Synthesis of new halogenated flavonoids by reaction with hydrogen halides in the presence of dimethyldioxirane

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This paper presents the synthesis and characterisation of new halogenated etherderivatives of flavans, flavanols and flavanones, obtained by reaction of the corresponding methyl ethers with hydrogen halides in the presence of dimethyldioxirane as an oxidative agent.

Keywords: flavanols, halogenation, dioxiranes, spectroscopy

More than 5000 flavonoids have been described and their biological and pharmacological properties studied, including anti-oxidative, anti-inflammatory, and anti-carcinogenic activity. It has been shown that some flavonoids are active on the CNS. The introduction of halogens in positions 6 and 3' of these molecules may increase the anxiolytic properties of these substances. The antiviral properties of halogenated flavonoids have been described.[1] Recently an aromatic ring chlorination and bromination with dimethyl dioxirane (DMD) in the presence of chloro and bromo ions has been described.[11] We have used the same reagent (DMD) with the goal of developing new halo derivatives starting from flavans obtained in large amounts from Dragon's blood resin.[12] We obtained the corresponding halo-derivatives (chloro, bromo and iodo) in high yields. We have extended the reaction to other substrates such as catechin, flavanones and tetralone methyl ethers and the corresponding halo derivatives were obtained. These halogenated flavanones may be useful intermediates for the synthesis of more complex natural products, such as the prenylated flavans and flavanones of the kushenols (prenyl and polyprenyl flavanones) produced by *Sophora japonica*, a plant used in traditional Chinese medicine with antibacterial and antiandrogenic activity. The halogenation of flavonoid derivatives **1a**–**8a** and of tetralone **9a** (Scheme 1 and 2) with DMD in the presence of 2M aqueous HCl, HBr and HI at –40°C in acetone, gave rise to products **1b**–**9b** in good yields. Halogenation of compound **1a** containing a methoxy group in position 5, and acetoxy in position 7 and an ethereal heterocyclic oxygen in position 1 afforded the disubstituted chloro and bromo derivatives, in the positions 6 and 8, *i.e.* *ortho* and *para* to these activating substituents (compounds **1b–c)**; on the contrary the corresponding iodination occurred only in the activated position 8 (compound **1d**) and not in position 6 probably for steric reasons. Compound **2a** with only the position 8 free and with *ortho* and *para* electron-releasing substituents produced the corresponding bromo **2b** and iodo **2c** derivatives in high yields, whereas no chlorinated compound was isolated, due to the decomposition of the substrate. Permethylated (+)catechin **3a** gave rise to a trichlorinated **3b** and tribrominated **3c** derivatives, with substitutions occurring in the latter not only in the activated positions 6,8 of the aromatic ring A but also in position 6′ of the ring C, *para* with respect to a methoxy group. Compound **3a** was iodinated only in position 8, and not in position 6, again most probably for steric reasons. We obtained a mixture of monochlorinated compounds **4b** and **4c** in a ratio 2/1 from compound **4a** due to the more activated position 8 (ortho to two ethereal oxygens) with respect to position 6. Compound **5a** possesses the more nucleophilic position at C–6 (*ortho* and *para* to two ethereal oxygens), and afforded in high yields the 6-chloro and 6-bromo derivatives respectively **5c** (83%) and **5d** (96%). Flavanone **6a** was chlorinated in position 6 to yield **6b** (70%), and brominated yielding a dibromo derivative **6c** (62%) in the activated nucleophilic positions 6 and 8. In the case of compound **7a** only brominated derivatives **7b** and **7c** were isolated in a 1:1 ratio. Methylated naringenin **8a** was chlorinated at positions 6, 8 (**8b**), and at positions 6,8 and 3' (**8c**) and iodinated only in 3'.

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References cited in this synopsis

1 A.C. Paladini; M. Marder, C. Viola, C. Wolfman, C. Wasowski and C. Medina, *J. Pharm. Pharmacol.* 1999, **51**, 519.
11 P. Bovicelli, R. Bernini, R. Antonioletti and E. Mincione, *Tetrahedron Lett.*, 2002, 556.
12 G. Cardillo, L. Merlini and G. Nasini, *J. Chem. Soc. C*, 1971, 3967.

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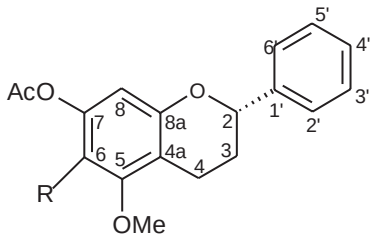
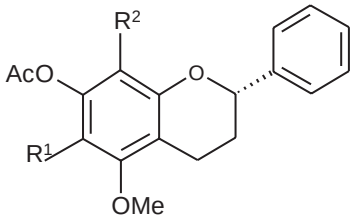


1a R = H

2a R = Me

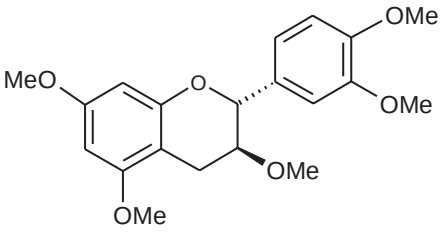
DMD / HX

- 40°C



1b $R^1 = R^2 = Cl$
1c $R^1 = R^2 = Br$
1d $R^1 = H$, $R^2 = I$

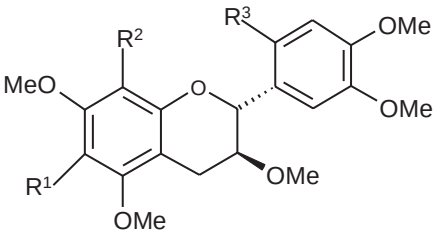
2b $R^1 = Me$, $R^2 = Br$
2c $R^1 = Me$, $R^2 = I$



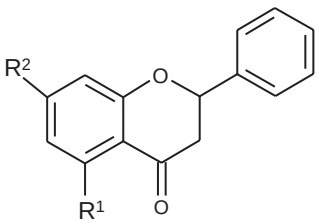
3a

DMD / HX

- 40°C



3b $R^1 = R^2 = R^3 = Cl$
3c $R^1 = R^2 = R^3 = Br$
3d $R^1 = R^3 = H$, $R^2 = I$



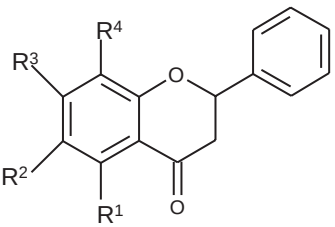
4a $R^1 = OAc$, $R^2 = OMe$

5a $R^2 = OMe$, $R^1 = H$

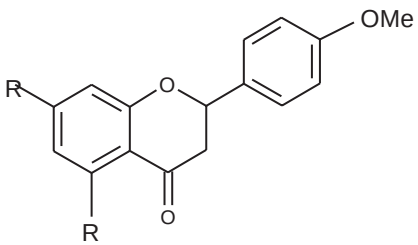
6a $R^1 = OMe$, $R^2 = H$

DMD / HX

- 40°C



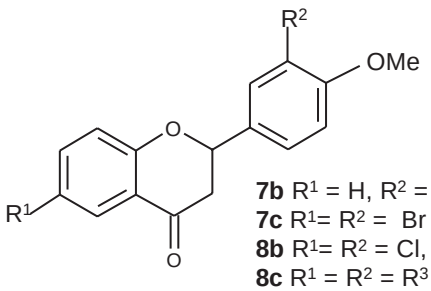
4b $R^1 = OAc$, $R^2 = H$, $R^3 = OMe$, $R^4 = Cl$
4c $R^1 = OAc$, $R^2 = Cl$, $R^3 = OMe$, $R^4 = H$
5b $R^1 = R4 = H$, $R^2 = Cl$, $R^3 = OMe$,
5c $R^1 = H$, $R^2 = R^4 = Cl$, $R^3 = OMe$
5d $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OMe$
6b $R^1 = OMe$, $R^2 = Cl$, $R^3 = R^4 = H$
6c $R^1 = OMe$, $R^2 = R^4 = Br$, $R^3 = H$



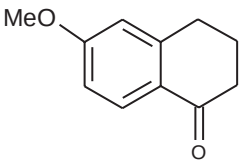
7a R = H
8a R = OMe

DMD / HX

- 40°C



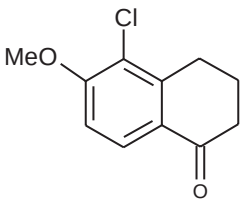
7b $R^1 = H$, $R^2 = Br$
7c $R^1 = R^2 = Br$
8b $R^1 = R^2 = Cl$, $R^3 = H$
8c $R^1 = R^2 = R^3 = Cl$
8d $R^1 = R^3 = H$, $R^2 = I$



9a

DMD / HCl

- 40°C



9b

Schemes 1 and 2