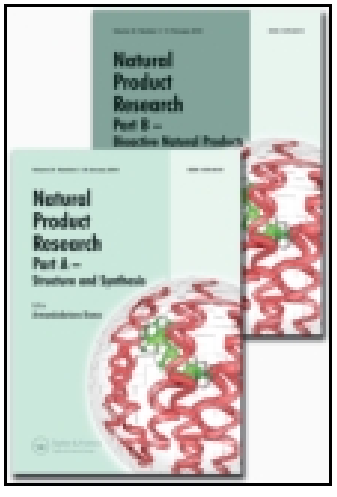

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DDQ oxidation of hydroxyisochromans and homologues

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DDQ oxidation of hydroxyisochromans and homologues

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Some hydroxyisochromans and hydroxyphthalans are tested under oxidative conditions obtaining hydroxybenzophenone derivatives. All reactions were followed by ^{1}H NMR spectroscopy. Some final main oxidation products were also isolated and characterised.

Keywords: hydroxyisochromans; hydroxyphthalans; hydroxy-1,3-dihydro-isobenzofurans; hydroxybenzophenones; oxidation; DDQ

1. Introduction

Phenolic compounds are very important for their antioxidant activity (Bonfili et al., 2008; Lien, Ren, Bui, & Wang, 1999), but the structures of their oxidation products very often remain unknown.

Some years ago we synthesised many hydroxyisochroman and hydroxyphthalan (hydroxy-1,3-dihydroisobenzofurans) derivatives (Guiso, Betrow, & Marra, 2008; Guiso, Bianco, Marra, & Cavarischia, 2003; Guiso, Marra, & Cavarischia, 2001). Two of these compounds, namely 1-phenyl-isochroman-6,7-diol (**1**) and 1-(4-hydroxy-3-methoxy-phenyl)isochroman-6,7-diol (**2**), have been studied for their interesting antioxidant activity (Lorenz et al., 2005; G. Togna, Franconi, A. Togna, Marra, & Guiso, 2003).

We investigate the structures of the oxidation compounds of some hydroxyisochromans, mainly those obtained by oxidising the isochromans prepared from 2-(3,4-dihydroxy-phenyl)ethanol (**3**), and aliphatic or aromatic aldehydes prepared by oxa-Pictet–Spengler reaction. Successively, we extended our investigations to the oxidation of isochromans obtained from 2-(3-hydroxyphenyl)ethanol (**4**) as well as to that of phthalan derivatives.

We tested many oxidation agents, but we chose DDQ because the course of the reaction could easily be followed recording the ^{1}H NMR spectra of the whole reaction mixture at different times without any work up, which also allowed us to investigate the structure of the initially formed oxidation products, even if a little stable.

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2. Results and discussion

Here we report the behaviour towards the oxidation of isochromans and phthalans derivatives.

We first performed, in the same reaction conditions, the oxidation of the parent alcoholic compound **3** to investigate if the behaviour towards the oxidation of its catechol function could change in the derived isochromans.

The first oxidation product of **3** was, as expected, the orthoquinone (**5**), which appears quite stable in the reaction medium for almost 24 h (Figure 1). Its formation was clearly demonstrated by the ^{1}H NMR spectrum, registered in the same reaction medium; in fact, the downfield shift of the H-6 double doublet and the contemporary upfield shift of the H-5 doublet and the H-2 broad singlet are all in accordance with the above transformation.

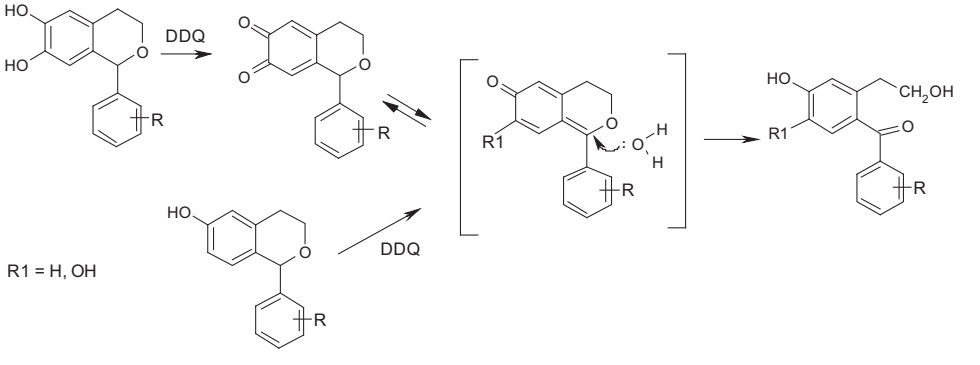
Successively we examined many isochroman-6,7-diols obtained by reacting **3** with differently substituted aromatic aldehydes. In all occasions, immediately after DDQ addition, the signals of the corresponding orthobenzoquinone appeared. During this time, the orthoquinone structure slowly converted into the main oxidation compound, a hydroxybenzophenone derivative arising from the oxidation of the C1 dibenzylic carbon to a carbonyl group (Scheme 1; Table 1).

All these benzophenone derivatives were stable; therefore it was possible to extract, purify and easily characterise these compounds.

We hypothesise that the orthoquinone may be in equilibrium with a quinone methide form which undergoes addition of water at C1. The subsequent opening of the hemiacetalic ring affords the hydroxybenzophenone derivative.

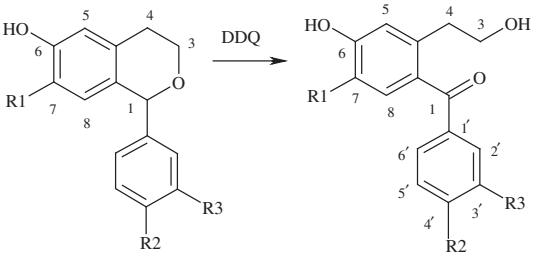
Also the isochroman-6,7-diols prepared by using aliphatic aldehydes first showed the orthoquinone formation, but, successively, the main oxidation product was a

Figure 1. Hydroxytyrosol oxidation.



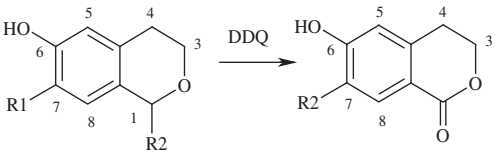
Scheme 1. Hydroxyisochroman derivatives' oxidation.

Table 1. Oxidation products of 1-aryl-hydroxyisochroman derivatives and their ^{1}H NMR data.

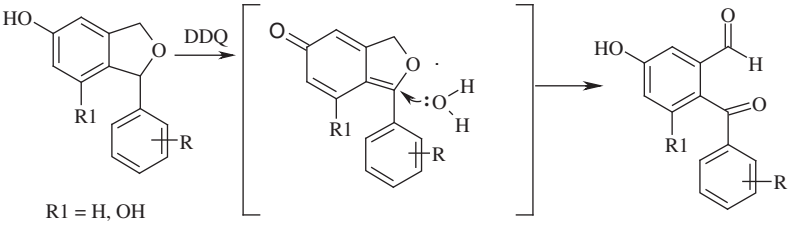


Reagents			Products	
R1	R2	R3	No.	^{1}H NMR data (ppm)
OH	OH	OMe	**7**	2.79 (2 H, t, $J = 7.0$ Hz, H-3); 3.67 (2 H, t, $J = 7.0$ Hz, H-4); 3.90 (3 H, s, OCH_3); 6.6-6.9 (3 H, H-5, H-8, H-5′); 7.25 (1 H, dd, $J = 8.4$ Hz, $J = 1.8$ Hz, H-6′); 7.46 (1 H, d, $J = 1.8$ Hz, H-2′)
OH	H	H	**8**	2.77 (2 H, t, H-3); 3.63 (2 H, t, $J = 6.6$ Hz, H-4); 6.77 (1 H, H-5); 6.84 (1 H, H-8); 7.0-8.0 (5 H, H-2′, H-3′, H-4′, H-5′, H-6′)
OH	Cl	H	**9**	2.76 (2 H, t, H-3); 3.59 (2 H, t, H-4); 6.76 (1 H, H-5); 6.84 (1 H, H-8); 7.2-7.8 (4 H, H-2′, H-3′, H-5′, H-6′)
OH	OMe	H	**10**	2.47 (2 H, t, H-4); 3.75 (2 H, t, H-3); 3.90 (3 H, s, OCH_3); 6.24 (1 H, s, H-5); 6.37 (1 H, s, H-8); 6.92 (2 H, d, $J = 7.8$ Hz, H-3′, H-5′); 7.54 (2 H, d, $J = 7.8$ Hz, H-2′, H-6′)
H	COOMe	H	**11**	2.90 (2 H, t, $J = 6.6$ Hz, H-3); 3.68 (2 H, t, $J = 6.$Hz 6, H-4); 3.88 (3 H, s, OCH_3); 6.66 (1 H, dd, $J = 8.4$ Hz, $J = 2.4$ Hz, H-7); 6.82 (1 H, d, $J = 2.4$ Hz, H-5); 7.74 (2 H, d, $J = 8.4$ Hz, H-2′, H-6′); 7.90 (1 H, d, $J = 8.4$ Hz, H-8); 8.01 (2 H, d, $J = 8.4$ Hz, H-3′, H-5′)
H	Cl	H	**12**	2.86 (2 H, t, $J = 6.6$ Hz, H-3); 3.66 (2 H, t, $J = 6.6$ Hz, H-4); 6.66 (1 H, dd, $J = 8.4$ Hz, $J = 2.4$ Hz, H-7); 6.81 (1 H, d, $J = 2.4$ Hz, H-5); 7.16 (1 H, d, $J = 8.4$ Hz, H-8); 7.45 (2 H, d, $J = 8.4$ Hz, H-3′, H5′); 7.66 (2 H, d, $J = 8.4$ Hz, H-2′, H-6′)
H	OCH_2O		**13**	2.87 (2 H, t, $J = 6.9$ Hz, H-3); 3.71 (2 H, t, $J = 6.9$ Hz, H-4); 6.73 (1 H, dd, $J = 8.1$ Hz, $J = 2.4$ Hz, H-7); 6.12 (2 H, s, O-CH_2-O); 6.86-6.93 (2 H, H-5, H5′); 7.18 (1 H, d, $J = 8.1$ Hz, H-8); 7.26 (1 H, H-2′); 7.27 (1 H, dd, $J = 6.3$ Hz, $J = 1.5$ Hz, H-6′)

Table 2. Oxidation products of 1-alkyl-hydroxyisochroman derivatives and their ^{1}H NMR data.



Reagents		Products	
R1	R2	No.	^{1}H NMR data (ppm)
OH	Octyl	**14**	2.86 (2 H, t, $J = 6.0$ Hz, H-3); 4.40 (2 H, t, $J = 6.0$ Hz, H-4); 6.67 (1 H, s, H-5); 7.43 (1 H, s, H-6′)
H	Butyl	**15**	2.98 (2 H, t, $J = 6.3$ Hz, H-3); 4.43 (2 H, t, $J = 6.3$ Hz, H-4); 6.76 (1 H, $J = 2.4$ Hz, H-5); 6.83 (1 H, dd, $J = 8.4$ Hz, $J = 2.4$ Hz, H-7); 7.82 (1 H, d, $J = 8.4$ Hz, H-8)



Scheme 2. 5-Hydroxyphthalan and 5,7-dihydroxyphthalan derivatives' oxidation.

lactone arising from the transformation of the benzylic C1 in a carboxylic function, with the loss of the remaining aliphatic chain owing to a further oxidation of the C2′ of the aldehyde moiety (see Table 2).

The ^{1}H NMR spectra recorded during the DDQ oxidation of the isochromans obtained from the alcohol (**4**) and aromatic aldehydes showed a very quick disappearance of the H-1 signal, while those of 2 H-3 and 2 H-4 turned into two triplets (near 2.89 and 3.67 ppm, respectively), indicating the opening of the heterocyclic ring. Also, in this case, a hydroxybenzoquinone derivative was formed, perhaps via a quinone–methide intermediate, too unstable to allow the registration of its spectrum, in our experimental conditions.

The oxidation performed on the isochroman prepared from alcohol (**4**) and an aliphatic aldehyde, as pentanal, behaved similarly to that on 1-alkyl-isochroman-6, 7-diol; in fact, the final oxidation compound is the related lactone, as shown by the triplet of the primary esterified alcoholic function at 4.43 ppm and the doublet of the aromatic proton at C-8 at 7.82 ppm.

The DDQ oxidation performed on 1,3-dihydrophthalans prepared from 3-hydroxybenzyl alcohol (**6**) and aromatic aldehydes also afforded benzophenone

derivatives, but with an aldehydic group arising from the oxidation of the C-3 benzylic etheral function involved in the dihydrophthalan ring (Scheme 2). It has been noted that the isolated benzophenones from isochroman oxidation gave clear ^{1}H NMR spectra in deuterated acetone or ACN, while their spectra recorded in deuterated methanol appear more complex, owing to the equilibrium between the carbonylic and the cyclic hemiacetalic structures, as confirmed by the presence of a hemiacetalic carbon signal in ^{13}C NMR spectra (around 100 ppm).

The oxidation of the 1,3-dihydro-5-hydroxy-phthalan obtained from *p*-hydroxybenzaldehyde was very rapid. Ten minutes after the addition of DDQ it was almost totally transformed into the related benzoquinone derivative (**18**), which remained unchanged after 24 h in the reaction medium.

The oxidation of phthalan from 4-methoxybenzaldehyde also afforded a stable benzophenone derivative (**17**) with aldehydic group, which was isolated and characterised by ^{13}C NMR spectrum.

The oxidation of the 1,3-dihydro-5,7-dihydroxy-phthalan prepared from *p*-chlorobenzaldehyde afforded, initially, an unstable oxidation product. In fact the related benzophenone derivative (**20**) reaches its maximum concentration after an hour and a half. Successively, degradation products showing proton aldehydic signals appeared (see Table 3).

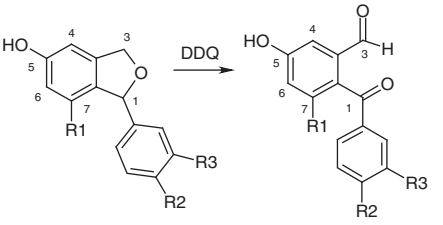
The 1,3-dihydro-5,7-dihydroxy-phthalan obtained from benzaldehyde showed a similar behaviour; in fact, after 10 reaction minutes the expected oxidation product (**19**) appeared. Its ^{1}H NMR spectrum was characterised from the presence of an aldehydic proton singlet at 9.63 ppm, the deshielding of H-2′ and H-6′ protons and the shift of the H-4 and H-6 protons signals to 6.91 and 6.65 ppm, respectively. Its maximum concentration was reached after an hour and a half and then it reduced.

3. Experimental

3.1. *General remarks*

^{1}H and ^{13}C NMR spectra were measured by a Varian Mercury 300 MHz spectrometer, chemical shifts are expressed in ppm relative to TMS and values of *J* are quoted in Hertz. NMR data marked with an asterisk (*) may be reversed. The product's purification was obtained by solid–liquid column chromatography on Merck 0.063–0.20 nm silica gel treated with diluted HCl, then washed with hot water to eliminate Cl^{-} ions, dried and activated at 120°C for 24 h. Silica gel was treated with 10% of water before using. The ratio of silica gel : product is 100 : 1. The eluting solutions were determined case by case. TLC: 5×20 Silica gel 60 F_{254} Merck. Plates were revealed by spraying with 2 N H_2SO_4, then heating at 120°C. Micro-analyses: CE Instruments. MS analyses were performed on a triple quadrupole PE-SCIEX API 365 (Perkin–Elmer Sciex Instruments, Foster City, CA, USA), equipped with Turboin Spray interface in negative ion mode. Reagents: Fluka. Solvents: Carlo Erba. All hydroxyisochromans and hydroxyphthalans used were prepared according to the procedure reported earlier (Guiso et al., 2008, 2003, 2001).

Table 3. Oxidation products of hydroxyphthalans derivatives and their ^{1}H NMR data.



Reagents			Products	
R1	R2	R3	No.	^{1}H NMR data (ppm)
H	OCH_2O		**16**	6.06 (2 H, s, O–CH_2–O); 6.86 (1 H, d, $J = 8.1$ Hz, H-5′); 7.09 (1 H, dd, $J = 8.4$ Hz, $J = 2.7$ Hz, H-6); 7.24 (1 H, dd, $J = 8.1$ Hz, $J = 1.8$ Hz, H-6′); 7.30 (1 H, d, $J = 1.8$ Hz, H-2′); 7.33 (1 H, $J = 2.4$ Hz, H-4); 7.40 (1 H, d, $J = 8.4$ Hz, H-7); 9.89 (1 H, s, H-3)
H	OMe	H	**17**	3.91 (3 H, s, OCH_3); 7.04 (2 H, d, $J = 8.8$ Hz, H-3′, H-5′); 7.18 (1 H, dd, $J = 8.4$ Hz, $J = 2.6$ Hz, H-6); 7.44 (1 H, d, $J = 2.6$ Hz, H-4); 7.50 (1 H, d, $J = 8.4$ Hz, H-7); 7.80 (2 H, d, $J = 8.8$ Hz, H-2′, H6′); 10.01 (1 H, s, H-3)
H	OH	H	**18**	6.87 (2 H, d, $J = 8.7$ Hz, H-3′, H-5′); 7.09 (1 H, dd, $J = 8.1$ Hz, $J = 2.4$ Hz, H-6); 7.33 (1 H, d, $J = 2.4$ Hz, H-4); 7.41 (1 H, d, $J = 8.1$ Hz, H-7); 7.67 (2 H, d, $J = 8.7$ Hz, H-2′, H6′); 9.91 (1 H, s, H-3)
OH	H	H	**19**	6.66 (1 H, d, $J = 2.4$ Hz, H-6); 6.92 (1 H, d, $J = 2.4$ Hz, H-4); 7.2-7.8 (5 H, phenyl moiety); 9.62 (1 H, s, H-3)
OH	Cl	H	**20**	6.65 (1 H, d, $J = 2.4$ Hz, H-6); 6.92 (1 H, d, $J = 2.4$ Hz, H-4); 7.43 (2 H, d, $J = 8.4$ Hz, H-3′, H-5′); 7.66 (2 H, d, $J = 8.4$ Hz, H-2′, H-6′); 9.63 (1 H, s, H-3)

3.2. *General oxidation procedure*

Twenty milligrams of compound for oxidation was dissolved in CD_3CN and the ^{1}H NMR spectrum was recorded. Then, directly into the NMR tube, a 2 molar amount of DDQ was added. Different controls were effectuated by recording ^{1}H NMR spectra at different times until complete disappearance of the substrate.

3.2.1. *Compound* ***5***

The quinone formation was complete after 10 reaction minutes and compound **5** remained unchanged until 10 h.

^{1}H NMR (ppm): 7.06 (H, dd, $J = 9.9$, 1.8 Hz, H-6); 6.29 (H, d, $J = 9.9$ Hz, H-5); 6.20 (H, bs, $J = 1.8$ Hz, H-2); 3.74 (2 H, t, $J = 6.0$ Hz, H-2′); 2.55 (2 H, t, $J = 6.0$ Hz, H-1′).

3.2.2. *Compound 7*

The quinone (**21**) formation was complete after 10 reaction minutes. The disappearance of **21** was complete after 24 h. The main oxidation product (**7**, 20 mg, yield 95%) was obtained by chromatography on silica gel column eluted by $CHCl_3$: MeOH = 9 : 1. ^{1}H NMR data are reported in Table 1. ^{13}C NMR: 197.2 (R_2C=O); 151.0 (C-4′); 147.0 (C-3′); 146.0 (C-6); 141.8 (C-7); 133.6 (C-8a); 130.1 (C-1′); 129.7 (C-4a); 125.5 (C-6′); 119.0 (C-8); 116.9 (C-5); 115.9 (C-5′); 111.8 (C-2′); 62.9 (C-3); 54.5 (OCH_3); 35.0 (C-4). IR 3300, 2950, 2850, 1690, 1650, 1590, 1560, 1460, 1390, 1300, 1240, 1130 and 1090 cm^{-1}. $[M–H]^-$ = 303.3. Elemental analysis of $C_{16}H_{16}O_6$ (304.30): Calcd: C 63.15, H 5.30, Found: C 62.84, H 5.46.

Compound **21**: ^{1}H NMR (ppm): 2.77 (1H, m, H-4a); 2.91 (1H, m, H-4b); 3.75 (1H, m, H-3a); 3.81 (3H, s, OCH_3); 4.04 (1H, m, H-3b); 5.30 (1H, d, J = 1.5 Hz, H-1); 5.63 (1H, s, H-5); 6.21 (1H, s, H-8); 6.65–6.92 (3H, m, H2′, H5′, H6′).

3.2.3. *Compound **8***

The quinone (**22**) formation was complete after 10 reaction minutes. The disappearance of **22** was complete after 48 h. The main product (**8**) remained unchanged for a week. ^{1}H NMR data are reported in Table 1.

Compound **22**: ^{1}H NMR (ppm): 2.80 (1H, m, H-3a); 2.90 (1H, m, H-3b); 3.79 (1H, m, H-4a); 4.05 (1H, m, H-4b); 5.42 (1H, d, J = 1.8 Hz, H-1); 5.58 (1H, d, J = 1.8 Hz, H-8); 6.23 (1H, s, H-5), 7.39 (5H, m, H-2′, H-3′, H-4′, H-5′, H-6′).

3.2.4. *Compound **9***

The quinone (**23**) formation was complete after 7 reaction minutes. The disappearance of **23** was complete after 24 h. The main product (**9**) remained unchanged for two days. ^{1}H NMR data are reported in Table 1.

Compound **23**: ^{1}H NMR (ppm): 2.79 (1H, m, H-3a); 2.89 (1H, m, H-3b); 3.78 (1H, m, H-4a); 4.04 (1H, m, H-4b); 5.41 (1H, d, J = 1.8 Hz, H-1); 5.59 (1H, s, H-8); 6.22 (1H, s, H-5); 7.25-7.45 (4H, m, H-2′, H-3′, H-5′, H-6′).

3.2.5. *Compound **10***

The quinone (**24**) formation was complete after 10 reaction minutes. The disappearance of **24** was complete after 24 h. The main product (compound **10**) remained unchanged for two days. ^{1}H NMR data are reported in Table 1.

Compound **24** (quinone): ^{1}H NMR (ppm): 2.79 (1H, m, H-3a); 2.95 (1H, m, H-3b); 3.80 (1H, m, H-4a); 3.82 (3H, s, CH_3O); 4.10 (1H, m, H-4b); 5.95 (1H, s, H-1); 6.39 (1H, s, H-5); 6.84 (2H, d, J = 8.4 Hz, H-3′, H-5′); 7.19 (2H, d, J = 8.4 Hz, H-2′, H-6′).

3.2.6. *Compound **11***

The disappearance of the substrate was quite complete after 45 min. The compound **11** became quite prevalent and remained unchanged for two days. ^{1}H NMR data are reported in Table 1.

3.2.7. *Compound* ***12***

The disappearance of the substrate was quite complete after 25 min. The compound **12** became quite prevalent and remained unchanged for two days. ^{1}H NMR data are reported in Table 1.

3.2.8. *Compound* ***13***

Disappearance of the substrate was quite complete after 25 min. The compound **12** became quite prevalent and isolated. The main oxidation product (**13**, 13 mg, yield 90%) was obtained by chromatography on silica gel column eluted by $CHCl_3$: MeOH = 9 : 1. $[M–H]^- = 285.3$. ^{1}H NMR data are reported in Table 1. Elemental analysis of $C_{16}H_{14}O_5$ (286.29): Calcd: C 67.13, H 4.93, Found: C 66.98, H 5.01.

3.2.9. *Compound* ***14***

The quinone (**25**) formation was complete after 10 reaction min. The disappearance of **25** was quite complete after 72 h. The main product (**14**, 13 mg, 95% yield) remained unchanged for ten days, which was successively isolated by chromatography on silica gel column eluted by $CHCl_3 : MeOH = 9 : 1$. ^{1}H NMR data are reported in Table 2. $[M–H]^- = 277.4$. Elemental analysis of $C_9H_8O_4$ (278.39): Calcd: C 73.35, H 9.41 Found: C 73.01, H 9.44.

Compound **25** (quinone): ^{1}H NMR (ppm): 0.86 (3H, t, $J = 7.0$ Hz, CH_3); 1.1–1.6 (12H, m, H-2′, H-3′, H-4′, H-5′, H-6′, H-7′); 1.77 (2H, m, H-1′); 2.71 (2H, m, H-3); 3.62 (1H, m, H-4a); 3.95 (1H, m, H-4b); 4.41 (1H, m, H-1); 6.12* (1H, s, H-5); 6.14* (1H, s, H-8).

3.2.10. *Compound* ***15***

The reaction was not complete after two days, the main oxidation product (**15**, 14 mg, 93% yield) was isolated by chromatography on silica gel column eluted by $CHCl_3 : MeOH = 9 : 1$. ^{1}H NMR data are reported in Table 2. $[M–H]^- = 205.3$. Elemental analysis of $C_9H_8O_3$ (206.29): Calcd: C 75.69, H 8.80, Found: C 75.71, H 8.87.

3.2.11. *Compound* ***16***

The main oxidation product of **16** became clearly prevalent after 1 h and remained unchanged for one day. ^{1}H NMR data are reported in Table 3.

3.2.12. *Compound* ***17***

The main oxidation product (**17**, 19 mg, 90% yield) was obtained by chromatography on silica gel column eluted by $CHCl_3$. ^{1}H NMR data are reported in Table 3.

^{13}C NMR (CD_3COCD_3)(ppm): 192.8 ($R_2C=O$); 189.9 (HC=O); 163.0 (C–OCH_3); 159.1 (C-4′); 138.0 (C-3a); 132.3 (C-1′); 131.4 (C-2′, C-6′); 131.1 (C-6); 130.0 (C-7a); 118.6 (C-6); 114.3 (C-5); 113.0 (C3′, C5′); 54.4 (OCH_3). $[M–H]^- = 255.1$. Elemental analysis of $C_{15}H_{12}O_4$ (256.26): Calcd: C 70.31, H 4.72, Found: C 69.58, H 4.87.

3.2.13. *Compound **18***

The main oxidation product of **18** became clearly prevalent after 10 min and remained unchanged for one day. ^{1}H NMR data are reported in Table 3.

3.2.14. *Compound **19***

The main oxidation product of **19** became clearly prevalent after 90 min and remained unchanged for one day. ^{1}H NMR data are reported in Table 3.

3.2.15. *Compound **20***

The oxidation product was formed in 1 h, but it resulted to be less stable. Many signals attributable to aldehydic protons were observed after this time. ^{1}H NMR data are reported in Table 1.

4. Conclusions

It is interesting to note that the first involved position in this oxidation reaction is always the benzylic or dibenzylic tertiary C-1 carbon. The lactone formation at C-1, that is the classical oxidative product of the C-1 unsubstituted isochroman or phthalan derivatives, is observed when the substituent at C-1 is aliphatic. This is in accordance with the easy cleavage of the aliphatic moiety.

The different stability of the phthalan oxidation products could be explained on the basis of the different substitution pattern of the parent benzylic alcohol; in fact, the presence of two hydroxyl groups on the alcoholic aromatic ring makes further oxidation easier.

The hydroxybenzophenone derivatives obtained from oxidation reaction may be interesting also for their antioxidant properties; already, some hydroxybenzophenones are used to inhibit the oxidation process of polymers and other kinds of compounds (Dobashi, Kondou, & Ohkatsu, 2005).

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