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Condensation of All-*E*-Retinal

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Abstract: A novel base induced self condensation product of all-*E*-retinal is presented. The scope of the reaction is investigated with three analogous α,β-unsaturated aldehydes.

Retinoids form an important class of biologically active molecules. They serve as chromophores for the visual signal transduction systems of animals (rhodopsins),[1, 2] the purple membranes for protonpumping (bacteriorhodopsins)[3, 4] and chloride ion pumping (halorhodopsins).[5, 6] To study the structure and function of these intrinsic membrane proteins, an impressive number of chemically modified and isotopically labelled retinals has been reported in literature.[7-10]

Recently, a novel biologically active compound was reported comprising two retinal moieties.[11] The accumulation of this compound in the retina, is thought to be the main cause of age-related macular degeneration, the leading cause of blindness in elderly people. It is suggested that the compound is formed *via* a condensation of two retinal molecules and an ethanol amine unit.[11] In this letter we wish to report a novel base induced condensation product of all-*E*-retinal. From several observations in our laboratories, it is known that retinal is not stable in basic media. The basic conditions during the work up of *e.g.* a dibal-H reduction of C_{20}-nitrile[12] yielding retinal, promotes the formation of a dark-red byproduct. To elucidate the structure of the byproduct, we synthesized the red compound on a half gram scale and in 80 % yield by treating all-*E*-retinal with 1 equivalent of sodium hydride in dry tetrahydrofuran. Mass spectrometry determined the molecular mass of the product compound to be m/z = 550, indicating that the reaction product was formed *via* a base induced self condensation of retinal, which mass is 284. High resolution ^{1}H and ^{13}C NMR enables us to present the structure of the compound, 4,6-di-(4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1*E*,3*E*,5*E*-1,3,5-hexatrienyl)-6-methyl-cyclohexa-1,3-diene carbaldehyde, an all-*E*-retinal condensation product (**1**),[13] which structure is depicted in Figure 1. It is well known, that α,β-unsaturated aldehydes possessing a β-methyl substituent are prone to base induced condensations.[14-16] Under the basic conditions provided by the sodium hydride, one of the relative acidic C20-methyl protons is abstracted by the strong base. The resulting anion of retinal reacts in a Michael addition with a neutral retinal molecule at C13, resulting in the formation of a non-cyclic C_{40} adduct (**I**) as shown in Scheme 1.

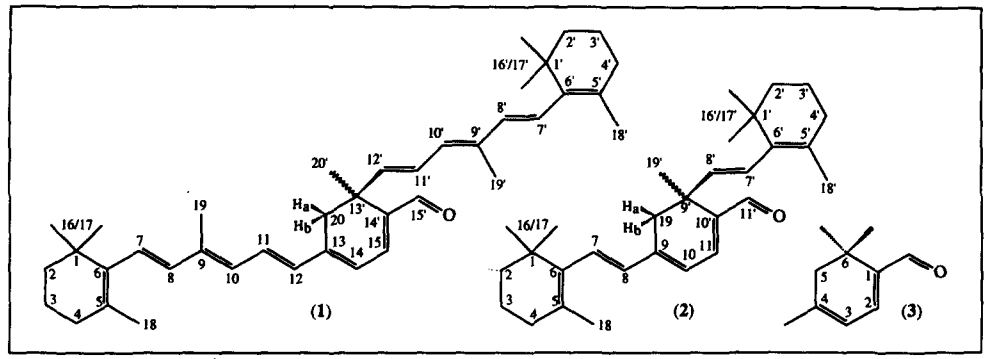
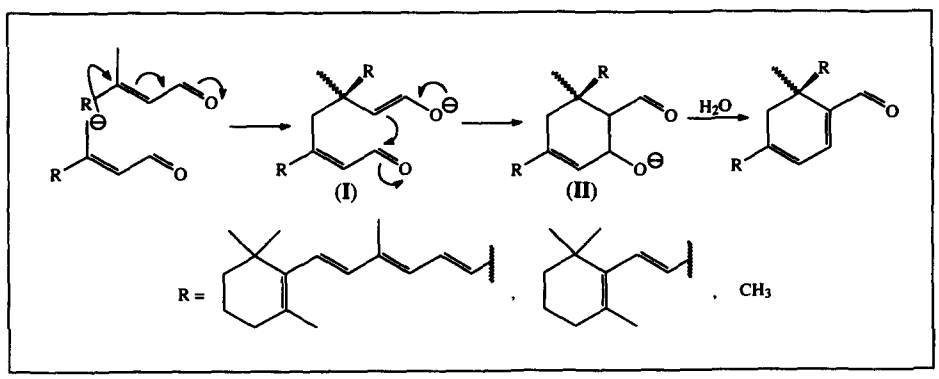


Figure 1. Structure of the condensation products of all-*E*-retinal (**1**), C_{15}-aldehyde (**2**) and C_5-aldehyde (**3**).

A subsequent intramolecular aldol coupling leads to closure of the six membered ring, yielding a stable sodium alkoxide, product **II**. During the aqueous workup, the alkoxide anion is protonated and the basic conditions result in dehydration, promoted by the formation of a conjugated system of double bonds. Following the reaction mechanism, only half of the retinal molecules need to be deprotonated to complete the reaction. In order to test this, we repeated the reaction using only a half equivalent of sodium hydride. According to expectations, the reaction product was still formed with the same yield.

To investigate the regioselectivity of the reaction, we applied the same reaction conditions to 13-*Z*-retinal. In this compound, the methyl group that needs to be deprotonated, is oriented *trans* with respect to the aldehyde moiety. Model studies of the intermediate **I** with the 13 bond *cis* indicate that the orientation of the aldehyde moiety with respect to the enolate doesn't allow an intramolecular aldol condensation to occur to form the six-membered ring. Surprisingly, the same condensation product as for all-*E*-retinal was observed, together with a trace of all-*E*-retinal as byproduct. This implies that after proton abstraction the 13-*Z*-retinal anion isomerizes to an all-*E* geometry, prior to coupling with the neutral retinal.



Scheme 1. Proposed mechanism for the condensation reaction.

To investigate the scope of the reaction, we repeated the reaction with three other analogous compounds: 3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2*E*,4*E*-2,4-pentadienal[17] (C_{15}-aldehyde), 3-methyl-2-butenal (C_5-aldehyde) and crotonaldehyde, all three containing the β-methyl ethene-aldehyde moiety. As expected, the first two compounds showed the same reactivity as for retinal and formed a condensation product, providing evidence that the reaction is a general occuring reactivity of the β-methyl ethene-aldehyde moiety. Crotonaldehyde, however, failed to form a condensation product under our reaction conditions, but polymerized, probably due to the absence of the second double bond stabilizing methyl substituent.
We fully characterized the structure of the C_{15}-aldehyde condensation product (4,6-di-((2,6,6-trimethyl-1-cyclohexen-1-yl)-1*E*-ethenyl)-6-methyl-cyclohexa-1,3-diene carbaldehyde)[18] using two dimensional high resolution NMR techniques, mass spectrometry and UV-VIS spectroscopy. The physical data of the C_5-aldehyde condensation product (4,6,6-trimethyl-cyclohexa-1,3-diene carbaldehyde) were in agreement with previously published data.[16]

Conclusion. In this letter we show that condensation of all-*E*-retinal can be easily performed by exposing retinal to sodium hydride, a non-nucleophilic strong base. The reaction is general for three compounds possessing the β-methyl ethene aldehyde moiety, providing a promising synthetic tool for the preparation of chemically modified retinoids.

General experimental procedure. Tetrahydrofuran was dried over 4Å molecular sieves; petroleum ether (40-60) was distilled over phosphorous pentoxide. All-*E*-retinal was purchased from Fluka, 3-methyl-2-butenal and crotonaldehyde from Aldrich and sodium hydride from Acros. In a dry nitrogen flushed reaction setup, 1 equivalent of sodium hydride was washed three times with dry petroleum ether. Dry tetrahydrofuran was added and *via* a dropping funnel 1 equivalent of aldehyde in tetrahydrofuran was slowly added. After three hours stirring at room temperature saturated ammonium chloride was added and the reaction mixture was three times extracted with diethylether. The combined organic layers were washed with a saturated sodium chloride solution and dried with magnesium sulphate. After evaporation of the solvent *in vacuo* the crude product was purified with silica gel (Merck 0.040-0.063 mm, 230-400 mesh) column chromatography using a diethylether/petroleum ether mixture (20%/80%) as eluent. Yields: 80 % (all-*E*-retinal), 80 % (C_{15}-aldehyde) and 75 % (C_5-aldehyde).

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13. 300.1 MHz ^{1}H NMR: δ 9.45 (s, 1H, H15'); 6.97 (q, 1H, $^3J_{H11H10}$ 7.52 Hz, $^3J_{H11H12}$ 13.98 Hz, H11); 6.81 (d, 1H, $^3J_{H15H14}$ 6.10 Hz, H15); 6.42 (d, 1H, $^3J_{H12H11}$ 13.98 Hz, H12); 6.35 (q, 1H, $^3J_{H11'H10'}$ 10.40 Hz, $^3J_{H11'H12'}$ 15.24 Hz, H11'); 6.30 (d, 1H, $^3J_{H7H8}$ 16.06 Hz, H7); 6.20 (d, 1H, $^3J_{H10H11}$ 7.52 Hz, H10); 6.16 (d, 1H, $^3J_{H8H7}$ 16.06 Hz, H8); 6.16 (d, 1H, $^3J_{H14H15}$ 6.10 Hz, H14); 6.08 (d, 1H, $^3J_{H7'H8'}$ 16.31 Hz, H7'); 6.01 (d, 1H, $^3J_{H8'H7'}$ 16.31 Hz, H8'); 6.00 (d, 1H, $^3J_{H10'H11'}$ 10.40 Hz, H10'); 5.85 (d, 1H, $^3J_{H12'H11'}$ 15.24 Hz, H12'); 2.69 (d, 1H, $^2J_{H20aH20b}$ 16.89 Hz, H20a); 2.42 (d, 1H, $^2J_{H20bH20a}$ 16.89 Hz, H20b); 2.02 (t, 2H, $^3J_{H4H3}$ 6.3 Hz, H4); 2.00 (s, 3H, H19); 1.99 (t, 2H, $^3J_{H4'H3'}$ 6.3 Hz, H4'); 1.85 (s, 3H, H19'); 1.73 (s, 3H, H18); 1.66 (s, 3H, H18'); 1.60 (m, 2H, H3); 1.60 (m, 2H, H3'); 1.48 (s, 3H, H20'); 1.46 (m, 2H, H2); 1.46 (m, 2H, H2'); 1.04 (s, 6H, H16 + H17); 0.98 (s, 6H, H16' + H17') ppm. 75.5 MHz ^{1}H-noise decoupled-^{13}C NMR: δ 191.94 (C15'); 144.12 (C13); 144.04 (C15); 141.41 (C14'); 139.49 (C9); 138.18 (C12'); 137.81 (C6'); 137.77 (C8'); 137.65 (C6); 137.24 (C8); 134.94 (C9'); 132.60 (C12); 130.12 (C5); 130.08 (C10); 129.65 (C10'); 129.25 (C11); 128.75 (C5'); 128.63 (C7); 126.16 (C7'); 123.65 (C11'); 122.69 (C14); 39.53 (C2); 39.42 (C2'); 38.48 (C13'); 37.90 (C20); 34.20 (C1); 34.11 (C1'); 33.10 (C4); 32.87 (C4'); 28.93 (C16 + C17); 28.48 (C16' + C17'); 24.32 (C20); 21.75 (C18); 21.60 (C18'); 19.20 (C3); 19.20 (C3'); 12.93 (C19); 12.62 (C19') ppm. S (EI, 70 eV): $^{12}C_{40}{}^1H_{54}{}^{16}O_1$; exp. mass 550.41854; theor. mass 550.41747; *m/z* 550 ($M^{+\bullet}$). UV-VIS: λ_{max} (*n*-hexane) 420 (C5-C15' chain) + 289 (C5'-C12' chain) nm.
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18. 300.1 MHz ^{1}H NMR: δ 9.49 (s, 1H, H11'); 6.83 (d, 1H, $^3J_{H11H10}$ 6.83 Hz, H11); 6.53 (d, 1H, $^3J_{H7H8}$ 16.19 Hz, H7); 6.22 (d, 1H, $^3J_{H8H7}$ 16.19 Hz, H8); 6.10 (d, 1H, $^3J_{H10H11}$ 5.93 Hz, H10); 5.65 (d, 1H, $^3J_{H7'H8'}$ 16.11 Hz, H7'); 5.34 (d, 1H, $^3J_{H8'H7'}$ 16.11 Hz, H8'); 2.68 (d, 1H, $^2J_{H19aH19b}$ 17.00 Hz, H19a); 2.38 (d, 1H, $^2J_{H19bH19a}$ 17.00 Hz, H19b); 2.03 (t, 2H, $^3J_{H4H3}$ 5.92 Hz, H4); 1.90 (t, 2H, $^3J_{H4'H3'}$ 6.09 Hz, H4'); 1.71 (s, 3H, H18); 1.61 (m, 2H, H3); 1.56 (s, 3H, H18'); 1.54 (m, 2H, H3'); 1.53 (s, 3H, H19'); 1.47 (m, 2H, H2); 1.38 (m, 2H, H2'); 1.04 + 1.03 (2s, 2 × 3H, H16 + H17); 0.88 + 0.87 (2s, 2 × 3H, H16' + H17') ppm. 75.5 MHz ^{1}H-noise decoupled-^{13}C NMR: δ 192.01 (C11'); 144.58 (C11); 144.17 (C9); 141.47 (C10'); 137.40 (C6); 137.34 (C6'); 137.14 (C8'); 133.71 (C8); 131.51 (C7); 131.19 (C5); 127.47 (C5'); 124.55 (C7'); 121.57 (C10); 39.44 (C2); 39.12 (C2'); 38.43 (C9'); 37.75 (C19); 34.14 (C1); 33.93 (C1'); 33.06 (C4); 32.35 (C4'); 28.85 (C16 + C17); 28.51 (C16' + C17'); 24.98 (C19'); 21.65 (C18); 21.06 (C18'); 19.23 (C3'); 19.03 (C3) ppm. MS (EI, 70 eV): $^{12}C_{30}{}^1H_{42}{}^{16}O_1$; exp. mass 418.32248; theor. mass 418.32357; *m/z* 418 ($M^{+\bullet}$). UV-VIS: λ_{max} (*n*-hexane) 346 nm.

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