Tetrahedron Letters, Vol.32, No.21, pp 2379-2382, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

REACTION OF VITAMIN A WITH 1,2,4-TRIAZOLINE-3,5-DIONES

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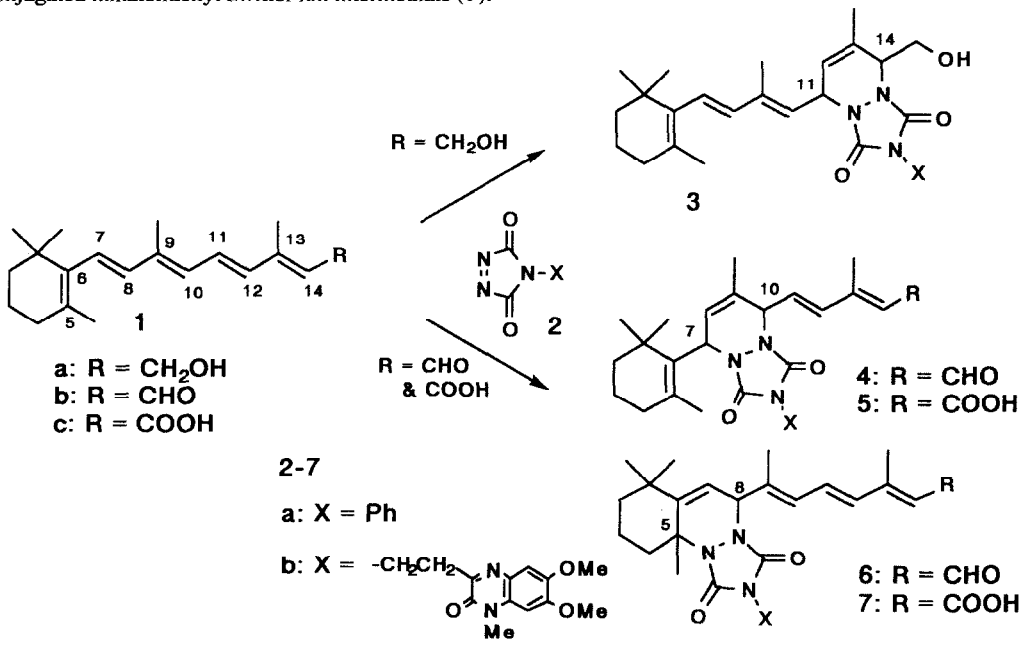
Summary: *Vitamin A and its metabolites reacted with 1,2,4-triazoline-3,5-diones to give 11,14- (retinol) or 7,10-adduct (retinal and retinoic acid) with high regioselectivity depending on the nature of the terminal functional group. The regioselectivity of the reaction was discussed in compared with that with singlet oxygen.*

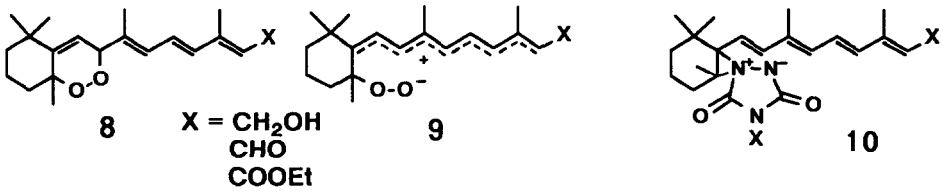
1,2,4-Triazoline-3,5-diones (TAD) and singlet oxygen undergo similar reactions, [4 + 2], [2 + 2], and ene reactions. Extensive studies have been conducted recently to compare the reactivity of the two reagents.[1-5] In ene reactions, TAD[1,2] and singlet oxygen[1,3] showed remarkably similar reactivity though some differences were found in regio- and stereoselectivities.[1b,1c] However in the reaction with dienes they showed major differences; TAD undergoes 1,4-addition in a concerted manner when the *s-cis* conformation of the diene is not sterically congested,[4] while singlet oxygen adds to dienes in a stepwise manner via a zwitter ionic intermediate regardless of the structure of the diene.[5] As a part of our studies on the chemical detection of dienes in biological fluid with fluorescent triazoline,[6] we found that TAD reacted with vitamin A pentaene system with high regioselectivity, which is distinct from that reported for the reaction with singlet oxygen.[7,8] We report here the reaction of vitamin A derivatives with TAD and discuss the regioselectivity of the reaction in comparison with those with singlet oxygen.

All-trans vitamin A derivatives, retinol (**1a**), retinal (**1b**), and retinoic acid (**1c**), were treated with 4-phenyltriazolinedione (PTAD, **2a**) or with the triazoline DMEQ-TAD (**2b**) having the fluorescent chromophore, dimethoxyquinoxalinone group, at the 4-position in CH_2Cl_2 at -78 °C. The reactions were surprisingly regioselective. Retinol reacted instantaneously to give exclusively (85-90% yield) the adduct at the 11,14-position (**3**) together with a small amount of bis-adducts.[9] The structure of the adducts (**3**) was determined by the spectral data.[10] For example, the ^1H NMR spectrum of **3a** shows the signals of the C(15) methylene protons as a pair of double doublets (δ 3.86 (J = 12 and 6 Hz) and 4.23 (J = 12 and 2 Hz)) indicating the adduct formation at the neighboring position. The base peak at m/e 272 (resulting from the 10,11-bond cleavage) of the mass spectrum of **3a** also supports the 11,14-adduct formation. Retinal (**1b**) and retinoic acid (**1c**) reacted rather slowly (30-60 min for completion) to yield the 7,10-adduct (**4** and **5**)[10] as the major product (selectivity 85-95%) and the 5,8-adduct (**6** and **7**)[10] as a minor product (85-95% total isolated yield). The regiochemistry of the adducts (**4-7**) is evident from their UV spectra. The absorption maxima of the 7,10-adducts of retinal and retinoic acid (**4a**, 277 nm; **5a**, 254 nm) are consistent with those calculated for a dienal and a dienoic acid by the Woodward-Fieser rule,[11] and the absorption maxima of the 5,8-adducts (**6a**, 329 nm; **7a**, 297.4 nm) are in good agreement with those calculated for a trienal and a trienoic acid. The adducts (**3-7**) were all obtained as a

single stereoisomer which is assumed to be derived from *cis*-addition. The regioselectivities were little affected by the nature of the substituent at the 4-position of the TADs.

The regioselectivities found in the reaction of vitamin A with TADs were similar to those reported for the reaction with tetracyanoethylene[8,12] but completely different from that with singlet oxygen.[7,8] Singlet oxygen gave the only 5,8-adducts (**8**) regardless of the nature of the terminal functional group. The distinct regioselectivities of TADs and singlet oxygen in the reaction with vitamin A might reflect the different mechanisms with which the two heterodienophiles react with dienes. The difference can be explained as follows. TAD undergoes concerted 1,4-addition at the diene part where it can take a planer *s-cis* form, while singlet oxygen reacts only in a stepwise manner adding first to a single double bond and subsequently forming a zwitter ionic intermediate which in turn gives the 1,4-adduct (**8**) by cyclization. Thus, TAD can undergo concerted 1,4-addition at the 7,10- and 11,14-diene parts, since there is a single substituent at their both terminal positions and they can take a planar *s-cis* conformation. Retinol (**1a**) reacts at the least congested terminal 11,14-diene, whereas retinal and retinoic acid react at the 7,10-diene because of the terminal electron-withdrawing carbonyl group. The minor products (**6** and **7**) might be produced via an aziridinium imide (**10**) intermediate by a mechanism similar to that with singlet oxygen.[4] It is known from the X-ray analysis[13] that the most stable conformation of retinoic acid is a skewed *s-cis* conformation in which the plane of the 5,6-double bond makes an angle of 41.9 ° with the plane of the side chain tetraene system. The same conclusion was obtained from the MO calculation.[14] So the 5,6-double bond is expected to be significantly localized, then it is reasonable that singlet oxygen preferably add to the localized 5,6-double bond yielding the most highly conjugated nonatetraenyl zwitter ion intermediate (**9**).





This postulation was supported by MO calculation. Table 1 shows the HOMO, second HOMO, an charge densities of 1c by MNDO.[15,16] It is clear from the calculation that the HOMO is the π-MO of the sid chain tetraene system and the highest HOMO coefficients reside at the 7,10-diene part coinciding with th reaction site with TADs. The π-MO of the localized 5,6-double bond is the second HOMO but that bond is of th most electron-rich in accord with the high reactivity towards singlet oxygen.

Table 1.

HOMO, second HOMO, and charge of retinoic acid (1c) by MNDO

atom	$2(C_{HOMO,j})^2$	$2(C_{2nd\text{-}HOMO,j})^2$	charge
5	0.1619	0.4432 (1)	-0.1124 (1)
6	0.0811	0.4196 (2)	-0.0434
7	0.2897 (3)	0.0324	-0.0368
8	0.2058 (5)	0.1600 (5)	-0.0524 (5)
9	0.2918 (2)	0.0804	-0.0627 (4)
10	0.3282 (1)	0.0032	-0.0483
11	0.1348	0.1934 (4)	-0.0195
12	0.2708 (4)	0.1444	-0.0727 (3)
13	0.0263	0.0926	0.0062
14	0.1337	0.2130 (3)	-0.1025 (2)

Retinoic acid (1c) is an active metabolite of vitamin A having many important biological activitie: However no highly sensitive method for analyzing a trace amount of 1c in biological fluid has been know The regioselective reaction of 1c with DMEQ-TAD (2b),[17] therefore, provides a useful supersensitiv analytical method for retinoic acid. We are currently examining the possibility.

References and Notes

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10. The structures of the new compounds were determined by spectral analysis (^1H and ^{13}C NMR including H-H COSY and H-C COSY, mass, IR, and UV spectra). Typical spectra data are shown below (NMR assignments are in vitamin A numbering). **3a**: ^1H NMR ($CDCl_3$) δ 0.991, 0.996 (each 3 H, s, H-16,17), 1.67 (3 H, s, H-18), 1.91, 1.99 (each 3 H, s, H-19,20), 3.86, 4.23 (each 1 H, dd, J = 12 & 6 Hz, 12 & 2 Hz, H-15), 4.44 (1 H, bd, J = 6 Hz, H-14), 5.22 (1 H, d, J = 9 Hz, H-10), 5.31 (1 H, m, H-11), 5.71 (1 H, d, J = 5 Hz, H-12), 5.99, 6.18 (each 1 H, d, J = 16 Hz, H-7,8); MS m/e (% relative intensity) 461 (M+, 6.5), 430 (2), 272 (100); IR (KBr) 2928, 1771, 1711, 1504, 1423 cm^{-1}. **3b**: ^1H NMR ($CDCl_3$) δ 0.985, 0.998 (each 3 H, s, H-16,17), 1.66 (3 H, s, H-18), 1.86, 1.89 (each 3 H, s, H-19,20), 3.66 (3 H, s, NMe), 3.94, 4.00 (each 3 H, s, OMe), 5.07 (1 H, bd, J = 9 Hz, H-11), 5.17 (1 H, d, J = 9 Hz, H-10), 5.52 (1 H, d, J = 4 Hz, H-12), 5.96, 6.12 (each 1 H, d, J = 16 Hz, H-7,8), 6.66 (1 H, s, Ar), 7.25 (1 H, s, Ar). **4a**: ^1H NMR ($CDCl_3$) δ 1.06, 1.15 (each 3 H, s, H-16,17), 1.75 (3 H, s, H-18), 1.83 (3 H, s, H-19), 2.20 (3 H, s, H-20), 4.86 (1H, s, H-7), 4.88 (1 H, d, J = 8.5 Hz, H-10), 5.50 (1 H, s, H-8), 5.98 (1 H, d, J = 8 Hz, H-14), 6.13 (1 H, dd, J = 15, 8.5 Hz, H-11), 6.53 (1 H, d, J = 15 Hz, H-12), 10.10 (1 H, d, J = 8 Hz, CHO; ^{13}C NMR ($CDCl_3$) δ 13.05 (20), 19.06 (2), 19.77 (19), 20.51 (18), 28.21 & 29.11 (16 & 17), 34.33 (4), 35.56 (1), 40.03 (3), 56.54 (7), 58.57 (10), 124.12 (8), 125.28 (Ar), 127.90 (Ar), 129.00 (Ar), 129.28 (11), 130.91 (14), 131.37, 133.99, 138.65 (12), 151.4, 152.01, 152.7, 191.14 (15); MS m/e 459 (M+, 93), 457 (92), 363 (59), 336 (70), 324 (62), 283 (100); IR (KBr) 2934, 1775, 1721, 1667, 1504, 1412 cm^{-1}; UV (95% EtOH) 277 nm. **4b**: ^1H NMR ($CDCl_3$) δ 0.88, 0.96 (each 3 H, s, H-16,17), 1.62 (3 H, s, H-18), 1.78 (3 H, s, H-19), 2.19 (3 H, s, H-20), 3.67 (3 H, s, NMe), 3.93, 4.01 (each 3 H, s, OMe), 4.62 (1 H, bs, H-7), 4.75 (1 H, d, J = 8 Hz, H-10), 5.40 (1 H, bs, H-8), 5.97 (1 H, d, J = 8 Hz, H-14), 6.08 (1 H, dd, J = 15, 8 Hz, H-11), 6.47 (1 H, d, J = 15 Hz, H-12), 6.65 (1 H, s, Ar), 7.21 (1 H, s, Ar), 10.09 (1 H, d, J = 8 Hz, CHO). **5a**: ^1H NMR ($CDCl_3$) δ 1.05, 1.15 (each 3 H, s, H-16, 17), 1.75 (3 H, s, H-18), 1.81 (3 H, s, H-19), 2.21 (3 H, s, H-20), 4.84 (1 H, s, H-7), 4.85 (1 H, d, J = 8 Hz, H-10), 5.48 (1 H, s, H-8), 5.84 (1 H, s, H-14), 6.03 (1 H, dd, J = 15, 8 Hz, H-11), 6.47 (1 H, d, J = 15 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 13.94 (20), 19.12 (2), 19.81 (19), 20.53 (18), 28.25 & 29.15 (16 & 17), 34.38 (4), 35.59 (1), 40.1 (3), 56.57 (7), 58.71 (10), 123.94 (8), 125.39 (Ar), 127.91 (Ar), 128.20, 128.50, 129.02 (Ar), 131.21, 131.38 (11), 134.06 (14), 139.03 (12), 151.30, 152.42, 152.55, 170.30 (15); MS m/e 475 (M+, 46), 352 (42), 299 (64), 177 (48), 119 (100); IR (KBr) 2932, 1775, 1719, 1613, 1415 cm^{-1}; UV (95% EtOH) 221 nm (log ε 4.40), 254 nm (log ε 4.37). **5b**: ^1H NMR ($CDCl_3$) δ 0.88, 0.95 (each 3 H, s, H-16, 17), 1.59 (3 H, s, H-18), 1.77 (3 H, s, H-19), 2.19 (3 H, s, H-20), 3.67 (3 H, s, NMe), 3.93, 4.01 (each 3 H, s, OMe), 4.61 (1 H, s, H-7), 4.74 (1 H, d, J = 8 Hz, H-10), 5.37 (1 H, s, H-8), 5.86 (1 H, s, H-14), 5.96 (1 H, dd, J = 15, 8 Hz, H-11), 6.35 (1 H, d, J = 15 Hz, H-12), 6.66 (1 H, s, Ar), 7.22 (1 H, s, Ar). **6a**: ^1H NMR ($CDCl_3$) δ 1.20, 1.26 (each 3 H, s, H-16, 17), 1.61 (3 H, s, H-18), 1.81 (3 H, s, H-19), 2.29 (3 H, s, H-20), 4.93 (1 H, d, J = 5 Hz, H-8), 5.53 (1 H, d, J = 5 Hz, H-7), 5.98 (1 H, d, J = 8 Hz, H-14), 6.30 (1 H, d, J = 10 Hz, H-10), 6.41 (1 H, d, J = 16 Hz, H-12), 6.91 (1 H, dd, J = 16, 10 Hz, H-11), 10.11 (1 H, d, J = 8 Hz, CHO); UV (20% 2-PrOH/hexane) 329 nm. **7a**: ^1H NMR ($CDCl_3$) δ 1.20, 1.26 (each 3H, s, H-16, 17), 1.60 (3 H, s, H-18), 1.79 (3 H, s, H-19), 2.31 (3 H, s, H-20), 4.93 (1 H, d, J = 4 Hz, H-8), 5.53 (1 H, d, J = 4 Hz, H-7), 5.81 (1 H, s, H-14), 6.27 (1 H, d, J = 10 Hz, H-10), 6.32 (1 H, d, J = 15 Hz, H-12), 6.81 (1 H, dd, J = 15, 10 Hz, H-11); IR (KBr) 1717 cm^{-1}; UV (95% EtOH) 297.4 nm.
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17. Detection limit of that chromophore by HPLC (fluorescence detector) is about 1 fmol.

(Received in Japan 8 February 1991)