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Short Communication

Selenium Carotenoids 2.† Synthesis of ε,ε-Carotene-3,3′-dione from Rhodoxanthin

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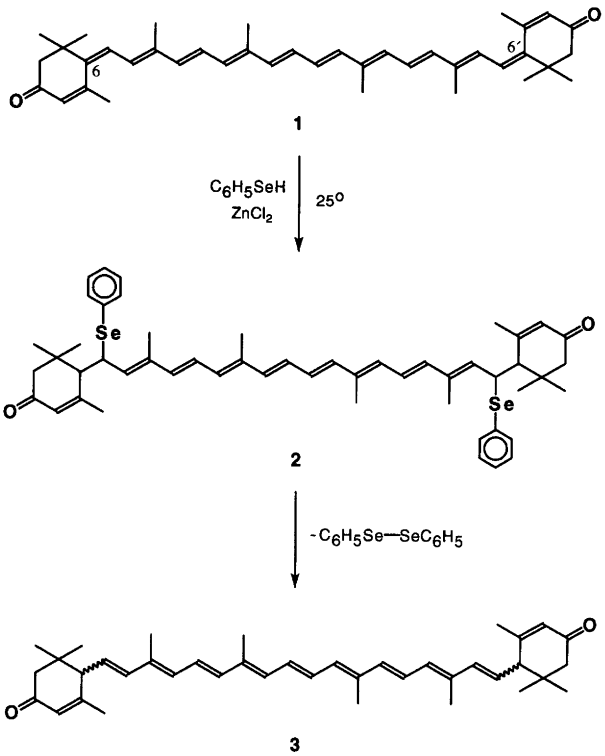
In connection with the synthesis of selenium carotenoids[1] we were interested in selenoketals. With common carotenoid diones such as canthaxanthin and rhodoxanthin (**1**) the selenoketalisation reaction should, in principle, allow the introduction of four selenium atoms per carotenoid molecule. In this way it was hoped to combine the physical and biological functions of both selenium and carotenoids.[1,2] However, canthaxanthin did not react and the attempted selenoketalisation of rhodoxanthin (**1**) led to ε,ε-carotene-3,3′-dione (**3**).

α,β-Unsaturated carbonyl compounds have been transformed into selenoketals, whereby 1,4-addition products were encountered as by-products.[3] When canthaxanthin was treated with benzeneselenol[3] and $ZnCl_2$, no reaction took place. Rhodoxanthin (**1**), however, under the same conditions slowly formed a yellow major product and three minor products. The mass spectrum of the predominant product, measured immediately after work-up of the reaction mixture, showed a molecular ion corresponding to $C_{52}H_{62}O_2Se_2$ and a fragment ion compatible with $C_{46}H_{56}O_2Se$ ($M^+ - C_6H_5SeH$) with characteristic patterns consistent with the calculated isotopic contribution of two and one selenium atoms, respectively.

The products were purified by preparative TLC prior to the measurements of NMR and VIS spectra. The VIS spectrum (λ_{max} and fine structure) was compatible with an aliphatic nonaene chromophore[4] and identified by MS and ^1H and ^{13}C NMR spectra as ε,ε-carotene-3,3′-dione (**3**). In the ^1H NMR spectrum of the main product no phenyl protons could be detected.

Apparently, the initially obtained phenylseleno compound was an unstable intermediate,[3] which had reacted during the purification procedure. The reaction from rhodoxanthin (**1**) to ε,ε-carotene-3,3′-dione (**3**) via a diseleno intermediate (**2**) is rationalized in Scheme 1. Based on the nucleophilic character of the selenide anion, a Michael addition is assumed to occur.[3] Because of steric hindrance at C(5),C(5′) the normally favoured 1,4 (conjugate) addition of the selenide may be difficult and therefore the 1,6 addition product **2** could be formed preferentially. The diseleno *retro*-carotenoid **2** apparently expels diphenyl diselenide,[3] providing the dione **3**. This



Scheme 1. Reaction of rhodoxanthin (**1**) with benzeneselenol. Only the 6,6′-*cis* isomer of **1**[12] is given.

† Part 1: Ref. 1.
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reaction is probably the first example of selenium-mediated synthesis in carotenoid chemistry and bears some analogy with the synthesis of carotenoids via sulfones.[5]

ε,ε-Carotene-3,3′-dione (**3**) is a naturally occurring carotenoid, the three optical isomers of which have been encountered in hen's egg yolk,[6] in the eggs of dolphin and flying fish,[7,8] in plants and in the eyes of reptiles.[9] Dione **3** is an *in vivo* carotenoid oxidation product in humans[10] and the intermediate in the metabolic interconversion of lutein and zeaxanthin.[6] The total synthesis of the dione **3** has been achieved via ε,ε-carotene-3,3-diol.[11]

Experimental

General methods[1]. Synthetic rhodoxanthin (**1**) (66.3 mg, 0.11 mmol, 93% all-*trans*,[12] ^{1}H NMR evidence) was dissolved in CH_2Cl_2 (4 ml) and benzeneselenol (48 μl, 0.45 mmol) and $ZnCl_2$ (3.2 mg, 0.02 mmol) were added.[3] The mixture was stirred for 47 h at 25°C after which a further 20 μl benzeneselenol were added. After 65 h the products were separated by flash chromatography with gradient elution (heptane–acetone mixtures). Three minor products were separated from the predominant selenocarotenoid **2**. R_F 0.54 [R_F **1** 0.45 (40% acetone–heptane)] MS (IP 70 eV; 210°C, *m/z*): 878 (*M* for ^{80}Se; Se_2-isotopic pattern), 722 (Se-isotopic pattern, $M - C_6H_5SeH$), 564 (722 – C_6H_5SeH), 472 (564 – 92), 458 (564 – 106), 427 (564 – 137).

Attempted purification of the selenocarotenoid **2** by prep. TLC (Merck 60 G) gave 2.7 mg (4%) (6*RS*,6′*RS*)-ε,ε-carotene-3,3′-dione (**3**). R_F 0.50; VIS (CH_2Cl_2): 445, 474 nm, % III/II = 66; IR (KBr, film): 1718, 1664 cm^{-1}; ^{1}H (500 MHz), ^{13}C (125 MHz) NMR and mass spectra were in agreement with published data.[8,13]

Canthaxanthin did not react with benzeneselenol under the same conditions as employed for rhodoxanthin.

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