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Total Synthesis of a 10,14-Sulphur-bridged 11-*cis*-Retinal Analogue: 6-Formyl-2-[4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-ylidene]-2*H*-thiopyran

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The synthesis of the title compound, a purple coloured retinoid having a fixed 11-*cis*,12s-*cis*-geometry, is described.[†]

Vitamin A, its naturally occurring and synthetic derivatives, and its analogues (retinoids) are of considerable current research interest. Retinoids have been shown to be of therapeutic value in the treatment of certain dermatological disorders and epithelial tumours¹ and serve in studies directed towards the clarification of the many biologically important roles of vitamin A, especially in those concerning the process of visual transduction.

The chromophore of visual pigments may be derived from 11-cis-retinal (1).² Recently many isotopically³ and chemically⁴ modified retinals have been used to elucidate previously unknown aspects of the visual process and bacteriorhodopsin-mediated photosynthesis.⁵

In the crystalline state (1) can occur in two different 12scis-conformations (1b),^{6,7} while in solution an equilibrium between 12s-cis- (1b) and 12s-trans-conformers (1a) exists.⁸ In the course of our studies we needed an 11-cis-retinal analogue having a 12s-cisoid-locked conformation.[‡] Bridging the polyene side chain positions 10 and 14 leads to such a derivative.

In this communication we describe the total synthesis of a 10,14-sulphur-bridged§ 11-*cis*-retinal analogue (**8a**) and its 9E-geometrical isomer (**8b**). The main features of these new visual chromophore model compounds are the impossibility of *cis*-*trans* isomerization around the 11-double bond (important with respect to the primary photochemical event)



and their interesting visible spectral properties making them the first purple coloured retinals so far reported in the literature.

The retinoid carbon skeleton was constructed as follows (Scheme 1). Treatment of the C_{14} -aldehyde (2)⁹ with excess of (dibromomethylene)triphenylphosphorane (from triphenylphosphine, Zn, and carbon tetrabromide, 2 equiv. of each, in CH_2Cl_2 , 23 °C)¹⁰ afforded the dibromide (3) (78 %).¶ Treatment of (3) with n-butyl-lithium [2.1 equiv., tetrahydrofuran (THF) –n-hexane, -60 to 23 °C] followed by addition of 4,4-diethoxybut-2-yn-1-al¹¹ (1.2 equiv., -30 °C) and room temperature aqueous work-up resulted in the formation of the diacetylenic alchohol (4) (89 %) which was oxidized (MnO₂, CH₂Cl₂, 0 °C) to the corresponding ketone (5) (76%). The 10,14-sulphur bridge was introduced by treating (5) with thiourea¹² (1.2 equiv., dimethylformamide, 23 °C) yielding the 4*H*-thiopyran-4-one (6) as the main product (38 %).

Conversion of (6) into the required conjugated pentaene system was effected in a novel di-isobutylaluminium hydride (DIBAL-H) reduction-elimination. Addition of DIBAL-H (3 equiv., n-hexane, -60 °C) to a solution of (6) in THF resulted, presumably *via* initial hydride attack on the carbonyl

[†] Standard carotenoid numbering has been used according to: *Pure Appl. Chem.*, 1975, **41**, 407.

[‡] Recently a 12s-*trans* locked analogue has been synthesized: see ref. 4.

[§] Synthetic considerations led to the choice of sulphur as bridging atom and to the omission of the 13-Me group; the latter fact does not *a priori* prevent pigment formation, see: R. Nelson, J. K. de Riel, and A. Kropf, *Proc. Natl. Acad. Sci. USA*, 1970, **66**, 531.

 $[\]P$ Satisfactory spectral and analytical data were obtained for all new compounds.



function followed by 1,4-elimination of $Bu_{2}^{i}AlOH$ from the alkoxyaluminium intermediate, in a mixture of (7a) and (7b). Since (7a) and (7b) appeared to be rather unstable they were directly submitted to formolysis¹³ (HCO₂H, 3 equiv., CHCl₃, 0 °C) yielding the more stable aldehydes (8a) and (8b) which were separated by means of h.p.l.c. The ¹H n.m.r. spectra (300 MHz, CDCl₃) of (**8a**) and (**8b**) exhibited the following resonances in the aldehydic and olefinic regions (δ with regard to SiMe₄ as internal standard, coupling constants in Hz): (**8a**) 9.34 (s, H-15), 7.04 (d, J 10.4, H-11), 6.78 (d, J 6.7, H-13), 6.46 (d, J 15.8, H-8), 6.16 (br. d, J 15.8, H-7), and 5.97 (dd, J 10.4 and 6.7, H-12); (**8b**) 9.31 (s, H-15), 6.85 (d, J 10.4, H-11), 6.78 (d, J 6.7, H-13), 6.52 (d, J 15.8, H-8), 6.33 (br. d, J 15.8, H-7), and 6.02 (dd, J 10.4 and 6.7, H-12). Structural assignments for (**8a**) and (**8b**) were made on the basis of n.O.e. measurements, indicating the close proximity of H-11 and H-19 in (**8a**).

The remarkable purple colour of (8a) $[(\lambda_{max}(n-hexane) 542 nm, \epsilon_{max} 19900]$ and (8b) $[\lambda_{max}(n-hexane) 546 nm, \epsilon_{max} 8300]$ can, at least partly, be attributed to the presence of both a sulphur atom and an electron-attracting aldehyde group inducing opposite charges on the carbon atoms in the pyran system [the mixture of (7a) and (7b) has $\lambda_{max}(n-hexane) 420 nm$]. Compounds (8a) and (8b) are photochemically interconvertible.

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