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Hypervalent Iodine Oxidation Products of Papaverine and Its Microbial Metabolites

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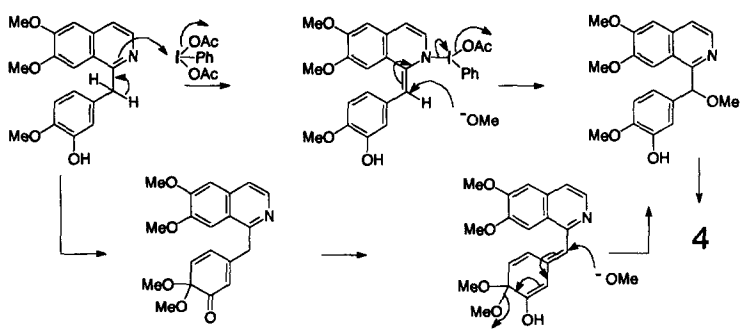
Abstract: (Diacetoxyiodo)benzene (DAIB) oxidizes papaverine to papaveraldine (2) and to 1-hydroxymethyl-6,7-dimethoxyisoquinoline (3), whereas 3'-desmethylpapaverine and 6-desmethylpapaverine are converted into novel products (4) and (5), respectively.

Papaverine(1) is a smooth muscle relaxant known to cause hepatotoxicity in man, by an unknown mechanism[2] even though the major routes of its metabolism are known.[3] The major mammalian metabolites are 6- and 4'-desmethylpapaverines (3'- and 7-desmethyl compounds are minor) and one feasible mechanism for the hepatotoxicity in the case of 4'-desmethylpapaverine might be its oxidation to the corresponding p-quinone methide, which would serve as an electrophile (via Michael addition by a biological nucleophile) similar to acetaminophen.[4] While attempting to generate quinone methide intermediates and related compounds, we tried DAIB reagent on papaverine and its microbial metabolites.[5]

It is known that excess of DAIB reagent[6] oxidizes monohydric phenols to p-quinone ketals. 4'-Desmethylpapaverine with DAIB reagent yielded intractable products. However, 3'-desmethylpapaverine when treated with two equivalents of DAIB in methanol at room temperature yielded an unusual product 4 in 16% yield.[7] The mechanism of this reaction is proposed in Scheme 1. However, papaverine with DAIB in methanol at room temperature gave papaveraldine(2) in 26% yield, but at reflux temperature benzylic cleavage occurred with the formation[8] of 1-hydroxymethyl-6,7-dimethoxyisoquinoline (3) in 12% yield. It is known that papaverinol (6) when treated with 90% H_2SO_4 yielded 6,7-dimethoxyisoquinoline 1-carboxaldehyde.[9] In analogy with this, the formation of 3 is being pursued.

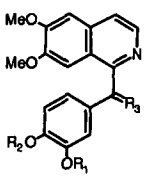
Scheme 1



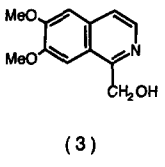
6-Desmethylpapaverine on treatment with excess of DAIB in methanol at room temperature gave a compound in 10% yield (apart from other minor unidentified compounds) with neither a methoxy nor an acetoxy group[10] in the position para to the oxidized phenol but rather an iodophenyl group(5). This is quite conceivable as iodobenzene serves as a nucleophile, and evidence that the position ortho to the

iodo group participated in nucleophilic attack comes from the ^{1}H-NMR (COSY spectrum).[11] In compound 5, a one proton broad doublet at δ6.81 for the 3" proton is strongly coupled to the 4"- and 5"-protons at δ7.30 which in turn are coupled to the 6"-proton at δ7.04. The 5'-proton at δ6.83 is coupled to the 6'-proton at δ6.91.

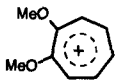
A sharp peak at 1648 cm^{-1} in the infrared spectrum of 5 supported the presence of a carbonyl group. The fragment at m/z 151 in the EI mass spectrum indicated an intact dimethoxy benzyl moiety.



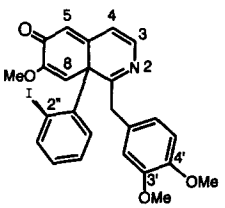
(1) $R_1 = R_2 = CH_3$; $R_3 = H_2$
(2) $R_1 = R_2 = CH_3$; $R_3 = O$
(4) $R_1 = H$; $R_2 = CH_3$; $R_3 = (OCH_3)_2$
(6) $R_1 = R_2 = CH_3$; $R_3 = H$, OH



(3)



m/z 151



(5)

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7. 500MHz ^{1}H-NMR(COSY spectrum) of 4 ($CDCl_3$) δ: 3.2(s,2xOCH_3), 3.81(s,OCH_3), 3.84(s,OCH_3), 3.98(s,OCH_3), 6.75(d,J=8.4Hz,5'-H), 6.98(s,8-H), 7.12(dd,J=8.4 and 2.1Hz, 6'-H), 7.18 (d,J=2.1Hz,2'-H), 7.41(d,J=5Hz,4-H), 7.89(s, 5-H) and 8.48(d,J=5Hz,3-H). 5'-H at 6.75 was spin coupled with 6'-H at 7.12. High resolution EI-MS accounted for the formula $C_{21}H_{23}NO_6$ (Found: 385.152981; Calculated: 385.152538).
8. In compound 3 the PMR signal for -CH_2OH appeared at δ5.14 which is relatively downfield compared to the benzylic protons at δ4.50 in papaverine. High resolution EI-MS (Found: 219.089504; Calculated: 219.089543) indicated it to be $C_{12}H_{13}NO_3$ with a major fragment at m/z 189 corresponding to the loss of -CH_2O).
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11. 500MHz ^{1}H-NMR (COSY spectrum) of 5 (CD_3COCD_3) δ: 3.72(s, OCH_3), 3.73(s, OCH_3), 3.85(s, OCH_3), 4.65(s, -CH_2-), 6.81(br d, J=8Hz, 3"-H), 6.83(m, 2'-H and 5'-H), 6.91(dd, J=8 and 2Hz, 6'-H), 7.04(m, 5-H and 6"-H), 7.30(dd, J=8Hz, 4"-H and 5"-H), 7.81(d, J=5.2Hz,4-H), 7.86(s, 8-H) and 8.51(d,J=5.2Hz,3-H). High resolution EI-MS (Found: 527.058905; Calculated: 527.059360) accounted for the formula $C_{25}H_{22}INO_4$.

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