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Formation of novel tetrahydroisoquinoline retinoids by Pictet–Spengler reaction of dopamine and retinaldehyde under conditions of relevance to biological environments

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Abstract—Some constituents of vitamin A react with dopamine, under conditions of relevance for biological environments, to give tetrahydroisoquinoline retinoid derivatives. Three main products, from 13-*cis* retinaldehyde, were isolated in low yields and characterized. The formation of a Schiff base intermediate has been confirmed by HPLC analysis and the effect on reaction course of metal ions has been valued.

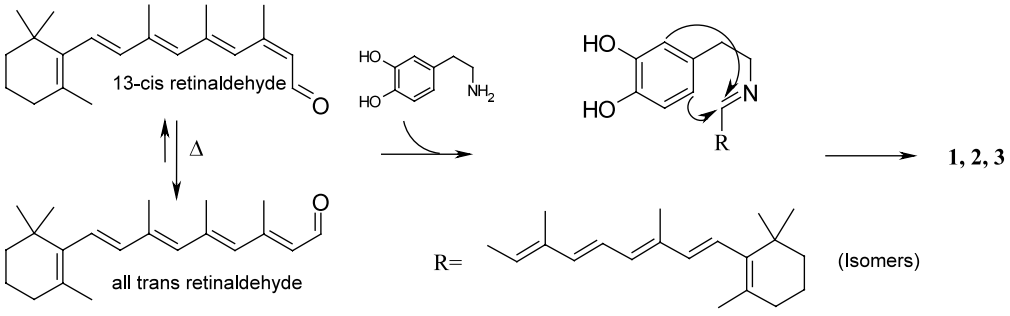
1. Introduction

Accumulation of lipofuscin in retinal pigment epithelium is implicated in the pathogenesis of several forms of macular degeneration potentially resulting in blindness.[1,2] A major constituent of lipofuscin has been characterized as a pyridinium bis-retinoid, originating from the condensation of all-*trans* retinaldehyde with ethanolamine.[3,4]

In light of this, we examined the reaction of retinaldehyde, in conditions mimicking biological environments, with a number of biogenic amines focusing on dopamine which is known to be present at significant level in retinal epithelium.[5–7] This was done with the aim of investigating the formation of retinoid derivatives featuring 6,7-dihydroxytetrahydroisoquinolinc subunit, an etherocyclic system which is known to originate in vivo, via the Pictet–Spengler reaction of aldehydes and biogenic amines through a Schiff base adduct,[8] and to exert cytotoxic action.[9]

2. Results and discussion

In order to mimic biological environments, 0.1 M phosphate buffer at pH 7.4 with SDS (1–2% w/w) added was used as the medium for the reaction of dopamine with 13-*cis*-retinaldehyde.[10] In these conditions HPLC analysis[11] revealed, in the first 10 min of reaction time, the formation of an unstable intermediate[12] which grad-



Scheme 1.

Keywords: dopamine; retinaldehyde; tetrahydroisoquinoline; lipofuscin.

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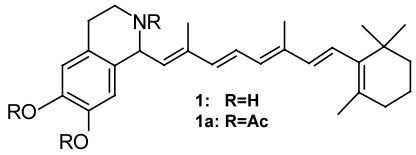
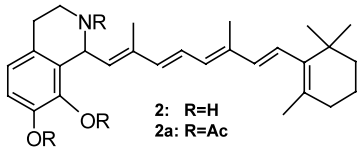
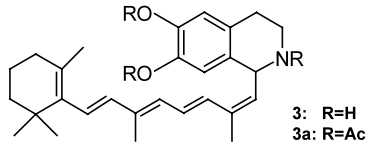
ually disappeared to give three main products. These were acetylated with AcO_2 and pyridine, isolated by preparative[11] HPLC and characterized by EI MS and ^1H NMR as the products **1a**–**3a**.[13]







Formation of **1**–**3** may be interpreted in terms of condensation of dopamine with retinaldehyde in a Pictet–Spengler reaction, which is known to efficiently run under biomimetic conditions[14] and in vivo[8] (Scheme 1). The relative yields of products arising by cyclization of the imine intermediate, respectively, at the positions 6 and 2 of the dopamine ring are about 1/0.3, a value quite unusual for such a reaction path[8,14] which is probably the consequence of the amphiphylic nature of the imine and of the SDS containing medium.

Formation of **1** and **2** may be explained as the consequence of the thermal isomerization of retinal[15a] as well as of Schiff bases[15b] and the higher stability of the all-*trans* form with respect to the other isomers. This is in agreement with the observed recovery of all-*trans* retinaldehyde from imine hydrolysis.[12]

The effect of metal ions, able to be chelated by the catechol system, on product yields was also assessed. As reported in Table 1 both Cu^{2+} and Fe^{3+} are able to increase the yields of all the isomers as expected on the base of the Pictet–Spengler reaction mechanism. The effect of Fe^{3+} is more pronounced on the yield of **2** probably because iron chelation induces an enhancement of electronic density at position 2.

Table 1. Effect of metal ions on relative product yields[a]

	Yields (%)		
	1	**2**	**3**
Blank	7	2	5
Iron(III) 0.1 equiv.	15	10	7
Copper(II) 0.1 equiv.	25	5	10

[a] Isolation yields; blank conditions are those reported in head of discussion; metal ions equivalents are relative to dopamine.

In summary the products isolated suggest the formation of tetrahydroisoquinoline retinoid derivatives to occur in vivo in those tissues rich in both dopamine and retinaldehyde and thus indicate potential constituents of the lipofuscin pigment.

Moreover, to our knowledge, this is the first evidence of a Pictet Spengler path involving conjugate aldehydes.

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10. Reaction of 0.5 mM dopamine with 13-*cis*-retinaldehyde in molar ratios ranging from 1/0.5 to 2/1, were run in a thermostatic bath at 37°C under vigorous stirring. Control experiments in a SDS free medium showed no retinaldehyde consumption.
11. RP18 Spherisorb S50DS2 (4.0×250 mm, Phase Separation Ltd.) and Econosil C-18 10U (22×250 mm, Alltech) columns were used for analytical and preparative purposes, with flow rates of 1 and 15 mL/min, 0.4 M formic acid/methanol from 3/7 to 2/8 as mobile phase, and UV detection.
12. The UV spectrum of the intermediate presented a λ_{max} at 367 nm. A mild heating in aqueous buffer of the intermediate gave both dopamine and a mixture of retinaldehyde isomers (mainly all *trans* isomer), proving the intermediate to be the Schiff base of dopamine and retinaldehyde (HPLC evidence).
13. 1-((1*E*,3*E*,5*E*,7*E*)-2,6-Dimethyl-8-(2,6,6-trimethylcyclohex-1-en-1-yl)octa-1,3,5,7-tetraenyl)-1-acetyl-6,7-diacetoxy-1,2,3,4-tetrahydroisoquinoline (**1a**). Pale yellow oil. UV (MeOH): λ_{max} 330 nm, 280 nm (shoulder). LREI MS: *m*/*z* (relative intensity) 545 (7, M^+), 503 (2), 461 (4), 419 (2), 302 (90), 290 (75), 248 (100), 206 (40), 164 (50); HR MS calcd for $C_{34}H_{43}NO_5$ (M^+) 545.3141, found 545.3145.

^{1}H NMR ($CDCl_3$), δ (ppm): 1.04 (6H, bs); 1.49 (2H, m,); 1.64 (2H, m); 1.72 (3H, s); 1.97 (3H, s,); 2.05 (2H, m); 2.15 (3H, s); 2.18 (3H, s); 2.28 (6H, bs); 2.83 (1H, m); 2.92 (1H, m); 3.60 (1H, m); 3.86 (1H, m); 5.52 (1H, d, J=6.6 Hz); 6.07 (1H, d, J=11.2 Hz); 6.13 (1H, d, J=16.0 Hz); 6.20 (1H, d, J=16.0 Hz); 6.23 (1H, d, J=15.2 Hz); 6.43 (1H d, J=6.6 Hz); 6.67 (1H, dd, H-4′, J=15.2, 11.2 Hz); 6.86 (1H, s); 6.99 (1H, s).

1-((1*E*,3*E*,5*E*,7*E*)-2,6-Dimethyl-8-(2,6,6-trimethylcyclohex-1-en-1-yl)octa-1,3,5,7-tetraenyl)-1-acetyl-7,8-diacetoxy-1,2,3,4-tetrahydroisoquinoline (**2a**). Pale yellow oil. UV (MeOH): λ_{max} 329 nm, 280 nm (shoulder). LREI MS: m/z 545 (4, M^+), 503 (4), 461 (5), 419 (6), 302 (80), 290 (80), 248 (100), 206 (45), 164 (50); HR MS calcd for $C_{34}H_{43}NO_5$ (M^+) 545.3141, found 545.3146. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.04 (6H, bs); 1.50 (2H, m); 1.63 (2H, m); 1.71 (3H, s); 1.97 (3H, s); 2.04 (3H, bs); 2.14 (3H, s); 2.16 (6H, bs); 2.18 (3H, s); 2.24 (3H, s); 2.85 (1H, m); 2.98 (1H, m); 3.52 (1H, m); 3.81 (1H, m); 5.49 (1H, d, J=6.2 Hz); 6.06 (1H, d, J=11.6 Hz); 6.15 (1H, d, J=15.9 Hz); 6.23 (1H, d, J=15.9 Hz); 6.28 (1H, d, J=15.2 Hz); 6.49 (1H, d, J=6.2 Hz); 6.65 (1H, dd, H-4′, J=15.2, 11.6 Hz); 7.06 (1H, d, J=8.8 Hz); 7.09 (1H, d, J=8.8 Hz).

1-((1*Z*,3*E*,5*E*,7*E*)-2,6-Dimethyl-8-(2,6,6-trimethylcyclohex-1-en-1-yl)octa-1,3,5,7-tetraenyl)-1-acetyl-6,7-diacetoxy-1,2,3,4-tetrahydroisoquinoline (**3a**). Pale yellow oil. UV (MeOH): λ_{max} 330 nm. LREI MS: m/z 545 (7), 503 (3), 461 (4), 419 (7), 302 (85), 290 (100), 248 (90), 206 (50), 164 (55); HR MS calcd for $C_{34}H_{43}NO_5$ (M^+) 545.3141, found 545.3145. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.04 (6H×2, bs); 1.55 (2H, m); 1.59 (2H×2, m); 1.74 (3H, s); 1.94 (3H, s); 2.03 (2H, m); 2.10 (3H, s); 2.15 (3H, s); 2.26 (6H, bs); 2.75 (1H, m); 2.83 (1H, m); 3.55 (1H, m); 3.85 (1H, m); 4.70 (1H, d, J=7.2 Hz); 5.78 (1H, d, J=7.2 Hz); 6.06 (1H, d, J=11.4 Hz); 6.13 (1H, d, J=16.0 Hz); 6.19 (1H, d, J=15.2 Hz); 6.21 (1H, d, J=16.0 Hz); 6.80 (1H, dd, J=15.2, 11.4 Hz); 6.86 (1H, s); 6.99 (1H, s).

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