Carotenoids of Higher Plants. 7.* On the Absolute Configuration of Lutein

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Lutein (*1*) possesses three chiral centers at C-3, C-3′, and C-6′. The absolute configurations at C-3 and C-6′ are generally agreed to be *R*.[1-3] However, the chirality at C-3′ of lutein has been assigned both the *R* and *S* configuration by different investigators. De Ville *et al.*[4] favoured the *S* configuration (*1a*) on the basis of biogenetic correlation of lutein (*1*) with (*R*)-β-cryptoxanthin. Later, Buchecker *et al.*[2,3] presented strong evidence for the *R* configuration at C-3′ of lutein (*1b*) on the basis of PMR analysis of (+)-3-methoxy-α-ionone, chemically derived from lutein (*1b*), and by chemical correlation with synthetic 3-methoxy-α-ionones of established stereochemistry.

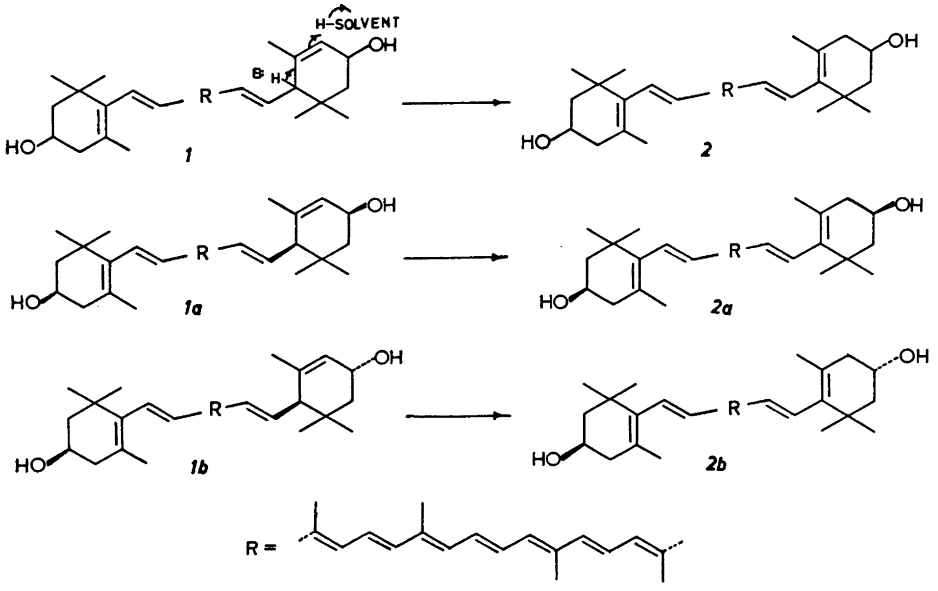
Recently, Andrewes[5] has reported an improved isomerization of lutein (*1*) to zeaxanthin (*2*, Scheme *1*). Provided extensive racemization of the asymmetric centers at 3,3′ of *1* and *2* was avoided, the isomerization of lutein (*1*) to zeaxanthin (*2*) would represent an independent check of the chirality at C-3′ of lutein (*1*). This logical inference has already been pointed out by Buchecker *et al.*[3]

In the absence of racemization, isomerization of (3*R*,3′*S*,6′*R*)-lutein (*1a*) would provide (3*R*,3′*R*)-zeaxanthin (*2a*, identical to natural zeaxanthin, stereochemistry known[6]). On the other hand, isomerization of (3*R*,3′*R*,6′*R*)-lutein (*1b*) would give (3*R*,3′*S*)-zeaxanthin (*2b*, Scheme *1*). From the well tested additivity hypothesis,[6] the former should be optically active while the latter is an optically inactive *meso* compound. CD measurement of zeaxanthin obtained from lutein should then reveal the chirality of lutein at C-3′.

A plausible mechanism for the isomerization of lutein to zeaxanthin is given in Scheme 1. Various mechanisms may be considered to account for possible racemization at C-3,3′ of *1* and *2* via a ketone/enolate type intermediate in alkaline DMSO. To check the extent of racemization to be expected, natural zeaxanthin (*2*, 1.0 mg) was treated with KOMe/MeOH in DMSO as previously described for the isomerization of lutein[5] (no methyl ethers were formed).

The CD spectrum of recovered *trans* zeaxanthin showed the following $\Delta\varepsilon$-values in EPA solution at 285 nm in two separate experiments: $\Delta\varepsilon = -11.7 \pm 10\ \%$ (0.093 mg sample, spectrophotometrically determined using E (1 %, 1 cm) = 2280 at 452 nm in

* No. 6 *Acta Chem. Scand.* *26* (1972) 4121.



Scheme 1.

acetone) and $\Delta\varepsilon = -11.2 \pm 10$ % (0.158 mg sample), compared with $\Delta\varepsilon = -14.8 \pm 10$ % (0.360 mg sample) obtained in a parallel measurement for natural, untreated *trans* zeaxanthin *ex* alfalfa.

The latter value for natural zeaxanthin in EPA solution is in satisfactory agreement with values reported at 285 nm (dioxane) by Buchecker [7] ($\Delta\varepsilon = -16.2$) and by Bartlett *et al.*[6] ($\Delta\varepsilon = -11.8$). The value ($\Delta\varepsilon = -29$) in EPA solution reported by us [8] for zeaxanthin *ex* Flexithrix is now considered erroneously high by a factor of two.

The quantitative CD data for alkali-treated and untreated natural zeaxanthin thus show that 76 – 79 % (± 10 %) retention of optical activity (corresponding to *ca.* 11 % inversion or 22 % racemization) was obtained after alkali treatment of natural zeaxanthin.

Natural lutein (*1*, 5 mg) yielded after isomerization under identical conditions *trans*-zeaxanthin (0.521 mg). The CD-spectrum of zeaxanthin thus prepared showed no optical activity, which supports structure *1b* for lutein.

It might be argued that the allylic 3′-position in the ε-ring of lutein (*1*) may be more susceptible to racemization than the non-allylic 3-position in the β-ring. If this were the case, then zeaxanthin obtained from the isomerization of lutein should still show optical activity due to the residual asymmetry at C-3.

The *R*-chirality of lutein, previously assigned by Buchecker *et al.*,[2,3] is thus considered confirmed.

Lutein and zeaxanthin were separated and identified as described earlier.[5] Instrumentation was as commonly used in our laboratories.[9]

Acknowledgements. A.G.A. was the recipient of a post-doctoral fellowship provided by the Royal Norwegian Council for Scientific and Industrial Research.

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Received December 6, 1973.