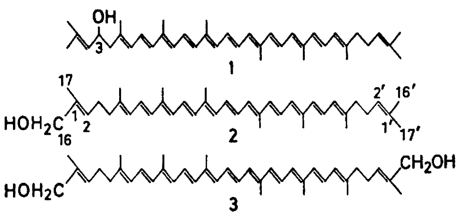
Carotenoids of Higher Plants

5.* Total Synthesis of Lycoxanthin

H. KJØSEN and S. LIAAEN-JENSEN

Organic Chemistry Laboratories, Norwegian Institute of Technology, University of Trondheim, Trondheim, Norway

Lycoxanthin was first isolated from ripe berries of *Solanum dulcamara* by Zechmeister and Cholnoky [1] and assigned the structure *1* (ψ,ψ-carotene-3-ol). The new IUPAC nomenclature rules [2] are used here. Later this structure has been revised to ψ,ψ-carotene-16 or 17-ol.[3,4] Recently, the stereochemistry of the isolated 1,2-double bond has been shown to be *trans*.[5] Lycoxanthin is therefore ψ,ψ-carotene-16-ol (*2*).



A small scale synthesis of lycoxanthin tetrahydropyranyl ether has been achieved by Kelly,[6] but the hydrolysis to lycoxanthin itself could not be effected.

We now report the first total synthesis of lycoxanthin according to the route outlined in Scheme 1.

Lycoxanthin, purified by chromatography on deactivated alumina and crystallized from acetone-petroleum ether had m.p. 173–174°C (uncorr.), undepressed on admixture with natural lycoxanthin of m.p. 173–174°C.

Synthetic and natural lycoxanthin could not be separated in any of six different chromatographic systems.

Synthetic lycoxanthin showed the following spectral characteristics: The absorption spectrum in visible light recorded in acetone solution exhibited absorption maxima at 448, 474 [E(1 %, 1 cm) = 3080], and 505 nm, and in petroleum ether (b.p. 40–65°C) at 443, 469, and 500 nm. The IR spectrum (KBr) showed absorptions characteristic of primary hydroxyl (3350–3150, 1005 cm^{-1}), olefinic CH (3030 cm^{-1}), CH_3 (1385, 1365 cm^{-1}), and carbon-carbon double bonds (1625, 1550, 960 (*trans* disubstituted) and 825 (trisubstituted) cm^{-1}). The NMR spectrum at 60 Mc in $CDCl_3$ solution exhibited singlets at τ 8.38 (3 H) due to one methyl of the isopropylidene end group; τ 8.31 (6 H) due to the other isopropylidene methyl and 17-methyl superimposed; τ 8.19 (6 H) caused by the two end-of-chain methyl groups; τ 8.05 (12 H) due to the four in-chain methyl groups, and τ 6.00 (2 H) caused by the methylene protons of the primary hydroxyl group. A narrow triplet centered at τ 7.85 (8 H) accounted for the four allylic methylene groups. Two broad multiplets centered at τ 4.83 (1 H) and τ 4.58 (1 H) were ascribed to the 2'- and 2- olefinic protons, respectively. The olefinic protons of the polyene chain gave rise to signals in the τ 3.0–4.3 region (16 H).

Only one signal was observed for the methylene protons of the primary hydroxy group demonstrating that the synthetic pigment was the pure 1,2-*trans* isomer.[5]

The mass spectrum showed the molecular ion at *m/e* 552, and fragment ions were observed at *m/e* 536 (M–16), 534 (M–18), 483 (M–69), 467 (M–85), 460 (M–92), 446 (M–106), and 394 (M–158).

The spectral data of the synthetic pigment are in complete agreement with those obtained for natural lycoxanthin.[3,5,7]

Lycophyll (ψ,ψ-carotene-16,16'-diol, *3*) was also prepared *via* Scheme 1, but lycophyll could not be obtained in the pure crystalline state.

The synthetic pigment could not be separated from natural lycophyll in any of four different chromatographic systems.

Synthetic lycophyll exhibited absorption maxima in visible light at 447, 474 and 504.5 nm in acetone solution. The IR spectrum (KBr) showed characteristic absorption for primary hydroxyl (3600–3100, 1005 cm^{-1}), olefinic CH (3030 cm^{-1}), CH_3 (1400–1350 cm^{-1}), and carbon-carbon double bonds (1530, 960 (*trans* disubstituted) and 825 (trisubstituted) cm^{-1}). The NMR spectrum ($CDCl_3$) showed singlets at τ 8.31 (6 H) caused by the 17- and 17'-methyl groups, τ 8.19 (6 H) due to end-of-chain methyl groups, τ 8.02 (12 H) due to in-chain methyl groups, and τ 6.00 (4 H) caused by the methylene protons of the primary hydroxy group. A signal at

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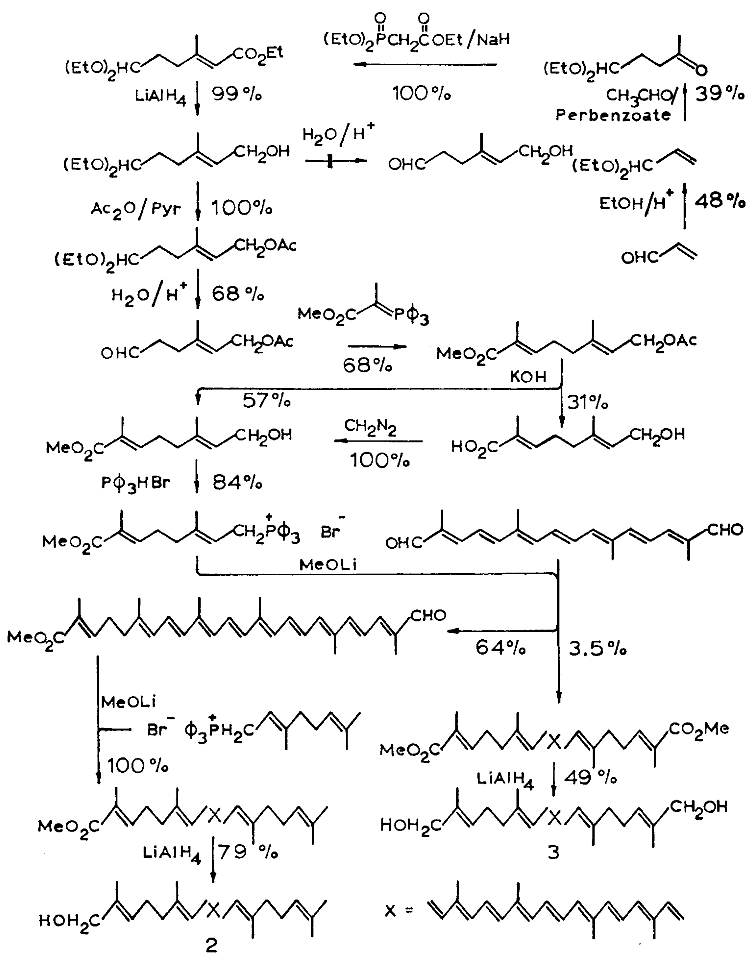

Scheme 1.

τ 7.85 (8 H) accounted for the allylic methylene groups and a broad multiplet centered at τ 4.58 (2 H) was assigned to the 2- and 2′- olefinic protons. The olefinic protons of the polyene chain gave rise to signals in the τ 3.0 – 4.3 region (16 H).

Again only the 1,2,1′,2′-di*trans* isomer was isolated, as evident from the NMR spectrum.

The mass spectrum showed peaks at *m/e* 568 (M), 551 (M – 17), 550 (M – 18), 483 (M – 85), 476 (M – 92), 462 (M – 106), and 410 (M – 158).

The data given agree with those obtained for natural lycophyll.[3,5,7]

Further details will be published.

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1. Zechmeister, L. and v. Cholnoky, L. *Ber.* **69** (1936) 422.

2. In Isler, O. *Carotenoids — A Progress Report*, Birkhäuser, Basel 1971.
3. Markham, M. C. and Liaaen-Jensen, S. *Phytochem.* 7 (1968) 839.
4. v. Cholnoky, L., Szabolcs, J. and Waight, E. S. *Tetrahedron Letters* **1968** 1931.
5. Kelly, M., Authen Andresen, S. and Liaaen-Jensen, S. *Acta Chem. Scand.* 25 (1971). *In press.*
6. Liaaen-Jensen, S. *Pure Appl. Chem.* 20 (1969) 421.
7. Enzell, C. R., Francis, G. W. and Liaaen-Jensen, S. *Acta Chem. Scand.* 23 (1969) 727.

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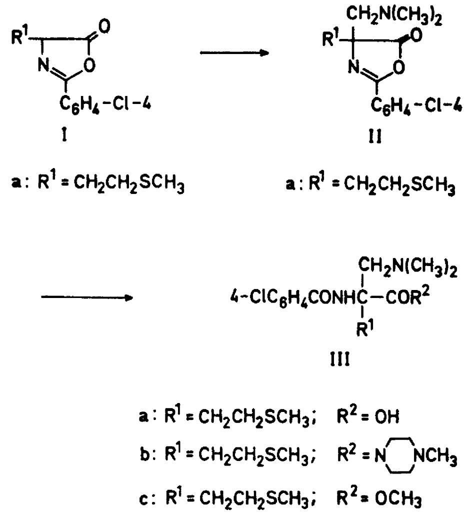

Synthesis of 2-*p*-Chlorophenyl-4-(2-methylthioethyl)-4-dimethylaminomethyloxazolin-5-one — a Reactive Mannich Base

HANS JØRGEN PETERSEN

Leo Pharmaceutical Products, 2750 Ballerup, Denmark

In a previous paper[1] the preparation of a number of 4-monosubstituted 2-*p*-chlorophenyloxazolin-5-ones (I) was reported, involving heating of the requisite α-*p*-chlorobenzamido acids in acetic anhydride.* With secondary amines, *e.g.* dimethylamine, and formaldehyde (aqueous solutions) in methanol or ethanol (I) underwent a Mannich reaction at the 4-position followed by alcoholysis of a hitherto not isolated intermediate (II), resulting in diamino acid esters (III) ($R^2 = OCH_3$ or OC_2H_5). The present communication describes the synthesis of a compound of class II (IIa) from the corresponding (IIIa).

* A low-temperature modification of this classical procedure was successfully employed for converting α-*p*-chlorobenzoyl-L-histidine in trifluoroacetic anhydride at 0° into a reactive oxazolin-5-one derivative which yielded racemic products with an unaffected imidazole ring.

The esters (III) proved to be rather refractory to aminolysis and saponification, in the latter case often suffering a certain amount of destruction. With the methionine azlactone (Ia) a Mannich reaction was conducted in 2-trifluoroethanol. The weakly alkaline conditions brought about a concerted reaction, in one step affording (IIIa), isolated as the hydrochloride in high yield. Thus, the difficulties in obtaining the pure diamino acid *via* methyl or ethyl esters were overcome as the result of a simultaneous smooth hydrolysis of the intermediate 2-trifluoroethyl ester.

The mixed anhydride from (IIIa) and isobutyl chloroformate was prepared in acetone-methylene chloride. When treated with dry hydrogen chloride, the crystalline hydrochloride of (IIa) was obtained. While this work was in progress a general method for oxazolin-5-one preparation by the mixed anhydride reaction has appeared.[2] (IIa) – in accordance with the postulated intermediacy in the proposed reaction sequence – was completely converted to (IIIb) and to (IIIc),[1] when dissolved in *N*-methylpiperazine and in methanol, respectively. An authentic sample of (IIIb) was prepared by reacting the mixed anhydride from (IIIa) and isobutyl chloroformate with an excess of *N*-methylpiperazine in acetone.

A certain stability of (IIa) in aqueous medium was demonstrated by the fact that treatment of an aqueous solution