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All-*CIS*-RETINAL and 7-*CIS*,9-*CIS*,11-*CIS*-RETINAL[1]

by

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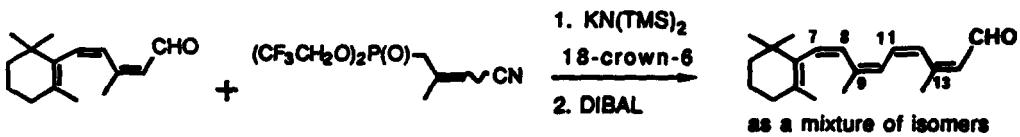
Abstract. A modified 15 + 5 route led to 7-*cis*,9-*cis*,11-*cis*-retinonitrile in high selectivity and also a lesser amount of all-*cis*-retinonitrile. DIBAL reduction gave the corresponding retinal isomers. The absorption maximum (287nm) of all-*cis*-retinal reveals the distorted nature of the chromophore.

The importance of the role of stereoisomers of retinal in the chemistry of the visual chromophore was demonstrated by Wald and coworkers[2] following the successful synthesis of six isomers (all-trans, 13-cis, 11-cis, 9-cis, 11,13-dicis and 9,13-dicis) of vitamin A by Oroshnik.[3] More recently, preparation of seven new isomers of retinal have been reported from this laboratory (7-cis, 7,9-dicis, 7,13-dicis, 7,9,13-tricis, 9,11-dicis, 7,11-dicis and 7,9,11-tricis)[4] and one (9,11,13-tricis) by Okamura and coworkers.[5] The two missing are the 7,11,13-tricis and all-cis isomers. In this paper we wish to describe the synthesis of the highly strained all-*cis*-retinal and properties of this labile isomer.

Recently, Still and Gennari[6] reported a modified procedure for the Horner's reaction leading to highly cis selective construction of disubstituted double bonds. This procedure was adapted by Mead[7] for construction of the 11-cis geometry in a fluorinated retinoid. It has now been incorporated into a sequence for preparation of all-*cis*-retinal as well as 7-*cis*,9-*cis*,11-*cis*-retinal.



The modified C-5 phosphonate reagent was prepared by a procedure similar to that described for the C-2 phosphonate.[6] Condensation of the phosphonate with 7-*cis*,9-*cis*-C-15-aldehyde 2, prepared by selective sensitization of the corresponding nitrile followed by partial reduction with DIBAL,[8] was carried out at -78°C in THF in the presence of $KN(TMS)_2$/18-crown-6,[6] followed by warming briefly to room temperature. The crude retinonitrile (45% yield) was found to contain four isomers (7,9-dicis : 7,9,11-tricis : 7,9,13-tricis : all-cis = 21 : 66 : 7 : 6). They were isolated by preparative hplc. The 7,9-dicis and 7,9,13-tricis isomers were characterized by comparison of known ^{1}H-nmr spectra

while 7-cis,9-cis,11-cis- and all-cis-retinonitrile exhibited expected spectroscopic properties.[9] All isomers were found to be stable at room temperature.

Conversion of the retinonitriles to the corresponding retinals were accomplished by reaction with DIBAL at low temperature (-78°), and subsequent hydrolysis with NaF/H_2O (-78°) followed by usual work-up, and product isolation by flash column chromatography. The high yield of retinals (>90%) coupled with the high selectivity in the formation of the tricis retinonitrile makes this procedure superior to the one reported earlier for preparation of 7-cis,9-cis,11-cis-retinal.[4]

In the case of the all-cis-retinal the crude product mixture also was found to contain essentially one single isomer. Its ^{1}H-NMR spectrum (benzene-d_6) is in agreement with one containing the all-cis geometry.[10] However, the compound was found to isomerize readily at room temperature to another isomer of retinal thus complicating the recording of spectral data, especially in the case of its uv-vis spectrum where the rearranged isomer absorbed much more strongly than the all-cis isomer. Only after the employment of a diode array detector a spectrum believed not to be complicated by absorption of the rearranged product, as indicated by the absence of a 360nm band, was successfully recorded (Figure 1). The much blue-shifted absorption maximum (287nm) clearly reflected the highly distorted nature of the all-cis chromophore to an extent even more than that of 9-cis,11-cis,13-cis-retinal.[11]

The product from thermal rearrangement of all-cis-retinal was subsequently shown, by comparison of ^{1}H-NMR spectra,[12] to be 7-cis,9-cis,13-cis-retinal. We have followed this rearrangement by nmr and by uv. The unimolecular nature of the rearrangement was indicated by kinetic plots and by the isosebestic point in plots of time dependent uv-vis spectra such as the one shown in Figure 2. Its rates at 40, 30, 20, 10°C are 6.99×10^{-3}, 2.99×10^{-3},

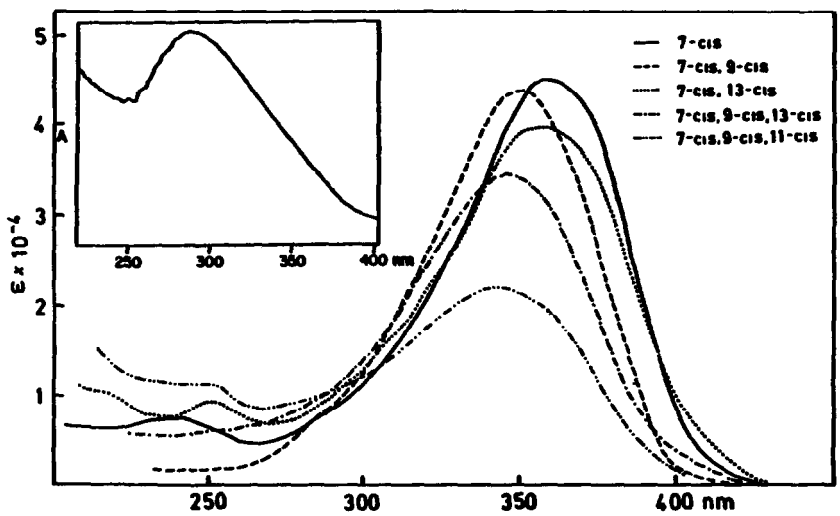


Figure 1. UV-vis absorption spectra of hindered (7-cis) isomers of retinal (hexane) all showing λ_{max} near 360nm.[4b] Insert. Absorption spectrum of all-cis-retinal recorded on a H.P.-1040A diode array hplc detector in 5% ether in hexane, λ_{max} = 287nm (ε, Figure 2).

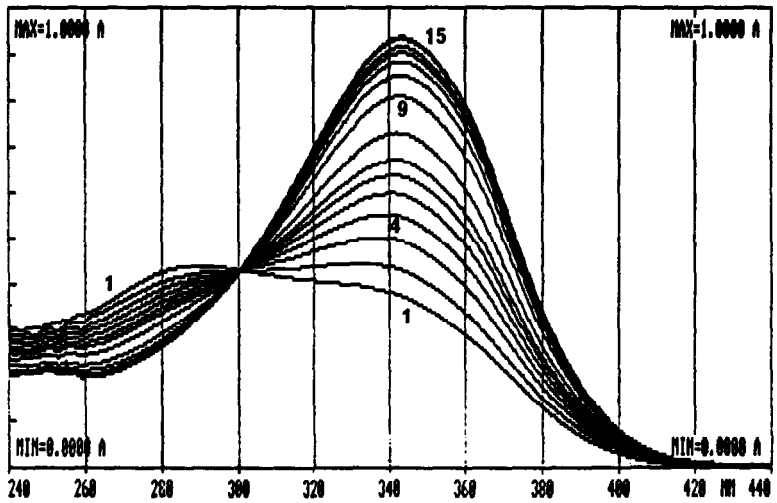
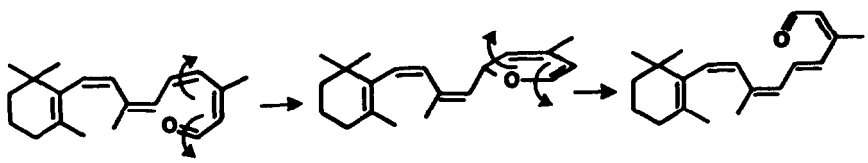


Figure 2. Conversion of all-*cis*-retinal to 7-*cis*,9-*cis*,13-*cis*-retinal at 40°C (in hexane), spectra recorded at the following time delays: 0 (spectrum 1), 15, 30, 45, 60, 75, 90, 120, 180, 240, 300, 360, 415, 535, 576 (spectrum 15) min. Based on ϵ = 36,600[12] for 7-*cis*,9-*cis*,13-*cis*-retinal, the ϵ for all-*cis*-retinal was determined to be 5,300.

1.64×10^{-3}, 1.46×10^{-4} sec^{-1} respectively giving an activation energy of 21.7 kcal/mole for the reaction.

This rearrangment appears to be characteristic of those isomers of retinal containing the 11,13-dicis geometry.[2,4d,e,5] In agreement with the suggestion made by Kluge and Lillya for dienones,[13] we believe the isomerization involves two consecutive 6e electrocyclization processes via an α-pyran intermediate:



This rearrangement should be a reversible one. The absence of the all-cis isomer in the equilibrium mixture is likely due to an energy difference between the all-cis and 7,9,13-tricis isomers. Indeed a recent calculation (by MMP2-85) showed that all-*cis*-retinal is higher by 6.4 kcal/mole than 7-*cis*,9-*cis*,13-*cis*-retinal.[14]

In summary, we have shown that all-*cis*-retinal, despite the severe steric crowding, is sufficiently stable for isolation.[15] The procedure described herein is also applicable for preparation of all other hindered isomers of retinal, including the remaining 7-*cis*,11-*cis*,13-*cis*-retinal. Results from these extended studies will be disclosed in a full paper in the future.

Acknowledgment. The work described in this paper was supported by a grant from the U.S. Public Health Services (DK 17806) and partially by the UH Biomedical Program. Dennis Mead first suggested preparation of all-*cis*-retinal by the route reported herein.

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9. 7-Cis,9-cis,11-cis-retinonitrile: ^{1}H-NMR (300 MHz, $CDCl_3$, TMS) same as that reported (ref. 12) except that the assignments for 7-H and 10-H were reversed. ^{13}C-NMR (75 MHz, $CDCl_3$) 19.2 (3-C), 21.5 (20-C), 21.7 (18-C), 22.2 (19-C), 29.0 (16-C, 17-C), 32.5 (4-C), 34.5 (1-C), 39.4 (2-C), 98.5 (14-C), 117.5 (15-C), 124.8 (10-C), 126.5 (12-C), 127.4 (8-C), 130.5 (5-C), 130.6 (11-C), 132.1 (7-C), 136.7 (6-C), 142.7 (9-C), 157.6 (13-C). All-cis-retinonitrile: ^{1}H-NMR ($CDCl_3$) 1.05 (s, 16-CH_3, 17-CH_3), 1.46 (s, 18-CH_3), 1.88 (s, 19-CH_3), 2.19 (s, 20-CH_3), 5.13 (d, 14-H), 6.15 (d, 7-H), 6.28 (d, 12-H), 6.34 (d, 10-H), 6.54 (d, 8-H), 6.72 (dd, 11-H) ppm; $J_{7,8}$ = 12.7 Hz, $J_{10,11}$ = 12.4 Hz, $J_{11,12}$ = 12.0 Hz. ^{13}C-NMR (75 MHz, $CDCl_3$) 19.2 (3-C), 21.8 (18-C), 22.5 (19-C), 24.1 (20-C), 29.0 (16-C, 17-C), 32.4 (4-C), 34.4 (1-C), 39.2 (2-C), 97.5 (14-C), 123.8 (12-C), 125.0 (10-C), 127.2 (8-C), 130.6 (5-C), 131.4 (11-C), 132.3 (7-C), 136.6 (6-C), 143.0 (13-C). ^{13}C assignments based on ^{1}H-^{13}C correlation plots.
10. All-cis-retinal: ^{1}H-NMR (300 MHz, C_6D_6, unstable in $CDCl_3$) δ 1.04 (s, 16-CH_3, 17-CH_3), 1.50 (s, 18-CH_3), 1.51 (s, 19-CH_3), 1.77 (s, 20-CH_3), 5.56 (12-H), 5.90 (14-H), 6.06 (d, 7-H), 6.13 (d, 10-H), 6.41 (d, 8-H), 6.54 (dd, 11-H), 9.89 (d, 15-H) ppm; $J_{7,8}$ = 12.6 Hz, $J_{10,11}$ = 10.8 Hz, $J_{11,12}$ = 11.6 Hz, $J_{14,15}$ = 7.9 Hz. 7-cis,9-cis,11-cis-Retinal: ^{1}H-NMR identical to that reported (ref. 4d).
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14. Unpublished results of T. Mirzadegan and R. S. H. Liu.
15. No pigment formation was detected after 2 h incubation of all-cis-retinal with bovine opsin (preliminary results of M. Denny). Ready isomerization to an active isomer complicates results from extended incubation.

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