Tetrahedron Letters No. 35, pp 3223 - 3226.

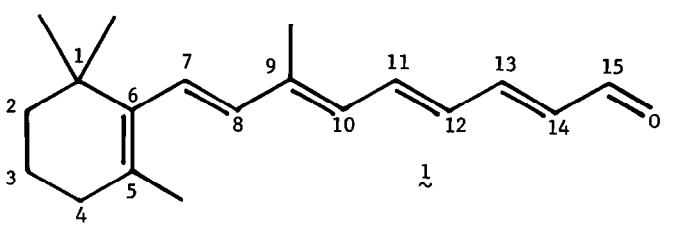
0040-4039/78/0822-3223$02.00/0

PHOTOCHEMICAL SYNTHESIS OF CIS ISOMERS OF RETINAL ANALOGS. 13-DEMETHYLRETINAL.

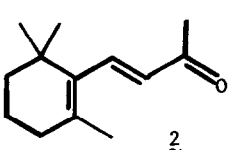
Walter H. Waddell,* Motokazu Uemura, and John L. West
Department of Chemistry
Carnegie-Mellon University
Pittsburgh, Pennsylvania 15213

Owing to the importance of Vitamin A related compounds to the visual protein rhodopsin,[1] bacteriorhodopsin,[2] retinochrome,[3] and as potential anticancer agents,[4] we[5-7] have previously examined the spectroscopic and photochemical properties of the all-trans isomers of retinal, 14-methylretinal, 10,14-dimethylretinal and 13-demethylretinal. Now we report the photochemical synthesis of certain cis isomers of the modified retinoid--13-demethylretinal.

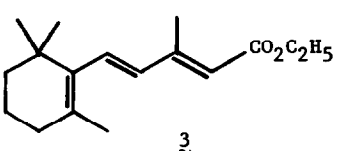
All-trans-13-demethylretinal (1) was synthesized according to the procedure of van den Tempel and Huisman.[8] The Emmons[9] reaction of β-ionone (2)[10] and the α-phosphonate of ethylacetate yielded a C-15 ethylester (3) which was reduced with lithium aluminum hydride then oxidized with manganese dioxide[11] giving β-ionylidene acetaldehyde (4, C-15 aldehyde). The reaction of 4 and the γ-phosphonate of methylcrotonate gave the C-19 methylester (5) which was reduced with diisobutylaluminum hydride to 13-demethylretinol (6). Manganese dioxide oxidation of 6 gave the desired product, all-trans-13-demethylretinal (1). Polyenes 1, 4 and 5 were isolated and purified using a Waters Prep LC/System 500 liquid chromatograph that was modified for uv detection by employing a Waters Model 440 Absorbance Detector. The separation conditions are similar to those reported by Pettei, Pilkiewicz and Nakanishi[12]--two 12 x 2 inch Waters silica gel columns, 5-8% ether in hexane, 250 ml/min, and 365 nm detection. Thus, gram quantities of the purified polyenes could be obtained via one chromatogram in > 95% purity. Figure 1 is a high pressure liquid chromatogram (HPLC) of 1 obtained in this manner.



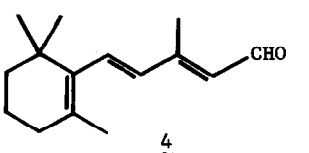
1



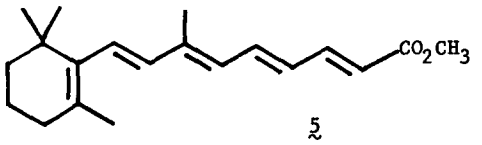
2



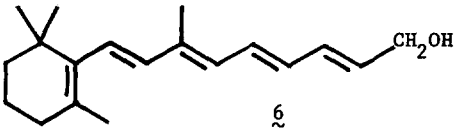
3



4



5



6

Upon 430 nm irradiation of room temperature solutions of all-trans-13-demethylretinal in ethanol (10^{-3} to 10^{-5}M) a number of products are formed. Upon continued irradiation, the concentration of these new compounds increases until a photoequilibrium mixture is established. Figure 2 is an analytical HPLC of the photoequilibrium mixture.

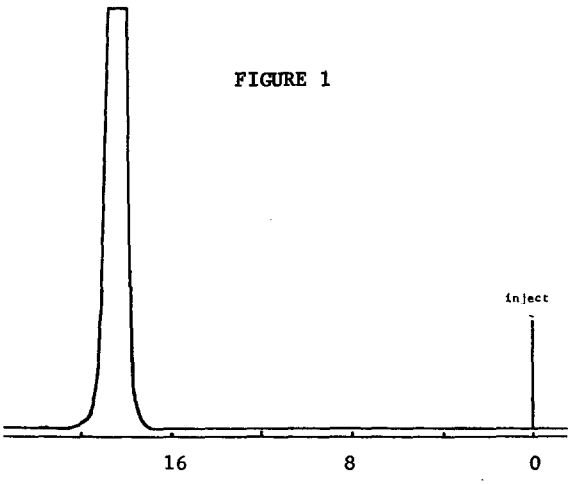


FIGURE 1

Relative Retention, min

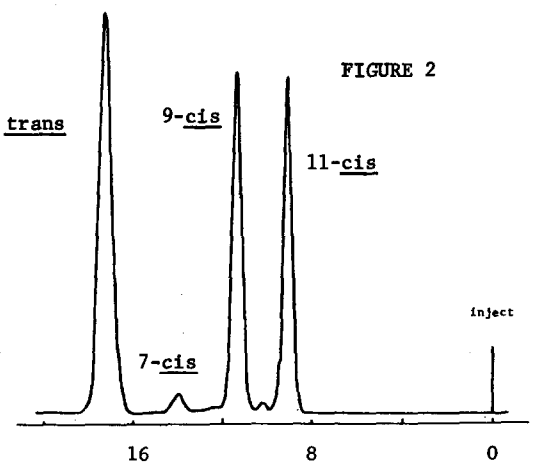


FIGURE 2

Relative Retention, min

Three of the major products were isolated and purified to > 99% using a Waters ALC/GPC 204 liquid chromatograph. Samples were identified using ^{1}H NMR spectra recorded on a HF 250 MHz NMR Spectrometer. Table I is a summary of the NMR chemical shift data of 1 and its three major photoproducts. Thus, it was determined that upon irradiation of 1 7-cis-, 9-cis-, and 11-cis-13-demethylretinal are formed. Figure 3 is a NMR spectrum of 9-cis-13-demethylretinal in C_6D_6. 13-cis-13-demethylretinal is not a photochemical product, but several dicis isomers are thought present. At photoequilibrium we obtained 37%, 3%, 30% and 27%, respectively of all-trans-, 7-cis-, 9-cis-, and 11-cis-13-demethylretinal.[13]

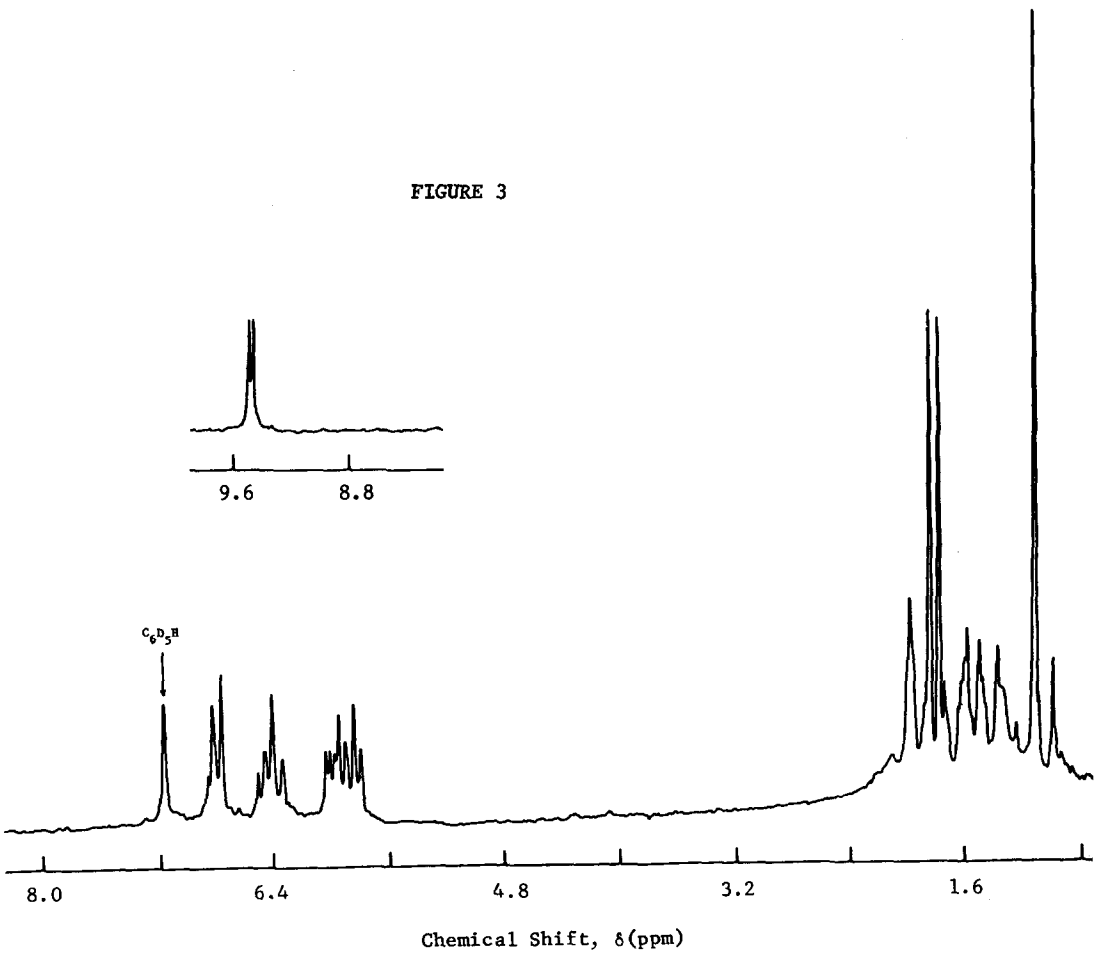
Tanis, Brown and Nakanishi[14] have recently reported the facile synthesis of several methylated retinals--10-methyl-, 14-methyl-, and 10,14-dimethylretinal. They employed preparative HPLC methods to obtain the 9-cis-, 13-cis-, and all-trans isomers. The important 11-cis retinoids were not obtained. 11-cis-13-demethylretinal is obtained as a major product upon irradiation of 1 in ethanol. In addition, the sterically hindered 7-cis isomer is formed. Since the distribution of the major isomers of the retinals is dependent upon excitation energy, irradiation time, solvent, and concentration,[1,6,15-17] we expect that the yields of the various cis isomers of these retinal analogs can be further optimized.

Table I. ^{1}H NMR Chemical Shift Data[a]

demethylretinal	$(CH_3)_2$-1	CH_3-5	H-7	H-8	CH_3-9	H-10	H-11	H-12	H-13	H-14	H-15
all-trans	1.14	1.70	6.38	6.22	1.77	5.96	6.65	6.21	6.56	6.02	9.47
7-cis	1.07	1.61	6.38	6.39	1.68	–	–	–	–	6.06	9.51
9-cis	1.09	1.75	6.37	6.79	1.83	5.93	6.80	5.85	6.46	5.99	9.47
11-cis	1.15	1.73	6.39	6.30	1.77	6.42	5.80	5.77	7.12	6.01	9.42

[a]Recorded on a HF 250 MHz NMR Spectrometer; C_6D_6 (Aldrich Chemicals, 100% atom D); chemical shift in δ (ppm).

FIGURE 3



ACKNOWLEDGEMENTS

The authors wish to thank the Health Research and Services Foundation and the National Eye Institute, National Institutes of Health (Grants EY 01777 and EY 01930) for their generous support of this research, and the Carnegie-Mellon University NMR Facility for Biomedical Studies supported by the National Institutes of Health (Grant RR 00292) for use of the NMR spectrometer.

REFERENCES AND NOTES

1. R. Hubbard and G. Wald, J. Gen. Physiol. 36, 269 (1952-53).
2. D. Oesterhelt and W. Stoeckenius, Nature, New Biology 233, 149 (1971).
3. T. Hara and R. Hara, Nature 214, 573 (1967).
4. M. B. Sporn, Nutrition Reviews 35, 65 (1977).
5. W. H. Waddell, R. Crouch, K. Nakanishi, and N. J. Turro, J. Amer. Chem. Soc. 98, 4189 (1976)
6. W. H. Waddell and D. L. Hopkins, J. Amer. Chem. Soc. 99, 6457 (1977).
7. W. H. Waddell, D. L. Hopkins, M. Uemura, and J. L. West, J. Amer. Chem. Soc. 100, 1970 (1978)
8. P. J. van den Tempel and H. O. Huisman, Tetrahedron 22, 293 (1966).
9. W. S. Wadsworth and W. D. Emmons, J. Amer. Chem. Soc. 83, 1733 (1961).
10. Purchased from Aldrich Chemical Company and vacumm distilled prior to use.
11. Active MnO_2 was prepared according to the procedure of J. Attenburro, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, J. Chem. Soc. 1094 (1952).
12. M. J. Pettei, F. G. Pilkiewicz, and K. Nakanishi, Tetrahedron Lett. 24, 2083 (1977).
13. Unidentified minor products total 3% of the irradiation mixture.
14. S. P. Tanis, R. H. Brown, and K. Nakanishi, Tetrahedron Lett. 10, 869 (1978).
15. M. Denny and R. S. H. Liu, J. Amer. Chem. Soc. 99, 4865 (1977).
16. R. Hubbard, R. I. Gregerman, and G. Wald, J. Gen. Physiol. 36, 415 (1952-53).
17. P. K. Brown and G. Wald, J. Biol. Chem. 222, 865 (1956).

(Received in USA 22 May 1978; received in UK for publication 4 July 1978)