

Synthetic Sulfur Carotenoids III:[†] Carotenoid Thiones – First Preparation and Spectroscopic Properties

Hans-Richard Sliwka* and Synnøve Liaen-Jensen

Institute of Organic Chemistry, Norwegian Institute of Technology, University of Trondheim-NTH, N-7043 Trondheim-NTH, Norway

Sliwka, H.-R., Liaen-Jensen S., 1994. Synthetic Sulfur Carotenoids III.* Carotenoid Thiones – First Preparation and Spectroscopic Properties. – Acta Chem. Scand. 48: 679–683 © Acta Chemica Scandinavica 1994.

The preparation of carotenoid thiones has been investigated. β,β -Caroten-4-thione, 4'-thioxo- β,β -caroten-4-one and 3'-thioxo-4',5'-didehydro-4,5'-retro- β,β -caroten-3-one were synthesized from echinenone, canthaxanthin and rhodoxanthin respectively. Characteristic spectroscopic properties of the polyene thiones are discussed and potential applications are outlined.

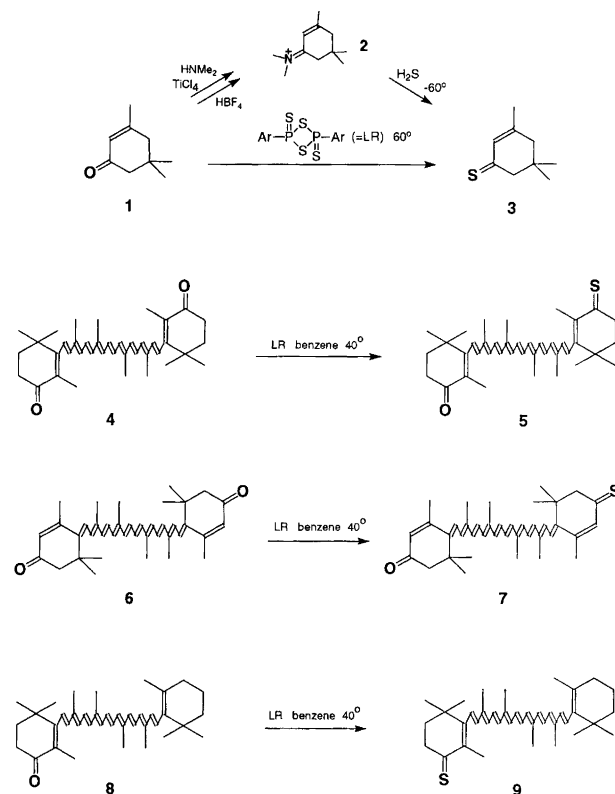
A characteristic property of thiones is their capacity to act as radical traps¹ and to quench $^1\text{O}_2$.² These properties are shared with carotenoids,^{3–5} which, in addition, may serve as cancer-preventive and immunoactive agents.⁶ For unnatural, synthetic carotenoid thiones the radical scavenging, the $^1\text{O}_2$ quenching and the prophylactic activity may possibly increase, compared with the parent compound.

There has been a growing interest in specifically designed push-pull polyenes based on carotenoids.^{7–10} The affinity of the electron-attracting sulfur in thioxo carotenones¹¹ towards metals may facilitate the preparation of monomolecular monolayers on surfaces such as Au, Ag, Cu^{12–14} for conductivity measurements. Carotenoid thiones might furthermore be useful in determining the obscured S_1 and T_1 transitions of polyenes^{15,16} and for studies of prosthetic group – apoprotein interactions.¹⁷ In view of their potential physical and biological properties and, in conjunction with our preparation of carotenoid thiois, ^{18,19} the synthesis of carotenoid thiones was of interest.

Results and discussion

Several thionation reactions^{20–29} were found inefficient for carotenones. Successful synthesis of carotenoid thiones was based on the Lawesson reaction.³⁰ Isophorone (**1**), canthaxanthin (**4**), rhodoxanthin (**6**) and echinenone (**8**) (Scheme 1) all reacted promptly with Lawesson's reagent³¹ [2,4-bis(*p*-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiaphosphetane] in benzene at 40 °C

to give the monothiones **3**, **5**, **7** and **9** in 7–56% yields. The carotenoid thiones **5**, **7** and **9** decomposed slowly on storage at –18 °C under N_2 , but appeared to be more stable than thione **3**.



Scheme 1.

[†] For parts I and II see Refs. 18 and 19.

* To whom correspondence should be addressed.

The described mild and fast synthesis, based on commercially available carotenones, provides a straightforward preparation of polyene thiones.

Spectroscopic properties. Compared with the corresponding carotenones, the λ_{\max} in the electronic spectrum of the carotenoid thiones was bathochromically shifted by 12–32 nm (solvent dependent), indicating an increased delocalisation of the π -electrons,³² as well as a lower-energy π - π^* transition. The violet colour of the thione **3** may be explained by the weak, long wavelength contribution of the n - π^* transition.³³ In the red (**5**, **9**) or violet (**7**) carotenoid thiones this excitation is submerged within the intense π - π^* transition of the polyene chain conjugated with the π -electrons of the carbon-sulfur double bond. This results in a broad absorption band tailing into the blue spectral region (Fig. 1). Blue carotenoids³⁴ originate normally from ionic³⁵ or charge-transfer complexes³⁶ and from aggregates.³⁷ The bathochromic shift of the thioxo ketone **5** and the monothione **9** was of the same order, confirming the conversion of only one keto group into a thione group in compound **5** (Table 1). In contrast with the carotenones the VIS spectra of the carotenoid thiones showed a stronger solvent dependence (Table 1). Apparently, the observed colour change implies that the overlapped n - π^* transition of the C=S group influences predominantly the solvatochromic effect.³⁸

In the IR spectrum the thione stretching vibration for isophorhione (**3**) at 1096 cm^{-1} was shifted to 1145 cm^{-1} in the carotenoid thiones **5**, **7**, **9**, compatible with a slight stabilization of the carbon-sulfur double bond in the carotenoid thiones.

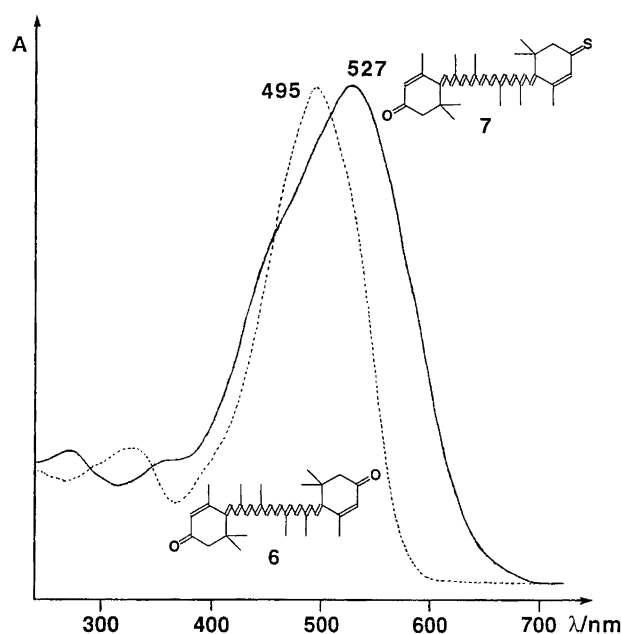


Fig. 1. VIS spectra of rhodoxanthin (**6**) and the thioxo ketone **7** in CH_2Cl_2 .

Table 1. Absorption (λ_{\max}/nm) and solvatochromic effect (Δ/nm) of carotenoid thiones **5**, **7**, **9** relative to the ketones **4**, **6**, **8**.

Solvent	5	4	Δ	7	6	Δ	9	8	Δ
CH_2Cl_2	496	476	20	527	495	32	490	467	23
Benzene	492	480	12	521	494	27			
EPA ^a				515	485	30	476	456	20
Et_2O -EtOH				503	490	13			
Hexane	476	Not soluble							

^a Ethanol-isopentane-ether 2:5:5.

The $^{13}\text{C}=\text{S}$ NMR spectral signals of the thioxocarotenones showed low intensity compared with the $^{13}\text{C}=\text{O}$ resonance, in line with different relaxation times T_1 for the keto and thione group. A linear relationship between $^{13}\text{C}=\text{O}$ and $^{13}\text{C}=\text{S}$ chemical shifts has been observed, and equations have been derived to predict the $^{13}\text{C}=\text{S}$ value.³⁹ Applying the formula for dithioesters, the calculated values for the thiones **3** and **7** agreed with the experimental signals. However, none of the established equations gave correct data for the thiones **5** and **9** (Table 2). A similar relationship between $^{13}\text{C}=\text{O}$, $^{13}\text{C}=\text{S}$ NMR chemical shifts and with λ_{\max} has been reported for unconjugated ketones and thiones.⁴⁰ A plot of the NMR and λ_{\max} data of the enones and enethiones (**4**-**9**) showed no correlation.

Experimental

General methods. General precautions for work with carotenoids were taken.⁴¹ After reaction the products were absorbed onto silica gel, dried *in vacuo* and separated by flash chromatography on silica gel with heptane-acetone mixtures, followed by further purification on preparative TLC silica plates. R_F values were determined on analytical TLC silica plates. For the mass spectra [IP 70 eV, 210°C] and IR spectra (CD_2Cl_2) only prominent or diagnostically useful peaks and absorptions are reported. ^1H (400 or 500 MHz) and ^{13}C (100 or 125 MHz) NMR spectra were recorded in CDCl_3 , if not otherwise stated, and interpreted in comparison with data of related compounds.^{42,43}

Table 2. Relationship between $^{13}\text{C}=\text{O}$ and $^{13}\text{C}=\text{S}$ NMR chemical shifts of the conjugated ketones **1**, **6** and thiones **3**, **7**.^a

C=O found CDCl_3	C=S calc.	C=S found CDCl_3	Difference C=S calc. - found
199.8 (1)	239.6 (3)	236.9 (3)	2.7 (3)
198.8 (6)	238.3 (7)	232.7 (7)	5.6 (7)

^a $\delta_{(\text{C}=\text{S})} = 1.31 \cdot \delta_{(\text{C}=\text{O})} - 22.1$ (Ref. 39).

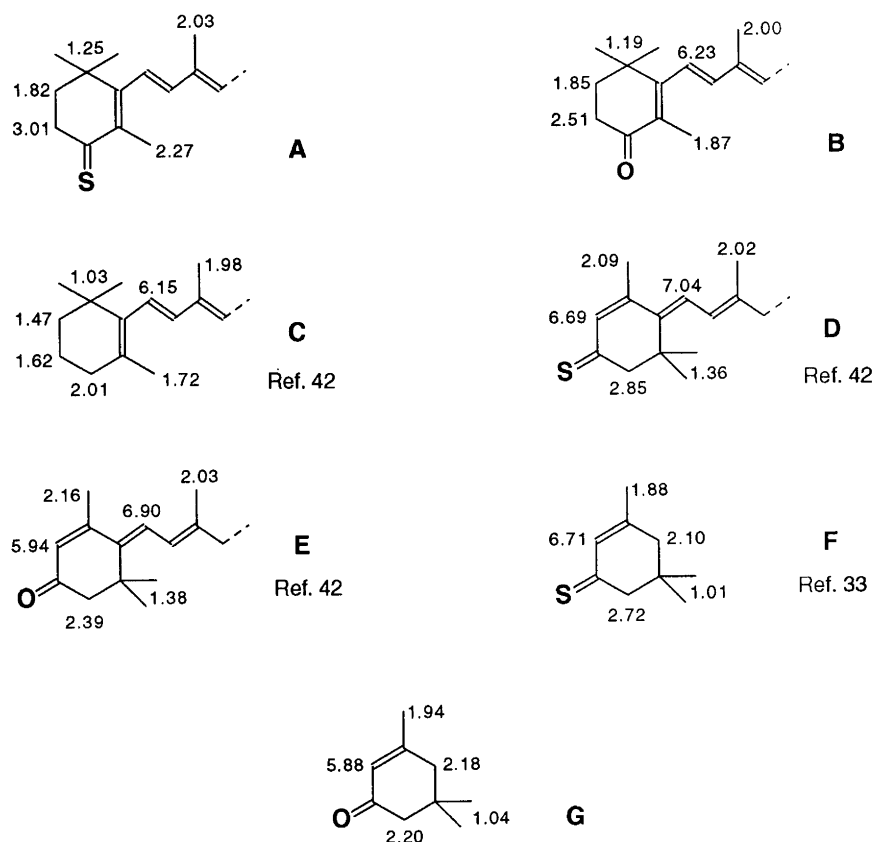
^1H NMR (δ) ^{13}C NMR (δ)

Fig. 2. ^1H (400 or 500 MHz) and ^{13}C (100 MHz) NMR data of ketones and thiones in CDCl_3 .

3,5,5-Trimethyl-2-cyclohexenethione (**3**). Isophorone (**1**) (1.5 ml, 12 mmol) and 2,4-bis(*p*-methoxyphenyl)-2,4-thioxo-1,2,3,4-dithiaphosphetane, Lawesson's reagent,³¹ (2.25 g, 6 mmol) were stirred in toluene (10 ml) under N_2 at 60°C for 45 min. Chromatographic work-up yielded the thione **3**. R_F **3** 0.47, R_F **1** 0.14 (10% acetone–heptane); UV–VIS (CH_2Cl_2) λ_{max} 304, 535, 562 nm, **1** λ_{max} 308 nm, cf. Ref. 33; IR 1096 cm^{-1} ; MS in accordance with Ref. 33; NMR Fig. 2, F,H.

Iminium salt **2** (0.4 g, prepared according to Ref. 44) was dissolved in DMF (10 ml). After addition of piperi-

dine (0.01 ml), H_2S was bubbled into the solution at -60°C for 1 h.²¹ Extractive and chromatographic work-up gave the thione **3**.

4'-Thioxo- β,β -caroten-4-one (**5**). Canthaxanthin (**4**) (104 mg, 0.18 mmol) and Lawesson's reagent (90 mg, 0.2 mmol) were stirred in benzene (10 ml) at 40°C for 4 h. Chromatographic work-up gave **5** (23 mg, 22%). R_F **5** 0.52, R_F **4** 0.42 (30% acetone–heptane). HPLC (RP-18 column, 25 cm, $5\ \mu\text{m}$, eluent CH_3CN 70%, CH_2Cl_2 20%, MeOH 10% v/v) t_R **5** 3.6 min, t_R **4** 2.9 min, better sepa-

ration on silica, 25 cm, 5 μm , (eluent: hexane 76%, isopropyl acetate 17%, acetone 7%, MeOH 0.1% v/v) t_{R} **5** 2.9 min, t_{R} **4** 4.3 min; VIS Table 1; IR 1145 cm^{-1} ; MS (m/z) 580 (*M*), 564, 548 (*M* - 32), unspecific fragmentation, cf. Refs. 45, 46; ^1H NMR Fig. 2, A,B; ^{13}C NMR δ 199.4 (C=O), 221.7 (C=S).

3'-Thioxo-4',5'-didehydro-4,5'-retro- β,β -caroten-3-one (**7**). Rhodoxanthin (**6**) (46.2 mg, 0.08 mmol, 93% all-*trans*,⁴⁷ ^1H NMR evidence) and Lawesson's reagent (40 mg, 0.08 mmol) were stirred at 40°C for 1 h. Chromatographic work-up gave **7** (27 mg, 56%). R_{F} **7** 0.47, R_{F} **6** 0.35 (30% acetone-heptane); VIS Table 1 and Fig. 1; IR 1145 cm^{-1} ; MS (m/z) 578 (*M*), 562, 548, 546 (*M* - 32); ^1H NMR Fig. 2, D,E; ^{13}C NMR δ 198.8 (C=O), 232.7 (C=S), CCl_4 195.5 (C=O), 231.7 (C=S).

β,β -Carotene-4-thione (**9**). Echinonone (**8**) (22 mg, 0.04 mmol) and Lawesson's reagent (10 mg, 0.025 mmol) were stirred in benzene (5 ml) at 40°C for 4 h. Chromatographic work-up gave two products. The main product was the thione **9** (2 mg, 7%). R_{F} **9** 0.72, R_{F} **8** 0.55 (30% acetone-heptane); VIS Table 1; MS (m/z) 566 (*M*), 536, 534 (*M* - 32), 474 (*M* - 92); ^1H NMR Fig. 2, A,C; ^{13}C NMR δ 221.7 (C=S).

Attempted synthesis of carotenoid thiones with other reagents. Bis(tricyclohexyltin) sulfide,²⁰ P_2S_5 ,²⁷ bis(trimethylsilyl) sulfide²⁸ and Lawesson's reagent in 1,2-dimethoxyethane²⁹ gave no or insufficient amounts of carotenoid thiones from the ketones **4**, **6** and **8**. Thione synthesis via the corresponding thioketals^{24,48,49} or the hydrazones, enamines and phenylimines²³ were unsuccessful.

Acknowledgements. We thank E. Palmadottir and H. N. Nissen for experimental assistance, J. Krane for the 500 MHz NMR measurements and B. Olsrød for the mass spectra. Samples of synthetic echinenone, canthaxanthin and rhodoxanthin were kindly provided by Dr. H. J. Mayer, Hoffmann-La Roche, Basel. This work was partly supported by a research grant from Hoffmann-La Roche to S. L.-J.

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Received February 21, 1994.