Retinoids and Related Compounds. Part 9.[1] Synthesis and Spectral Characteristics of Retinal Analogues involving the 11-*cis*-Locked-cyclopentatrienylidene Structure

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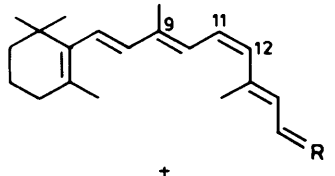
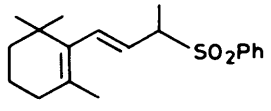
The 11-*cis*-locked-cyclopentatrienylideneretinals (**7a**), (**7b**), (**8a**), (**8b**), and (**9**) have been obtained in a short-path synthesis from the β-ionyl sulphone (**3**). Their characteristic spectral properties (u.v. and ^{1}H n.m.r.) are discussed.

The visual pigment rhodopsin (**1**) has been shown to contain the 11-*cis*-retinal (**2**) bound *via* a protonated Schiff-base linkage to the ε-amino group of a specific lysyl residue of the apoprotein opsin.[2] During the course of an investigation[3] into the photobleaching process of rhodopsin, we reported in a previous communication[4] the preparation of the 11-*cis*-locked[5] cyclopentatrienylidenerhodopsin (**7c**), whose chromophore consists of the 11-*cis*- and 12s-*trans*-fixed retinal analogue (**7a**). From the photochemical behaviour of the artificial pigment (**7c**) at low temperatures, the *cis-trans* isomerisation hypothesis for the conversion of rhodopsin into bathorhodopsin was chemically confirmed.[6] A circular dichroism (c.d.) spectrum[6] of (**7c**), having a non-twisted structure around a 12s-*trans* bond, showed a negligible α-band. A comparison of the c.d. data for rhodopsin (**1**) and cycloheptatrienylidenerhodopsin[7] with our results shows that the presence of the α-band in the induced c.d. of rhodopsin is due to the twisted 12s-bond in the chromophore. In this paper, we describe the full synthesis and characterisation of the 11-*cis*-locked cyclopentatrienylideneretinals.

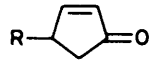
The lithium derivative obtained from the reaction of the β-ionyl sulphone (**3**)[8] with lithium di-isopropylamide (LDA) at −78 °C was treated with 4-acetoxycyclopentenone (**4a**)[9] in a mixture (*ca.* 2:1) of dry tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) at −50 °C—room temperature to give a mixture of two β-ionylidenecyclopentenone isomers (**5a**) and (**6a**) in *ca.* 24% yield, which could be cleanly separated by a combination of silica gel column chromatography and low-pressure liquid chromatography. The ratio of (**5a**) to (**6a**) was *ca.* 3:2. A *trans*-configuration was assigned to the newly formed tetrasubstituted 9,10-double bond in the faster eluted isomer (**5a**), the latter having a u.v. absorption maximum at 350 nm; a comparison with the ^{1}H n.m.r. data of the other isomer (**6a**) shows that the 8-H signal of (**6a**) (δ 6.66) is deshielded by the 11,12-double bond and that the 11-H signal (δ 8.22) appears at lower field owing to the anisotropic effect of the 7,8-double bond. The 14-H_2 signals for both isomers appear at δ *ca.* 3 as a singlet, which is characteristic for the position between two sp^2 carbons. This reaction failed both when (**4a**) was replaced by (**4b**)[9] and in the absence of HMPA. An Emmons-Horner reaction of the 9-*trans*-isomer (**5a**) with diethyl cyanomethylphosphonate using butyl-lithium in dry THF at 0 °C under argon produced a pentaene nitrile which, without purification, was subsequently reduced with di-isobutylaluminium hydride (DIBAH) in hexane at −70 °C to furnish a mixture (*ca.* 4:1) of the 11-mono-*cis*-aldehyde (**7a**) and the 11-*cis*,13-*cis*-isomer (**9**) in low yield. Each unstable isomer



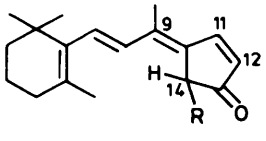
(**1**) R = $\overset{+}{N}$H–opsin
(**2**) R = O



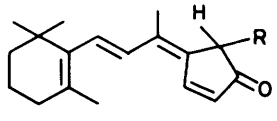
(**3**)



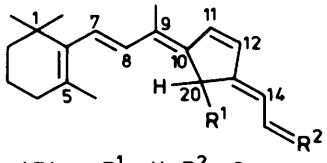
(**4**) a; R = OAc
b; R = Br



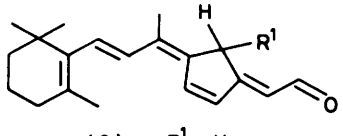
(**5**) a; R = H
b; R = Me



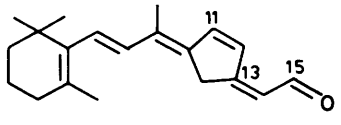
(**6**) a; R = H
b; R = Me



(**7**) a; R^1 = H, R^2 = O
b; R^1 = Me, R^2 = O
c; R^1 = H, R^2 = $\overset{+}{N}$H–opsin



(**8**) a; R^1 = H
b; R^1 = Me



(**9**)

Table. U.v. absorption maxima and ^{1}H n.m.r. data for cyclopentatrienylidene retinals (**7a**), (**7b**), (**8a**), (**8b**), and (**9**)

		(7a)	(7b)	(8a)	(8b)	(9)
U.v. (EtOH)		405 (18 500)	400	402 (11 500)	395	392 (10 000)
$\lambda_{max.}$ nm (ε)		263 (13 300)	260			
^{1}H n.m.r.	1-Me_2	1.05 (s)	1.03 (s)	1.04 (s)	1.05 (s)	1.04 (s)
(200 MHz)			1.07 (s)			
(δ, $CDCl_3$)	5-Me	1.76 (s)	1.75 (s)	1.74 (s)	1.74 (s)	1.75 (s)
(*J* in Hz)	9-Me	2.05 (s)	2.05 (s)	2.02 (s)	2.06 (s)	2.05 (s)
	7-H	6.32 (d, *J* 16)	6.37 (s-like)	6.27 (d, *J* 16)	6.28 (d, *J* 16)	6.33 (s-like)
	8-H	6.42 (d, *J* 16)		6.62 (d, *J* 16)	6.60 (d, *J* 16)	
	11-H	7.27 (d, *J* 5)	7.16 (d, *J* 5)	7.36 (d, *J* 5.5)	7.25 (d, *J* 5)	7.36 (dd, *J* 1.5, 5.5)
	12-H	6.61 (d, *J* 5)	6.49 (d, *J* 5)	6.59 (d, *J* 5.5)	6.48 (d, *J* 5)	7.28 (d, *J* 5.5)
	14-H	5.97 (td, *J* 1.5, 7)	5.89 (d, *J* 8)	5.98 (td, *J* 2, 7)	5.90 (d, *J* 8)	5.88 (dd, *J* 1.5, 8)
	20-H	3.73 (d, *J* 1.5)	4.04 (q, *J* 7)	3.70 (d, *J* 2)	3.98 (q, *J* 7)	3.48 (s)
	20-Me		1.35 (d, *J* 7)		1.38 (d, *J* 7)	
	CHO	9.88 (d, *J* 7)	9.90 (d, *J* 8)	9.89 (d, *J* 7)	9.91 (d, *J* 8)	9.99 (d, *J* 8)

was purified by preparative t.l.c. followed by h.p.l.c. in the dark. The 9-*cis*-isomer (**6a**) was treated in the same way as the 9-*trans*-isomer (**5a**) to provide mainly the 9-*cis*,11-*cis*-aldehyde (**8a**), together with (**7a**) and (**9**) in low yield, which were carefully separated into their respective isomers by a combination of preparative t.l.c. and h.p.l.c. in the dark. The structures of the three products were confirmed on the basis of their u.v. and ^{1}H n.m.r. data (Table). The three isomers have absorption maxima at longer wavelengths (*ca.* 20 nm) than that (380 nm) of the all-*trans*-retinal compound; this suggests that the former have greater chromophoric coplanarity. This behaviour is particularly notable for the 11-mono-*cis*-isomer (**7a**) the u.v. maximum of which is of 30 nm longer wavelength than that (375 nm) of 11-*cis*-retinal (**2**). This is the first example of a retinal analogue having the same chromophore as (**2**), indicating that (**7a**) has a considerable degree of coplanarity in its conjugated structure. The configuration of the 13,14-double bond was deduced on the basis of the chemical shifts of the 20-H_2 signals. In the 13-*trans*-isomers (**7a**) and (**8a**), C-20 protons were strongly deshielded by the anisotropic effect of the aldehyde group, although the corresponding protons in the 13-*cis*-isomer (**9**) were not so affected. Instead, 12-H in (**9**) was observed at low field; this is due to the effect of the aldehyde group. The stereochemistry of the 9,10-double bond was also determined from the chemical shifts of the 8-H signals which were subject to the anisotropic effects of the 11,12-double bond. Thus, the 8-H signal in the 9-*cis*-isomer (**8a**) appeared at lower field than the corresponding signals of the 9-*trans*-isomers (**7a**) and (**9**). The ^{1}H n.m.r. data of the most significant 11-mono-*cis*-isomer (**7a**) have also been compared with those[10] of all-*trans*-retinal. The 8-H signal (δ 6.42) of (**7a**) is further downfield than the corresponding resonance (δ 6.18) for the all-*trans*-retinal, presumably owing to the deshielding anisotropic effect of the C(10)–C(20) single bond. In addition, the 12-H signal (δ 6.61) appears at lower field than the corresponding signal (δ 6.37) of all-*trans*-retinal, showing the anisotropic effect of the 13,14-double bond. These spectral data confirm that the 11-*cis*-locked retinal (**7a**) has a high degree of coplanarity, particularly in the C(9)–C(14) triene part. This is further supported by MO calculations.[11]

Treatment of a mixture of the two cyclopentenone derivatives (**5a**) and (**6a**) with a 10 molar excess of MeI in the presence of lithium bis(trimethylsilyl)amide or LDA yielded the monomethylated compounds (**5b**) and (**6b**) which, without separation, were converted into a mixture of the pentaene aldehyde isomers in a similar manner to that used for the 20-unmethylated aldehydes (**7a**), (**8a**), and (**9**). The pure isomers (**7b**) and (**8b**) were obtained by preparative t.l.c. followed by h.p.l.c. in the dark. The structures of the isomers were deduced from a comparison of their spectral data (Table) with those of the 20-unmethylated aldehydes.

In a binding experiment[6] using bovine opsin, (**7b**) gave no pigment while (**7a**) produced the artificial pigment (**7c**) at a rate which was slow compared with that of the regeneration of rhodopsin. This suggests that, for the regeneration of rhodopsin, selective binding of opsin to a twisted 11-*cis*-retinal (**2**) in a 12s-*transoid* form, and a spatial restriction in an opsin cavity, are strict requirements.

Experimental

U.v. spectra were recorded on a Shimadzu UV 200S instrument in ethanolic solutions. ^{1}H N.m.r. spectra at 200 MHz were determined on a Varian XL-200 superconducting FT-NMR spectrometer in deuteriochloroform solutions using tetramethylsilane as an internal reference. The results are given mainly in the Table. Mass spectra were determined on a JEOL JMS-01SG or a Hitachi M-80 double-focusing GC mass spectrometer. Preparative t.l.c. was performed on silica gel plates (Merck silica gel $60F_{254}$ precoated plates, 0.25 or 0.5 mm thickness). Silica gel used for column chromatography was Merck Kieselgel 60 (particle size 0.063—0.200 mm, 70—230 mesh ASTM). Low-pressure column chromatography was carried out using a Lobar Column (Merck). H.p.l.c. was carried out on a Shimadzu LC-3A instrument with a u.v. detector.

Unless otherwise stated, solvent extracts were dried over anhydrous sodium sulphate and all operations were carried out under nitrogen or argon. Ether refers to diethyl ether.

trans- *and* cis-4-[1-*Methyl*-3-(2,6,6-*trimethylcyclohex*-1-*enyl*)*prop*-2-*enylidene*]*cyclopent*-2-*en*-1-*one* (**5a**) *and* (**6a**).—A solution (2.7 ml) of butyl-lithium (15% w/v in hexane) was added to a stirred solution of di-isopropylamine (650 mg) in dry THF (1 ml) at −78 °C, and the mixture was stirred for a further 30 min. To this LDA solution was added a solution of the β-ionyl sulphone (**3**) (2 g) in a mixture of dry THF (1.5 ml) and dry HMPA (1.5 ml) in portions. After the addition was complete, the mixture was stirred at a temperature of −78 °C to −50 °C for *ca.* 1 h, after which 4-acetoxycyclopent-2-en-1-one (**4a**) (600 mg) was added dropwise at −50 °C over a period of 30 min. The mixture was then stirred at −30 °C for 1 h before being allowed to warm to room temperature over 2 h with stirring. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The extracts were washed with brine, dried, and evaporated to give an oil which was purified by silica gel column chromatography (5% ether in benzene)

followed by low-pressure column chromatography (LiChroprep Si 60 Merck, hexane–benzene–ether 10:10:1) to afford, as yellow oils, the *trans*-isomer (**5a**) (150 mg), the *cis*-isomer (**6a**) (100 mg), and a mixture of both isomers (15 mg) (yield 24%). The *trans*-isomer (**5a**): $\lambda_{max.}$ 350 nm (ε 17 500); δ 1.05 (6 H, s, $_{gem}$Me), 1.73 (3 H, s, 5-Me), 2.08 (3 H, s, 9-Me), 3.05 (2 H, s, 14-H_2), 6.24 (1 H, d, *J* 5.6 Hz, 12-H), 6.30 (1 H, d, *J* 16 Hz, 8-H), 6.44 (1 H, d, *J* 16 Hz, 7-H), and 8.14 (1 H, d, *J* 5.6 Hz, 11-H) (Found: M^+, 256.184. $C_{18}H_{24}O$ requires M^+, 256.183). The *cis*-isomer (**6a**): $\lambda_{max.}$ 346 nm (ε 14 500); δ 1.04 (6 H, s, $_{gem}$Me), 1.74 (3 H, s, 5-Me), 2.00 (3 H, s, 9-Me), 3.03 (2 H, s, 14-H_2), 6.23 (1 H, d, *J* 5.6 Hz, 12-H), 6.37 (1 H, d, *J* 16 Hz, 7-H), 6.66 (1 H, d, *J* 16 Hz, 8-H), and 8.22 (1 H, d, *J* 5.6 Hz, 11-H) (Found: M^+, 256.184. $C_{18}H_{24}O$ requires M^+, 256.183).

trans- *and* cis-5-*Methyl*-4-[1-*methyl*-3-(2,6,6-*trimethylcyclohex*-1-*enyl*)*prop*-2-*enylidene*]*cyclopent*-2-*en*-1-*one* (**5b**) *and* (**6b**).—A solution (0.8 ml) of butyl-lithium (15% w/v in hexane) was added to a stirred solution of hexamethyldisilazane (0.4 ml) in dry 1,2-dimethoxyethane (DME) (0.6 ml). The mixture was boiled under reflux for 0.5 h and cooled to −75 °C. A solution of β-ionylidenecyclopent-2-en-1-one [a mixture of (**5a**) and (**6a**)] (273.7 mg) in dry DME (0.6 ml) was added to the above cooled mixture and a solution of MeI (1.52 g) in dry DME (1 ml) was added at −50 °C. The reaction mixture was stirred at −20 °C for 0.5 h, at 0 °C for 1 h, and at room temperature for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The ethereal extracts were washed with brine, dried, and evaporated to give an oily mixture (75 mg, 26%) which was separated using a centrifugal thin layer chromatotron (Harrison Model 7924, Merck silica gel $60PF_{254}$, 2 mm thickness, hexane–benzene 1:1) followed by h.p.l.c. (LiChrosorb 0.8 × 30 cm, 15% di-isopropyl ether in hexane) to give two pure isomers [(**5b**), longer R_t; (**6b**), shorter R_t] as yellow oils. This methylation using LDA as a base instead of lithium bis(trimethylsilyl)amide resulted in the same yield. The *trans*-isomer (**5b**): $\lambda_{max.}$ 350 nm; δ 1.03, 1.06 (each 3 H, s, $_{gem}$Me), 1.29 (3 H, d, *J* 7.6 Hz, 14-Me), 1.74 (3 H, s, 5-Me), 2.08 (3 H, s, 9-Me), 3.00 (1 H, q, *J* 7.6 Hz, 14-H), 6.15 (1 H, d, *J* 5.6 Hz, 12-H), 6.33 (1 H, d, *J* 16 Hz, 8-H), 6.46 (1 H, d, *J* 16 Hz, 7-H), and 8.11 (1 H, d, *J* 5.6 Hz, 11-H); *m/z* 270 (M^+). The *cis*-isomer (**6b**): $\lambda_{max.}$ 346 nm; δ 1.05 (6 H, s, $_{gem}$Me), 1.32 (3 H, d, *J* 7.5 Hz, 14-Me), 1.74 (3 H, s, 5-Me), 2.05 (3 H, s, 9-Me), 2.92 (1 H, q, *J* 7.5 Hz, 14-H), 6.15 (1 H, d, *J* 5.6 Hz, 12-H), 6.37 (1 H, d, *J* 15.9 Hz, 7-H), 6.66 (1 H, d, *J* 15.9 Hz, 8-H), and 8.19 (1 H, d, *J* 5.6 Hz, 11-H); *m/z* 270 (M^+).

11-cis-, 11-cis,13-cis-, *and* 9-cis,11-cis- 4-[1-*Methyl*-3-(2,6,6-*trimethylcyclohex*-1-*enyl*)*prop*-2-*enylidene*]*cyclopent*-2-*enylideneacetaldehyde* (**7a**), (**9**), *and* (**8a**).—Butyl-lithium (90 mg) (15% w/v in hexane; 0.6 ml) was added to a stirred solution of diethyl cyanomethylphosphonate (210 mg) in dry THF (2 ml) and stirring was continued at room temperature for *ca.* 1 h. This carbanion solution was added to a solution of *trans*-β-ionylidenecyclopent-2-en-1-one (**5a**) (230 mg) in dry THF (1 ml) at 0 °C in the dark and stirring was continued for 1 h. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with brine, dried, and evaporated under reduced pressure to give a brown oil which was submitted to preparative t.l.c. (15% ether in benzene) to yield a nitrile (58 mg) which was not further purified. A solution of DIBAH (44 mg) in hexane (1 ml) was added to a solution of the nitrile (58 mg) in hexane (2 ml) at −70 °C in the dark and the mixture was stirred for *ca.* 10 min. The reaction was quenched by addition of an excess of ether. The ether layer was washed with brine, dried, and evaporated to give a deep orange oil (14 mg) which was a mixture (*ca.* 4:1) of the 11-*cis*-isomer (**7a**) and the 11-*cis*,13-*cis*-isomer (**9**). Preparative t.l.c. (15% ether in hexane) and repeated h.p.l.c. [μ-Porasil (0.8 × 30 cm)/hexane–benzene–ether 16:16:1] of the mixture in the dark provided pure (**7a**) and (**9**) as orange oils. The 11-*cis*-isomer (**7a**): $\lambda_{max.}$ see Table (Found: M^+, 282.199. $C_{20}H_{26}O$ requires M^+, 282.198). The 11-*cis*,13-*cis*-isomer (**9**): $\lambda_{max.}$ see Table; δ, see Table (Found: M^+, 282.197. $C_{20}H_{26}O$ requires M^+, 282.198). 9-*cis*-β-Ionylidenecyclopent-2-en-1-one (**6a**) (230 mg) was treated in the same way as the 9-*trans*-isomer (**5a**) to yield the corresponding nitrile (37 mg) which was converted into the 9-*cis*,11-*cis*-isomer (**8a**) in 25% yield: $\lambda_{max.}$ see Table; δ, see Table (Found: M^+, 282.201. $C_{20}H_{26}O$ requires M^+, 282.198).

11-cis- *and* 9-cis,11-cis- 5-*Methyl*-4-[1-*methyl*-3-(2,6,6-*trimethylcyclohex*-1-*enyl*)*prop*-2-*enylidene*]*cyclopent*-2-*enylideneacetaldehyde* (**7b**) *and* (**8b**).—A mixture of (**5b**) and (**6b**) (375 mg), treated in a manner similar to that for the preparation of (**7a**), (**9**), and (**8a**) from (**5a**) and (**6a**), gave a mixture (47.2 mg) of the 11-*cis*-aldehyde (**7b**), the 9-*cis*,11-*cis*-aldehyde (**8b**), and other isomers which were separated and purified by preparative t.l.c. (5% ether in benzene) followed by h.p.l.c. [μ-Porasil (0.8 × 30 cm)/hexane–benzene–ether 16:16:1] to afford (**7b**) and (**8b**) as orange oils. The 11-*cis*-aldehyde (**7b**): $\lambda_{max.}$ see Table; δ, see Table (Found: M^+, 296.214. $C_{21}H_{28}O$ requires M^+, 296.214). The 9-*cis*,11-*cis*-aldehyde (**8b**): $\lambda_{max.}$ see Table; δ, see Table (Found: M^+, 296.213. $C_{21}H_{28}O$ requires M^+, 296.214).

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