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Synthetic Nitrogen Carotenoids: Optically Active Carotenoid Amines

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Abstract: (3*R*,3′*R*)-Zeaxanthin was reacted with hydrazoic acid in a Mitsunobu reaction to yield azides with inverted configuration. Reduction of these azides with hydrogen telluride provided (3*S*)-2′,3′-didehydro-β,β-caroten-3-amine, (3*R*,3′*S*)-3′-amino-β,β-caroten-3-ol and (3*S*,3′*S*)-β,β-carotene-3,3′-diamine.

Introduction

In nature ketocarotenoids are bound as prosthetic groups to proteins, forming a variety of N-containing carotenoproteins. However, natural carotenoids containing nitrogen attached to the carbon skeleton have so far not been encountered. On the other hand, various carotenoids with N-containing functional groups have been prepared, including carotenoid oximes, known since 1933[1] as well as hydrazones, semicarbazones[2], phenylimines[3] and nitriles.[4] Recently, nitrogen carotenoids have attracted interest as possible biologically active compounds and as organic conductors. Therefore, several pyridino,bipyridino, nitrilo and nitro carotenoids have been synthesized.[5-7] In the nitrogen containing carotenoids hitherto synthesized the nitrogen is part of functional groups unlikely to occur in nature. The amino function, however, is common in nature and frequently associated with biological activity. Moreover, the amino group may facilitate the preparation of molecular monolayers on metal surfaces such as Ti, Ag, Cu, Ni, Co[8] for studies on the electrical and non linear optical properties of carotenoids.[6] A previous synthesis of carotenoid amines may now be questioned, since the products were unstable.[9] Oximes, hydrazones and semicarbazones of carotenones have been prepared for subsequent reductions, which, however, failed.[10]

Results and Discussions

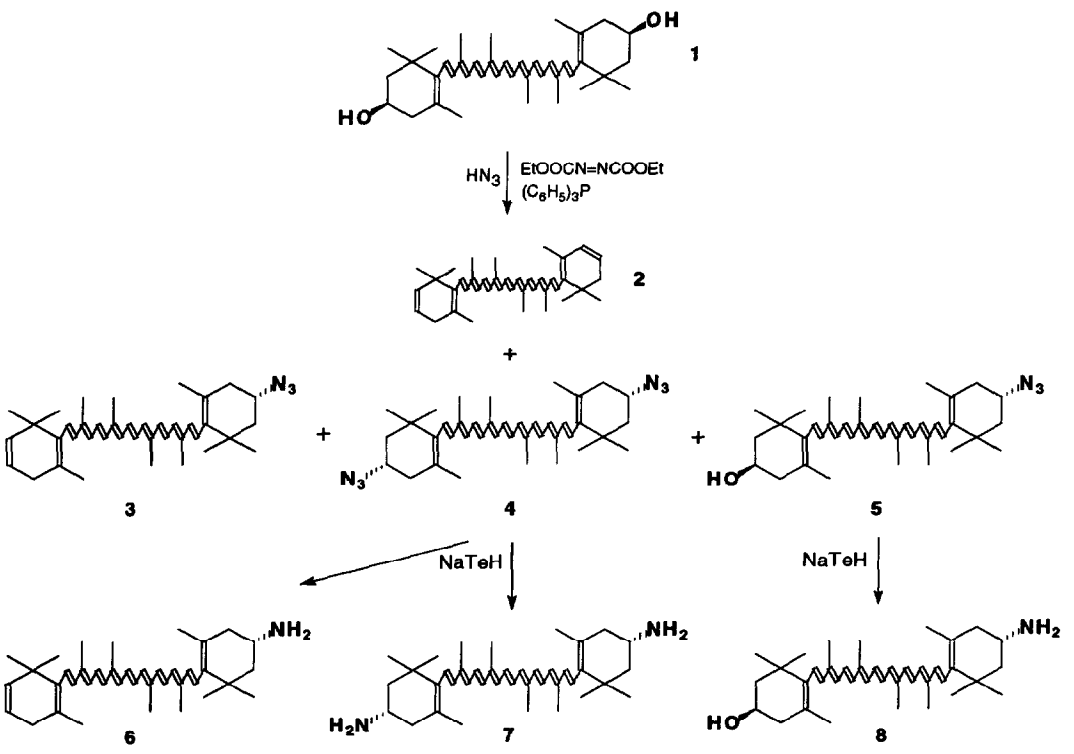
Mesylate replacements,[11] cf. Ref. 9, proved unsuccessful and our synthesis of carotenoid amines[12] was based on the Mitsunobu reaction,[13] already employed for the preparation of carotenoid thiols[14] and selenides.[15] When hydrazoic acid[16,17] was added to a suspension of (3*R*,3*R*)-zeaxanthin (1) in benzene at 30° in the presence of diethylazodicarboxylate and triphenylphosphine, a deep red solution reulted. Chromatographic work-up after 4 h

provided the elimination product **2** and, in 30% yield, the azides **4** and **5** in a ratio of ca. 1:1, *Scheme 1*. Upon changing the experimental conditions (20°, 15 min.) only the diazide **4** (46%) was isolated. After 2 h at 45°, HPLC analysis of the product mixture showed a fourth product, tentatively assigned as the monoazide **3**. In the IR spectra the azides exhibited a strong N_3-vibration at 2094 cm^{-1}.

Reduction of the azides by the Staudinger reaction[18] failed. When an ether solution of the azides was treated with lithium aluminium hydride an orange compound precipitated, which was poorly soluble in ether and methylene chloride, but could easily be dissolved in pyridine or triethyl amine. Presumably, the carotenoid amines are good ligands for Al and therefore difficult to recover from the metal complex.[19]

New efficient azide reduction reagents have been developed,[20] but because of its simplicity, sodium hydrogen telluride reduction[21] was preferred. An ether solution of the azides **4** or **5** was injected into an alcoholic hydrogen telluride solution. After work up and preparative TLC the amines **6** and **7**, formed in a ratio of ca. 1:2, could be isolated in 25% yield, the hydroxyamine **8** in 14% yield, *Scheme 1*. The amines **6**, **7** and **8** seemed upon storage to be as stable as zeaxanthin (**1**).

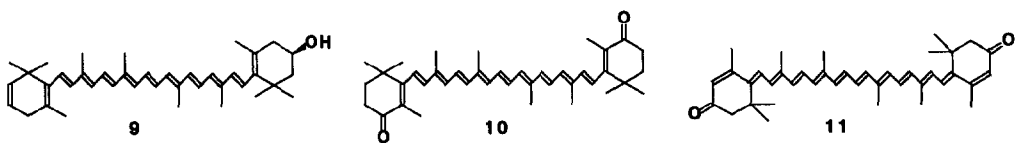
The VIS spectra of the amines **6**, **7** and **8** were identical with that of zeaxanthin (**1**). The CD spectra of the amines **6** and **7** had opposite Cotton effects to the spectra of (3*R*)-2′,3′didehydro-β,β-carotene-3-ol (**9**)[14] and (3*R*,3′*R*)-



Scheme 1

zeaxanthin (**1**), confirming the expected (3*S*) configuration for **6** and (3*S*,3′*S*) for **7**, see Figs. 1 and 2. In principle, the aminoalcohol (*R*,*S*)-**8** should be optically active due to its different functional groups. However, no reliable optical activity was detected by the dichrograph between 210 and 600 nm. The Cotton effect of chiral carotenoids originates predominantly from the configuration of the cyclohexene ring and the angle between the polyene chain and the end-ring around the formal cis-single bond C(6)-C(7). A conformational equilibrium is prevented by the equatorial C(3) substituent.[10,22] A contribution to the Cotton effect by the amino group is not expected, since the n→ σ* transition is assumed to occur near or below 200 nm.[23] Thus, (*R*,*S*)-**8** appeared as a *pseudo meso* compound in the usual CD range.

The preparation of carotenoid amines by other methods failed. Reductive amination[24] as well as condensation reactions to enamines[25] with canthaxanthin (**10**) and rhodoxanthin (**11**) provided no product. Since carotenoid oximes can easily be prepared, oxime reduction would represent a simple method for carotenoid amine synthesis. However, reaction of canthaxanthin(**10**)oxime[26] and rhodoxanthin(**11**)oxime[1] with complex metal hydrides[27] without or in the presence of $TiCl_4$[28] or $TiCl_3$[29,30] yielded no amines. Attempts to reduce several mono and di *N*,*N*-substituted hydrazones and carbazones, prepared from the ketones **10** and **11**, to the unsubstituted hydrazones, previously considered for the synthesis of carotenoid thiones,[31] were also unsuccessful.



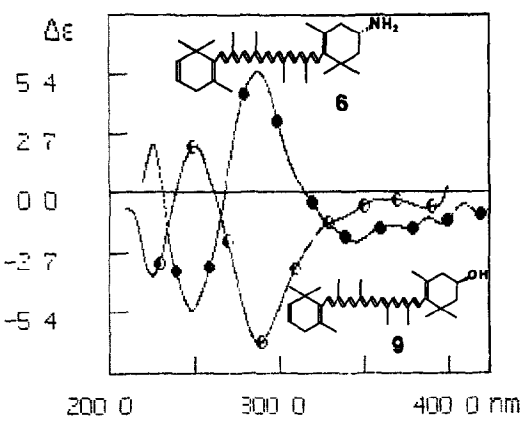


Figure 1
CD spectra (EPA) of (3*S*)-2′,3′-didehydro-β,β-caroten-3-amine (**6**) and (3*R*)-2′,3′-didehydro-β,β-caroten-3-ol (**9**)[14]

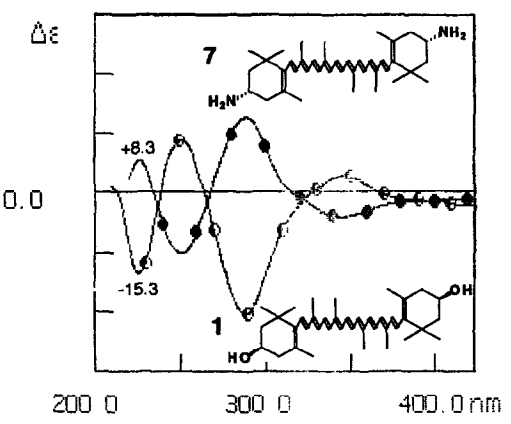


Figure 2
CD spectra (EPA) of (3*S*,3′*S*)-β,β-carotene-3,3′-diamine (**7**) and (3*R*,3′*R*)-zeaxanthin (**1**)

Experimental

General methods. All operations with nitrogen carotenoids were performed under N_2 with general precautions for work with carotenoids. For the mass spectra (IP 70 eV; 210°) and IR spectra (film, KBr) only prominent or diagnostic useful peaks and absorptions are cited. Reaction products were adsorbed on silicagel, dried *in vacuo* and separated by flash chromatography with heptane-acetone mixtures followed by further purification on preparative TLC plates. R_F-values were determined on analytical silica plates. ^{1}H-(400 MHz) NMR spectra were recorded in $CDCl_3$ and interpretated in comparison with data of similar products.[32] CD spectra were measured in EPA (ethanol-isopentane-ether 2:5:5).

Synthesis of azides

(3*R*,3′*R*)-Zeaxanthin (**1**) (113.6 mg, 0.2 mmol) and triphenylphosphine (113.2 mg, 0.43 mmol) were suspended in dry benzene (5 ml). Hydrazoic acid[16,17] (ca. 10% in benzene, 2 ml) and diethyl azodicarboxylate (69 µl, 0.45 mmol) were added by a syringe. After stirring for 4 h at 30° the suspension changed to a deep red solution. Chromatographic work-up yielded three products:

2,3,3′,4′-Tetradehydro-β,β-carotene (2) R_F=0.74 (R_F**1**=0.13, 30% acetone-heptane); VIS (CH_2Cl_2) λ_{max}: 464 nm (no spectral fine structure); MS (m/z): 532 (*M*), 440 (*M*-toluene).

(3*S*,3′*S*)-3,3′-Diazido-β,β-carotene (4) Available 19.0 mg, 16%; R_F = 0.69; VIS (CH_2Cl_2) λ_{max}: 458, 468 nm, same as for **1**; MS (m/z): 618 (*M*), 590 (*M*-N_2), 575 (*M*-HN_3), 547 (575-N_2), 532 (547-HN_3), 526 (*M*-toluene), 483 (575-toluene), 469 (575-xylene); IR: 2094 cm^{-1}.

(3*R*,3′*S*)-3′-Azido-β,β-caroten-3-ol (5) Available 17 mg, 14%; R_F=0.28; VIS (CH_2Cl_2) λ_{max}: same as for **4**; MS (m/z): 593 (*M*), 565 (*M*-N_2), 550 (*M*-HN_3), 532 (550-H_2O), 501 (*M*-toluene), 458 (550-toluene); IR: 2093 cm^{-1}.

When the same reaction was performed at 20° for 15 min the diazide **4** (57 mg, 46%) was the predominant product. At 45° and after 2 h reaction time HPLC analysis of the product mixture revealed a peak attributed to azide **3**. HPLC (CN-column, 76% hexane-17% isopropyl acetate-7% acetone-0.1% MeOH), t_R (min): **2** 1.61 (λ_{max}: 453 nm), **3** 1.64 (λ_{max}: 451 nm), **4** 1.69 (λ_{max}: 450 nm, no baseline separation), **5** 2.76 (λ_{max}: 450 nm), **1** 5.15 (λ_{max}: 450 nm).

Reduction of azides

a) With LAH: The azides **4** and **5** were dried in vacuo overnight, dissolved in dry ether and stirred with LAH at 25° for 2 h. A red compound precipitated immediately. After alcaline work-up[33] the poorly soluble precipitate was recrystallized in ether-methanol providing presumably Al-complexes of amines **6**, **7** and **8**. Purification by preparative TLC on polyamide, cellulose, silicagel or RP-plates with different solvents was unsuccessful, as was an attempt to recover the amines via the hydrochlorides.

b) With sodium hydrogen telluride: Tellurium powder (108.6 mg, 0.85 mmol) and $NaBH_4$ (774 mg, 20 mmol) were suspended in abs. EtOH.[21] After refluxing for 15 min. the red solution was cooled to 25° and the azide **4** (17 mg, 0.03 mmol), dissolved in dry ether, was added with a syringe. After 30 min. the precipitated Te was removed by filtration and ether (or CH_2Cl_2) was added to the green yellow solution. The organic phase was washed neutral with H_2O and dried over Na_2SO_4. Preparative TLC (eluent: triethylamine-EtOAc-MeOH 1:6:3) gave three products:

(3*S*)-2′,3′-Didehydro-β,β-caroten-3-amine (6) Available 1,4 mg, 9%; R_F=0.43 (R_F**1**=0.81, same eluent as for

preparative TLC); VIS λ_{max}: (CH_2CL_2) 458, 486 nm, (EPA) 447, 475 nm; MS (m/z): 549 (*M*), 533 (*M*-NH_2), 457 (*M*-toluene), 441 (*M*-xylene), NMR: see Fig. 3 A,B; CD: see Fig. 1.

(3*S*,3′*S*)-β,β–Carotene-3,3′-diamine (7) Available 2.5 mg, 16%; R_F = 0.14; VIS (CH_2Cl_2 and EPA) λ_{max} same as for **6**; MS (m/z): 566 (*M*), 549 (*M*-NH_3), 474 (*M*-toluene), NMR: see Fig. 3 B; CD: see Fig. 2.

The hydroxyazide **5** (10 mg, 0.02 mmol) was treated with NaTeH (four times excess) as described above and gave after preparative TLC:

3R,3′S)-3′-Amino-β,β-caroten-3-ol (8) Available 1.3 mg, 14%; R_F = 0.37; VIS (CH_2Cl_2): same as for **6**; MS m/z): 567 (*M*), 550 (*M*-NH_3), 475 (*M*-toluene), 461 (*M*-xylene); NMR: see Fig. 3, B,C; CD (210-600 nm): not optically active.

c) With triphenylphosphine: Diazide **4** was treated with triphenylphosphine in THF[18] at 45° for 48 h. No amines were obtained.

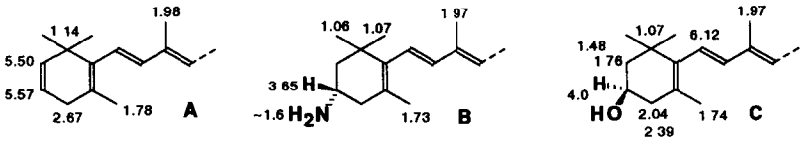


Figure 3

^{1}H-(400 MHz) NMR data of carotenoid amines in $CDCl_3$

Attempts to prepare carotenoid amines by other methods:

a) Reductive amination: Methanolic solutions of canthaxanthin (**9**), rhodoxanthin (**10**) and echinenon (**11**) were stirred several days at 40° with $NaBH_3CN$ in the presence of ammonium acetate or dimethylamine.[24] No amines were formed.

b) Reduction of oximes: Treating canthaxanthin(**10**)oxime[26] and rhodoxanthin(**11**)oxime[1] with $TiCl_4$ and $NaBH_4$ in 1,2-dimethoxyethane,[28] with $TiCl_3$ and $NaBH_3CN$ in MeOH,[29] with $TiCl_3$, ammonium acetate, MeOAc in dioxane,[30] with lithium triethylborohydride (superhydride) in THF at 70° for 2 h or with sodium dihydro-bis(2-methoxyethoxy)aluminate[27] at 70° for 2 h yielded no amines.

c) Enamines: Canthaxanthin (**10**) and rhodoxanthin (**11**) did not react with dimethyl amine and $TiCl_4$ in benzene[25] at 0° to the corresponding enamines.

Preparation of hydrazones and carbazones

Ethanolic solutions of canthaxanthin (**10**) and rhodoxanthin (**11**) were stirred at 50° with BF_3·Et_2O and *N,N*-dimethylhydrazine, *N*-methyl-*N*-phenylhydrazine,[34] or 9-fluorenylmethylcarbazate.[35] Chromatographic work-up provided the corresponding mono and dihydrazones and the 9-fluorenylmethyl-carbazones.

Attempts to prepare the unsubstituted hydrazones

When the above *N,N*-substituted hydrazones were refluxed in abs. EtOH with abs. hydrazine,[36,37] the unsubstituted hydrazones were not formed. No unsubstituted hydrazones were obtained after stirring the 9-fluorenylmethylcarbazones with morpholin[38] at 25° for 12 h.

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