α-tocopherol when benzoylperoxide was used as the initiator of the oxidation. We are currently reinvestigating the latter reaction.

REFERENCES

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Inglett, G. E. and Matill, H. A., J. Am. Chem. Soc. 77, 6552 (1955).

This is paper VI of a series. The two preceding papers are: Skinner, W. A. and Alaupovic, P., Science 140, 803 (1963); Skinner, W. A. and Alaupovic, P., J. Org. Chem. 28, 2854 (1963).

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