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Reaction of caffeic acid derivatives with acidic nitrite

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Abstract—Caffeic derivatives were reacted with acidic nitrite at controlled pH in order to mimic the gastric juice conditions. At pH 2, whereas caffeic acid reacts exclusively on the side chain, its esters are readily nitrated. Under more acidic conditions (pH 1), caffeic acid methyl ester undergoes a dimerisation into a norlignan derivative. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Caffeic acid and related compounds are widely distributed in fruits, vegetables, wine, olive oil, teas and coffee beans. Caffeic acid is generally not found as free acid but more likely esterified in chlorogenic acid (the quinic acid ester of caffeic acid).

Many studies have demonstrated that caffeic acid and related compounds are potent inhibitors of the *N*-nitrosation reactions.[1–3] *N*-Nitrosation is a potentially mutagenic reaction since *N*-nitrosamines have been implicated in human carcinogenesis. Precursors of *N*-nitrosamines are secondary amines and nitrite and the acidity of gastric juice is appropriate for *N*-nitrosation.[4] There are still complicated effects, inhibition or stimulation, on the formation of *N*-nitrosamines with chlorogenic acid depending upon the conditions used.[2,5]

The reactivity of caffeic acid derivatives with acidic nitrite is well documented,[1,3,5] but very little is known about the products formed. It has been reported that *para*-coumaric acid and ferulic acid react with acidic nitrite to give a mixture of several compounds, which are all issued from the reaction of nitrite on the side chain. For example, from the reaction of ferulic acid with acidic nitrite were isolated two minor products: the structure of one of them may be attributed to a furoxan heterocycle **5**,[6,7] the other one has been identified recently[8] as 7-hydroxy-6-methoxy-1,2-(4*H*)-benzoxazin-4-one **6** (Scheme 1). In connection with our continuing interests in nitrocatechol derivatives,[9–11] we examined the reaction of caffeic acid derivatives with acidic nitrite. This paper describes the characterisation of the products obtained from the reaction of caffeic acid methyl ester **1**, caffeic acid **2** and chlorogenic acid **3** with nitrite at pH 1 or 2. Reaction of caffeic acid and related derivatives with nitrite at acidic pH has been carried out according to Rousseau and Rosazza.[8]

2. Results and discussion

The reaction of caffeic acid with acidic nitrite results in a mixture of three products, which have been characterised by spectroscopic analysis. The main product (50% calculated from the ^{1}H NMR spectrum of the crude extract) has been identified as the furoxan derivative **4**. Its ^{1}H NMR spectrum[12] presents the characteristic pattern of a 1,2,4-trisubstituted benzene ring and a singlet at 9.06 ppm, which can be attributed to the heterocyclic proton. The second one (40%) has been identified as the 1,2-(4*H*)-benzoxazin-4-one derivative **6**.[12] Its simple ^{1}H NMR spectrum contained only three uncoupled aromatic proton signals. The third one (10%) is the known 6-nitro-3,4-dihydroxybenzaldehyde **8**.[13]

Conversely, the reaction of the caffeic acid esters **2** and **3** with acidic nitrite gives the 6-nitroderivatives **10**[14] and **11**[15] as the sole products in 89 and 11% yield, respectively. The low field region of their ^{1}H NMR spectra contained only two uncoupled aromatic proton signals and two doublets ($^3J=15.8$ Hz) which correspond to the double bond protons. Compound **10** has also been prepared from the known 6-nitrocaffeic acid **9**[9] and methanol in the presence of thionyl chloride and the hydrolysis of the ester function of **11** also gives **9**.

The difference in reactivity between caffeic acid and its esters can be explained by the mechanism depicted in Scheme 2. The caffeic acid derivatives may be oxidised

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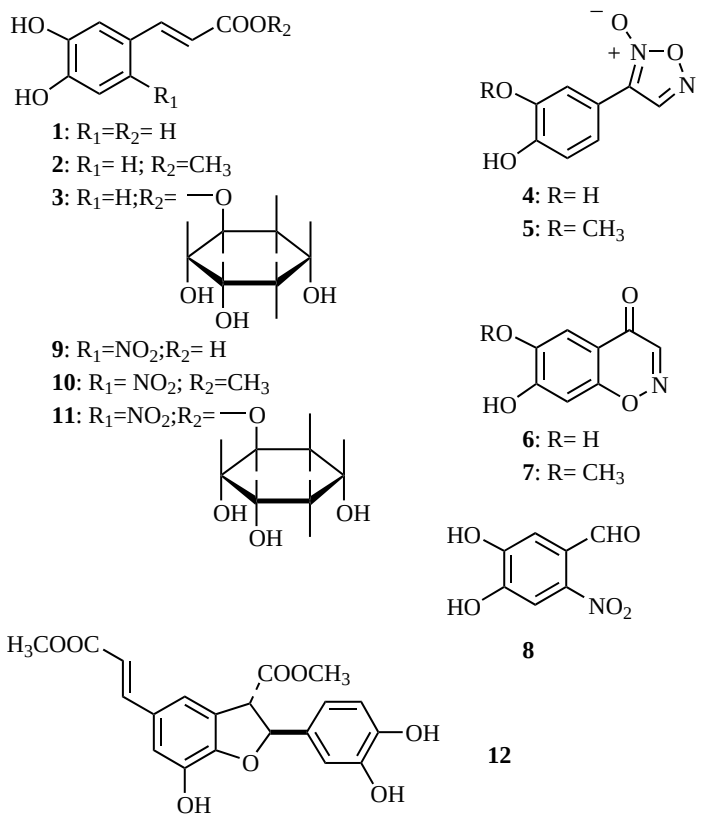
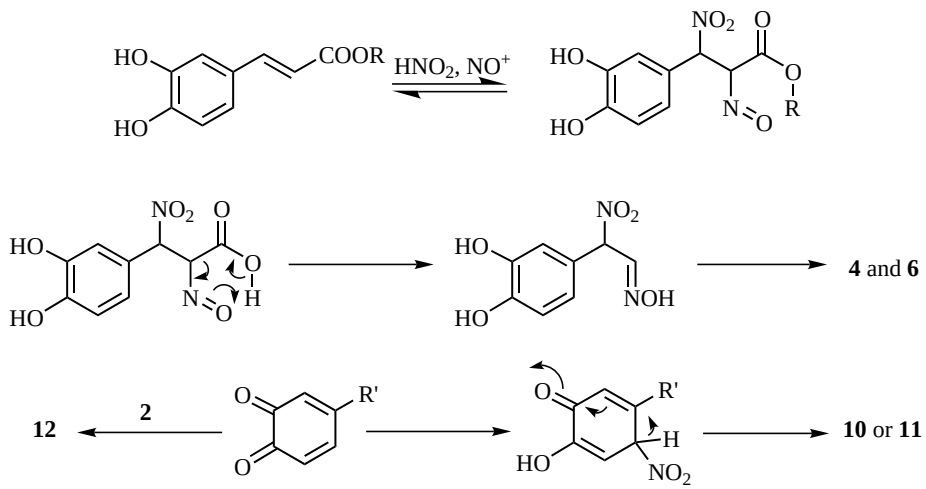


Scheme 1.



Scheme 2.

by nitrite, nitrous acid or the other nitrogen species present in the medium to give the *o*-quinone probably through disproportionation of the semiquinonic radical[16] or they may react with nitrite and nitrosonium ions.[7] In the case of caffeic acid, the product of addition of nitrite and nitrosonium ions may undergo an irreversible decarboxylation leading to **4**, **6** and probably 3,4-dihydroxybenzaldehyde which was finally nitrated to give **8**. For the caffeic acid esters, the decarboxylation cannot occur and the *o*-quinone reacts with nitrite to give **10** or **11**.

Since gastric juice pH is about **1**, caffeic acid and its methyl ester (**1** and **2**) were also treated with nitrite at pH 1. At this pH value, the nitrite concentration is expected to be very low and the *o*-quinone of **2** may react in a different way. Under this condition, in the two cases, dark polymeric precipitates were obtained. However, the extraction with ethyl acetate of the aqueous layer in the case of **2** allowed us to isolate a dimer that was identified as the benzofuran derivative **12**[17] in 20% yield. Under this pH condition, the nitrite concentration is expected to be too low and the nucle-

ophilic reaction of nitrite on the caffeic ester *o*-quinone does not occur. The unstable *o*-quinone may react therefore with **2** to give **12**. These results show that nitrite under strong acidic conditions may promote the oxidative dimerisation of caffeic acid ester leading to neolignan compound. The oxidative dimerisation of caffeic acid has also been demonstrated in the isolated perfused rat liver[18] but affords lignan derivatives.

3. Conclusion

The nitration of catechols with nitric oxide[19,20] at physiologic pH or nitrite under acidic conditions[20] is well-known and 6-nitrodopamine has been implicated in the neuronal degeneration.[21] On the other hand, it has been reported that caffeic acid and related compounds are potent scavengers of highly reactive nitrogen species such as peroxynitrite[22] or nitrogen dioxide radical.[23] Chlorogenic acid and related compounds that are widely present in various agricultural products in substantial quantities are important in human health and may be useful as antioxidants and anticancer agents. Therefore, it appears crucial to evaluate the toxicity of nitrocaffeic acids and related compounds. In summary, the present investigation has revealed that caffeates can react with nitrite under physiologic acidic conditions to differential extents depending on the function (ester or acid) to give nitroderivatives, nitrogen heterocycles or benzofuran dimers.

Acknowledgements

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12. Compounds **4**, **6** and **8** have been separated by flash chromatography. Compounds **4** and **6** have only been characterised by their ^{1}H NMR spectra because they degraded within a few hours at room temperature.
3-(3,4-Dihydroxyphenyl)furazan-2-oxide **4**: ^{1}H NMR (methanol-d_4): 6.99 (d, $^3J=7.4$ Hz, 1H), 7.43 (dd, $^3J=7.4$ Hz, $^4J=2.0$ Hz, 1H), 7.63 (d, $^4J=2.0$ Hz, 1H), 9.06 (s, 1H).
6,7-Dihydroxy-1,2-(4*H*)-benzoxazin-4-one **6**: ^{1}H NMR (methanol-d_4): 6.95 (s, 1H), 7.33 (s 1H), 8.13 (s, 1H).
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14. Methyl 2-nitrocaffeate **10** (89% yield): elemental analyses for $C_{10}H_9NO_6$; calcd C, 50.22; H, 3.79; N, 5.86; O, 40.13; found C, 50.54; H, 3.53; N, 6.04; O, 40.51; mp 132–133°C; ^{1}H NMR (methanol-d_4): 3.69 (s, 3H), 6.19 (d, $^3J=15.9$ Hz, 1H), 6.96 (s, 1H), 7.44 (s, 1H), 8.01 (d, $^3J=15.9$ Hz, 1H); IEMS (60 eV): 239 (19%), 225 (69%), 179 (56%), 51 (100%).
15. 2-Nitrochlorogenic acid **11** (11% yield): elemental analyses for $C_{16}H_{17}NO_{11}$; calcd C, 48.13; H, 4.29; N, 3.51; O, 44.07; found C, 48.14; H, 4.21; N, 3.34; O, 44.31; mp 240–245°C; ^{1}H NMR (DMSO-d_6): 1.79 (dd, $^2J=13.0$ Hz, $^3J=7.2$ Hz, 1H), 1.99 (m, 3H), 3.57 (dd, $^3J=7.2$ Hz, $^4J=2.5$ Hz, 1H), 3.93 (m, 1H), 5.10 (m, 1H), 6.21 (d, $^3J=15.8$ Hz, 1H), 7.11 (s, 1H), 7.54 (s, 1H), 7.96 (d, $^3J=15.8$ Hz, 1H); IEMS (60 eV): 339 (6%), 225 (45%), 179 (62%), 174 (38%), 51 (100%).
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