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Retinoids and Related Compounds. II.[1] High-Performance Liquid Chromatographic Analysis of the Irradiation Products of 9-*cis*-Retro-γ-retinal

MASAYOSHI ITO,* AKIKO KODAMA, and KIYOSHI TSUKIDA

Kobe Women's College of Pharmacy, 4-19-1 Motoyamakita-machi, Higashinada-ku, Kobe 658, Japan

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The photochemical behaviour of 9-*cis*-retro-γ-retinal (II) was investigated by high-performance liquid chromatography. A new isomer, 9,13-di-*cis*-retro-γ-retinal (III) was isolated from the irradiation products of II.

Keywords——retinoid; 9-*cis*-retro-γ-retinal; photochemical isomerisation; high-performance liquid chromatography; retinal

Retinoids have recently attracted interest in connection with vision, in addition to their importance in the areas of energy conversion,[2] cancer prophylaxis,[3] and acne therapy.[4] As a step towards clarifying the interaction between 11-*cis*-retinal and apoprotein opsin in the visual pigment, we had studied retro-γ-retinal as a new chromophore in rhodopsin analogues.[1] Our photochemical study at low temperature with 9-*cis*-retro-γ-rhodopsin (I) prepared from 9-*cis*-retro-γ-retinal (II) and cattle opsin is apparently the first report of a photosensitive rhodopsin analogue possessing dissected chromophores.[5] In the present paper, we report the photochemical behaviour of II, which contains one diene chromophore and one trienal chromophore in the molecule.

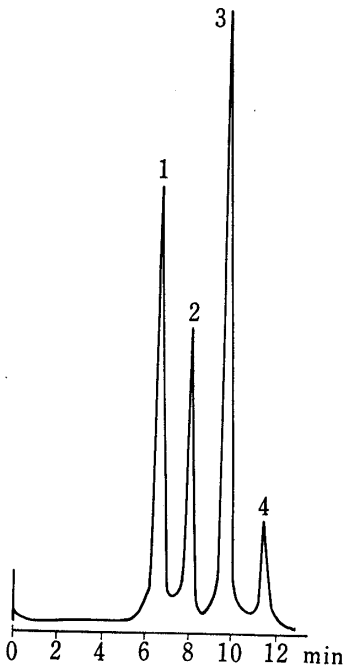


Fig. I. HPLC of Retro-γ-retinal Isomers

Shimadzu-DuPont 830, μ-Porasil 30×0.4 cm, 12% ether in *n*-hexane, UV 254, 20 kg/cm². 1: 11-*cis*, 2: 9-*cis*, 3: all-*trans*, 4: *o*-xylenol(*i.s.*).

Irradiation was carried out in various solvents with different polarities using a fluorescent lamp (30 W). The photochemical behaviour of II was investigated by high-performance liquid chromatography (HPLC). Typical chromatograms of retro-γ-retinal isomers are illustrated in Fig. I and the product distributions derived from the 9-*cis* isomer (II) by direct irradiation are summarised in Table I. The data are the results of determination after correction for the different molar absorptivities of isomers at 254 nm, the wavelength of analysis. A new peak with a shorter retention time than II was observed in all experiments. Its amount reached a maximum after irradiation for 3 to 5 h in hydroxylic solvents. The new compound was isolated by preparative HPLC. Its structure was determined to be 9, 13-di-*cis*-retro-γ-retinal (III) by analysis of its 200 MHz FT-^{1}H-NMR spectrum (Table II) in comparison with that of the starting 9-*cis* isomer (II); *i.e.*, a Δ^{13}-*cis* configuration in compound III was deduced from the downfield shift of the signal of C-12-H and the upfield shift of the signal of C-13-CH_3, and the unaltered chemical shifts of

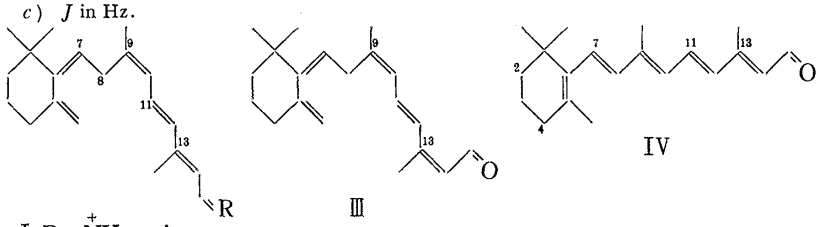
TABLE I. Photoisomerisation of 9-*cis*-Retro-γ-retinal (II) in Several Solvents

Type	Solvent	Irradiation time (h)	Percentage composition		
			9,13-Di-*cis*	9-*cis*	All-*trans*
Non-polar	*n*-Hexane	5	28.7	56.3	15.0
Polar protic	Methanol	5	48.8	42.3	8.9
	Ethanol	3	46.5	44.4	9.1
	n-Propanol	5	49.0	41.4	9.6
	Isopropanol	5	48.5	40.8	10.7
Polar aprotic	Acetonitrile	5	35.6	49.1	15.3

TABLE II. Characteristic NMR Data for Compounds II and III

	II[a]	III[b]
C_9–CH_3	1.84 (s)	1.85 (s)
C_{13}–CH_3	2.30 (s)	2.10 (s)
C_8–H_2	3.14 (d, J=7)[c]	3.12 (d, J=7.3)
exo-CH_2	4.64 (d, J=3)	4.62 (d, J=2.8)
	5.09 (m)	5.06 (m)
C_{11}–H	6.94 (dd, J=11, 15)	6.91 (dd, J=11, 15)
C_{12}–H	6.25 (d, J=15)	7.15 (d, J=15)
CHO	10.13 (d, J=8)	10.18 (d, J=8.1)

a) δ values (90 MHz) in $CDCl_3$,[1]
b) δ values (200 MHz) in $CDCl_3$,
c) J in Hz.



I: R = $\overset{+}{N}$H-opsin
II: R = O

III

IV

C-8-H_2 and *exo*-CH_2 indicated no modification in the diene moiety. Although the nature of the solvent employed influenced both the isomerisation rate and the relative amounts of the products to some degree, the photoisomerisation occurred mainly at the terminal trisubstituted C=C bonds of the conjugated trienal system.

In the case of the photoisomerisation of all-*trans*-retinal (IV) in various solvents, the amount of the *cis* isomer depended on the polarity of the solvent.[6] 13-*cis*-Retinal was predominantly formed in a nonpolar solvent such as *n*-hexane, and a substantial amount of 11-*cis*-retinal was produced in a polar, aprotic solvent such as acetonitrile. In the present work, the isomerisation yield at the Δ^{13}-double bond in a polar solvent was higher than in a nonpolar solvent and no 11-*cis*-retro-γ-retinal was formed in the solvents used. The differences in photoisomerisation behaviour in the trienal (retro-γ-retinal), the pentaenal (retinal), and the hexaenal (3-dehydroretinal)[7] systems are very interesting. Studies on the mechanisms of photochemical reaction in the conjugated polyenals are in progress.

Experimental

UV spectra were recorded on a Shimadzu UV 200S instrument. NMR spectrum at 200 MHz was determined on a Varian XL-200 superconducting FT-NMR spectrometer using deuteriochloroform solution. Mass spectrum was determined on a JEOL JMS-01SG mass spectrometer; high resolution measurement

was made relative to perfluorokerosene as a reference. All analytical studies were performed with a Shimadzu-DuPont 830 liquid chromatograph, equipped with a UV-202 spectrophotometer. Operating conditions for HPLC are as follows: column, μ-Porasil (30 × 0.4 cm); pressure, 20 kg/cm²; temperature, ambient; detector, UV at 254 nm; mobile phase, 12% diethyl ether in *n*-hexane. Irradiation was carried out as follows: *ca.* 0.1% solution of 9-*cis*-retro-γ-retinal in each solvent was stirred in a flask and exposed to light from a 43 cm long fluorescent lamp (30 W) at a distance of 15 cm.

9,13-Di-*cis*-retro-γ-retinal (III)——MS *m/e*: 284.212 (M^+, $C_{20}H_{28}O$ requires 284.214); UV λ_{max}^{EtOH} 335 nm; NMR δ ($CDCl_3$, 200 MHz), 1.03 (6H, s, *gem*.CH_3), 1.85 (3H, s, C-9-CH_3), 2.10 (3H, s, C-13-CH_3), 3.12 (2H, d, J=7.3 Hz, C-8-H_2), 4.62 (1H, d, J=2.8 Hz, *exo*CH_2), 5.06 (1H, m, *exo*CH_2), 5.14 (1H, t, J=7.3 Hz, C-7-H), 5.81 (1H, d, J=8.1 Hz, C-14-H), 6.00 (1H, d, J=11 Hz, C-10-H), 6.91 (1H, dd, J=11, 15 Hz, C-11-H), 7.15 (1H, d, J=15 Hz, C-12-H), 10.18 (1H, d, J=8.1 Hz, C-15-H).

UV data for retro-γ-retinal isomers

isomer	λ_{max}^{EtOH} nm[8]	ε	$\lambda_{max}^{n\text{-hexane}}$	ε
all-*trans*	340	24300	320	36500
9-*cis*	339	23400	320	35100
11-*cis*	339	13900	321	20800
	228	8900	225	10800
9,13-di-*cis*	335	18100	317	27200

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References and Notes

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8) The published[1] UV data for the retro-γ-retinals should have given the λ_{max}^{EtOH} values of the isomers as in this table.

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Asymmetric Synthesis by Using the Chirality of *l*-Ephedrine. II.[1] Synthesis of (*R*)-α-Phenylethylamine

Hiroshi Takahashi,* Kouichi Tomita, and Hiromi Noguchi

Hoshi Institute of Pharmaceutical Sciences, Ebara 2-Chome, Shinagawa-ku, Tokyo 142, Japan

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The chiral hydrazone (II), obtained by the condensation of *N*-aminoephedrine with benzaldehyde, was reacted with Grignard reagent to give the chiral hydrazine (IVa) in almost 100% diastereomeric excess. On the other hand, the chiral hydrazone (III) was reduced by lithium aluminium hydride to give the chiral hydrazine (IV).

Hydrogenolysis of the chiral hydrazine (IVa) gave (*R*)-α-phenylethylamine (Va) with more than 97% optical purity, and *l*-ephedrine used as a chiral auxiliary reagent was