Tetrahedron Letters,Vol.28,No.26,pp 2921-2924,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

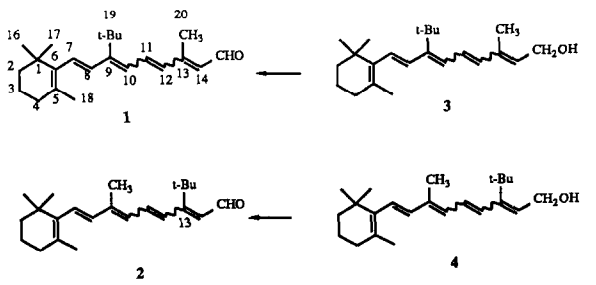
19,19,19- AND 20,20,20-TRIMETHYLRETINAL: SIDE CHAIN TERT-BUTYL SUBSTITUTED RETINALS

Angel R. de Lera and William H. Okamura*

Department of Chemistry, University of California, Riverside, California 92521

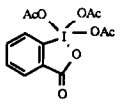
Abstract: The 11-cis, 13-cis, 11,13-dicis and 9,11,13-tricis isomers of 19,19,19-trimethylretinal (1) and the 13-cis and 11,13-dicis isomers of 20,20,20-trimethylretinal (2) were synthesized and characterized. The Dess-Martin reagent 5 is an effective oxidant for the retinol to retinal conversion.

The visual chromophore rhodopsin and bacteriorhodopsin, the chromophore in the proton pump system of Halobacterium halobium, both contain specific geometric isomers of retinal (vitamin A aldehyde) attached covalently via a protonated Schiff's base linkage to an ε-amino group of a lysine residue of their respective apoproteins. Retinal analogues are of interest in order to probe the structure and hence the molecular mode of action of these pigments in vision and in energy transduction, respectively.[1] A recent report[2] by Hopf and co-workers describes the preparation of several 9-cis, 13-cis and 9,13-dicis-retinals bearing side-chain tert-butyl groups. These include the 9-cis (1a) and 9,13-dicis (1b) isomers of 19,19,19-trimethylretinal (9-t-Bu) and the 9,13-dicis (2b) and 13-cis (2c) isomers of 20,20,20-trimethylretinal (13-t-Bu). The accompanying communication describes the preparation of several retinols also bearing side chain t-butyl groups at C-9 and C-13, but possessing 11-cis geometries.[3] It is the purpose of this communication to report the preparation and characterization of the 11,13-dicis (1d), the 9,11,13-tricis (1e) and the 11-cis (1f) isomers of 19,19,19-trimethylretinal and the 11,13-dicis isomer (2d) of 20,20,20-trimethylretinal. The 13-cis-isomers 1c and 2c, resulting from thermal isomerization of their respective 11,13-dicis-isomers, were also isolated and characterized.

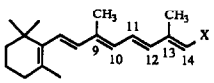


a, Δ^9=Z; Δ^{11}=Δ^{13}=E (9-cis)
b, Δ^9=Δ^{13}=Z; Δ^{11}=E (9,13-dicis)
c, Δ^{13}=Z; Δ^9=Δ^{11}=E (13-cis)
d, Δ^{11}=Δ^{13}=Z; Δ^9=E (11,13-dicis)
e, Δ^9=Δ^{11}=Δ^{13}=Z (9,11,13-tricis)
f, Δ^{11}=Z; Δ^9=Δ^{13}=E (11-cis)
g, Δ^9=Δ^{11}=Z; Δ^{13}=E (9,11-dicis)
h, Δ^9=Δ^{11}=Δ^{13}=E (all-trans)

The Dess-Martin periodinane reagent 5[4] proved to effect rapid, reproducible allylic oxidation of the highly sensitive retinols[3] to the correspondingly sensitive retinals. The 11-cis-isomer 3f upon treatment with 5 in dry CH_2Cl_2 for only 10 min at room temperature (or with ice cooling) afforded the corresponding retinal 1f in 75% yield after HPLC purification.[5] Similarly, oxidation of retinols 3d, 3e and 4d afforded retinals 1d (72%), 1e (60%) and 2d (66%), respectively, with no substantial attempts at optimization. Vitamin A (6a) itself afforded all-trans-retinal (6b) in similar yield (70%). The short reaction time needed for

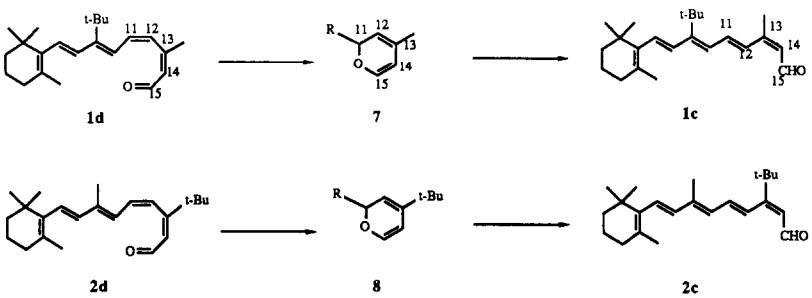


5, Dess-Martin Periodinane



6a, X=CH_2OH
b, X=CHO

this oxidation is especially useful for producing retinal isomers with 11,13-dicis geometries. The latter are prone to undergo rather facile electrocyclic isomerization to the corresponding 13-cis isomers[6,7] even at room temperature. For preparative purposes, the two 11,13-dicis-retinals 1d and 2d were observed to isomerize completely to the corresponding 13-cis-isomers 1c and 2c, respectively, within 3 h at 69 °C. These transformations are thought to proceed through the intermediacy of electrocyclized pyran tautomers 7 and 8.[7]



The various retinals prepared in this study were characterized by ^{1}H-NMR analysis including NOE studies and by UV spectroscopy. The data for each of the isomers is summarized in Tables I and II. Aside from the method of synthesis and the obvious presence of Δ^7 E and Δ^{11} Z or E configurations as well as a planar 10-s-trans conformation (from NMR coupling constants), the remaining NMR assignments including information on the configurations of the Δ^9 and Δ^{13} double bonds were made on the basis of detailed NOE experiments. The NOE studies also provided information regarding conformation of these highly hindered retinals. In the 9-t-butyl series, irradiation of the t-butyl signal of all four isomers (1c-1f) caused enhancement of both H_7 and H_8 signals (suggesting significant contribution from the 8-s-cis-conformation as also suggested by Hopf for 9-cis-1a[2]) and irradiation of the C-13 methyl signal of 11,13-dicis-1d and 9,11,13-tricis-1e gave enhancement of H_{12} and H_{14}

(suggesting 12-s-cis contribution as in the parent system[7b]). Like 9-t-butyl derivatives 1d and 1e, the two 13-t-butyl isomers 2c (13-cis; also synthesized by Hopf[2]) and 2d (11,13-dicis) exist as 12-s-cis conformers (as deduced from NOE enhancement of H_{12} and H_{14} upon saturation of the t-butyl group resonance). However, in contrast to the four 9-t-butyl isomers, irradiation of the C-9 alkyl caused enhancement of H_7 but not H_8 (suggesting little if any contribution by an 8-s-cis conformer as in the parent system).[8]

TABLE I ^{1}H-NMR SPECTRAL DATA[a]

	H_7	H_8	H_{10}	H_{11}	H_{12}	H_{14}	H_{15}	$C_{16,17}$ CH_3	t-Bu	C_{18} CH_3	$C_{19/20}$ CH_3	$(J_{7,8})$[b]	$(J_{10,11})$[b]	$(J_{11,12})$[b]	$(J_{14,15})$[b]
1c	6.25	6.17	6.35	7.30	7.20	5.86	10.23	1.05	1.30	1.72	2.14	(15.5)	(11.3)	(14.8)	(7.9)
1d	6.05	6.05	6.27	6.97	6.02	5.96	9.68	0.99	1.24	1.65	2.07	(br s)	(12.3)	(12.3)	(8.1)
1e	5.92	6.02	6.23	6.85	6.01	5.95	9.71	1.05	1.08	1.78	2.09	(15.8)	(11.6)	(11.6)	(7.7)
1f	6.16	6.16	6.59	6.91	5.91	6.09	10.08	1.02	1.26	1.70	2.36	(br s)	(12.0)	(12.0)	(7.9)
2c	6.31	6.13	6.19	6.70	6.33	6.11	9.70	1.04	1.18	1.73	1.97	(16.2)	(11.5)	(14.7)	(8.0)
2d	6.22	6.02	6.01	6.88	6.09	6.07	9.59	1.01	1.17	1.68	1.96	(16.0)	(11.9)	(11.9)	(7.8)

[a] ^{1}H-NMR (300 MHz, $CDCl_3$). Chemical shifts are in δ, ppm. [b] Coupling constants (J, hertz) are given in parentheses.

The UV electronic absorption spectra of retinals are generally characterized by a strong α-band at > 350 nm and a weaker β-band in the region 280~300 nm.[9] Shorter wave length bands (γ, δ, etc) of still ill-defined origin are also frequently observed. Perhaps not surprisingly, the 9-t-butyl series 1 exhibits a distinct hypsochromic shift (as well as attenuation

TABLE II UV ABSORPTION DATA

	$\lambda_{max}^{95\%\ EtOH}$ nm (ε)	$\lambda_{max}^{hexanes}$ nm (ε)	$\lambda_{max}^{CH_3CN}$ nm (ε)
1c	258 (10,300), 362 (22,600)	254 (8,200), 348 (22,300)	256 (12,300), 358 (24,700)
1d	234 (12,800), 278 (10,100) 344sh (5,800)	216 (13,100), 234sh (11,100) 278 (10,000), 338sh (7,500)	236 (12,800), 278 (10,500) 346sh (6,600)
1e	234 (19,400), 274 (14,300) 340sh (10,600),	218 (20,000), 226sh (19,100) 274 (14,400), 322 (14,900)	236 (17,400), 274 (14,000) 334 (19,100)
1f	252 (12,100), 286sh (8,400) 364 (11,000)	248 (11,000), 278sh (8,200) 348 (11,500)	252 (11,000), 278sh (8,700) 358 (11,500)
2c	224 (11,100), 256 (10,800) 328 (13,200), 366 (13,000)	222 (11,200), 248 (9,800) 326 (18,300)	224 (12,600), 252 (10,800) 330 (16,500)
2d	234 (19,600), 300 (25,000)	226 (18,500), 302 (24,900)	230 (19,700), 302 (25,400)

of absorption intensities throughout) of the λ_{max} (Table II; only the 95% ethanol data are discussed here) of the α-band with increasing steric congestion in the side chain (13-cis ~ 11-cis < 11,13-dicis ~ 9,11,13-tricis; 362 nm ~ 364 nm > 344 nm ~ 342 nm). However, the latter two very hindered isomers (**1d** and **1e**, respectively) differ strikingly from the parent series (t-Bu replaced by methyl) in their β-band λ_{max} positions (278 nm and 274 nm, respectively; 302 nm and 302 nm, respectively, for the corresponding parent isomers[7b] and related 12-s-cis isomers[9]). This difference may be associated with contribution by a significant 8-s-cis rotamer population as implied by the NOE results described above. The two 13-t-butyl retinals, 13-cis-**2c** and 11,13-dicis-**2d**, on the basis of the NMR results above, are considered to exist in the 8-s-trans,10-s-trans,12-s-cis conformation. These 13-t-butyl isomers (**2c** and **2d**) exhibit UV absorptions strikingly similar to the absorptions of the same geometric isomers of 12-s-cis locked (ring-fused) retinals,[9] which are considered to be conformationally similar.

Acknowledgements. The National Institutes of Health (USPHS Grant DK-16595), NATO (Postdoctoral Fellowship to A.R. de Lera) and Badische-Anilin und Soda Fabrk, Ludwigshafen (starting materials), are acknowledged for support of this study.

References and Notes

(1) Sporn, M.B.; Roberts, A.B.; Goodman, D.S. "The Retinoids", Academic Press: New York, 1984, Vol. 1 and 2.

(2) Ernst, L.; Hopf, H.: Krause, N. J. Org. Chem., 1987, 52, 398.

(3) Shen, G.-Y.; de Lera, A.R.; Norman, T.C.; Haces, A.; Okamura, W.H. Tetrahedron Lett., preceding communication.

(4) Dess, D.B.; Martin, J.C. J. Org. Chem., 1983, 48, 4155.

(5) In a typical experiment (dark room under a dim red light), 11-cis-**3f** (57 mg) in dry CH_2Cl_2 (1.5 mL) was added to a stirred solution of **5** (81 mg, 1.1 equiv) in dry CH_2Cl_2 (2 mL) under argon. After 10 min stirring (r.t. or ice-cooled), the reaction mixture was diluted with ether (5 mL) and then the mixture was poured into saturated aqueous $NaHCO_3$ containing $Na_2S_2O_3 \cdot 5H_2O$ (330 mg). After ether extraction and washing of the ether layer with aqueous $NaHCO_3$ and water, the vacuum dried residue from the ether solution was subjected to HPLC purification (Whatman Partisil M9 10/50 column, 5% EtOAc/Skellysolve B) to afford pure retinal **1f** (43 mg, 75%). Finally, it should be noted that freshly opened bottles of reagent **5** (stored in a refrigerator) appeared to effect higher yields.

(6) Classical manganese dioxide allylic oxidations are occasionally capricious for these sensitive molecules and reactions times can be unacceptably lengthy (r.t., 17 h) in some cases. For example, see pp. 51-52 in Volume 1 of reference 1.

(7) (a) Okamura, W.H. Acc. Chem. Res. 1983, 16, 81. (b) Knudsen, C.G.; Chandraratna, R.A.S.; Walkeapää, L.P.; Chauhan, Y.S.; Carey, S.C.; Cooper, T.M.; Birge, R.R. and Okamura, W.H. J. Am. Chem. Soc. 1983, 105, 1626. (c) Chandraratna, R.A.S.; Bayerque, A.L. and Okamura, W.H. J. Am. Chem. Soc. 1983, 105, 3588.

(8) (a) Rowan, R.; Warshel, A.; Sykes, B.D.; Karplus, M. Biochemistry 1974, 13, 970. (b) Becker, R.S.; Berger, S.; Dalling, D.K.; Grant, D.M.; Pugmire, R.J. J. Am. Chem. Soc. 1974, 96, 7008.

(9) Chandraratna, R.A.S.; Birge, R.R.; Okamura, W.H. Tetrahedron Lett. 1984, 25, 1007 and the references cited.

(Received in USA 20 March 1987)