Formation of Aromatic Compounds from Carbohydrates. IV.*
Chromones from Reaction of Hexuronic Acids in
Slightly Acidic, Aqueous Solution

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Two new chromones, 3,5,6-trihydroxy-2-methylchromone (I) and 3,5,8-trihydroxy-2-methylchromone (2) have been isolated and identified from treatment of D-glucuronic or D-galacturonic acid in aqueous solutions of pH 3.5 and 4.5, respectively, at 96 °C. Compound 2 was also isolated from similar treatment of D-xylene. The MS spectra of compounds I, 2 and 3,8-dihydroxy-2-methylchromone (6) are discussed. The former two (I, 2) seem to be new compounds.

In previous papers the isolation and identification of a series of phenolic compounds, furans and reductic acid from treatment of hexuronic acids or pentoses in slightly acidic, aqueous solution, were reported. Also isolated were 3-acetyl-2,3,6-trihydroxyxycyclohexanone (3), 5,6,7,8-tetrahydro-3,5-dihydroxy-2-methyl-8-oxo-benzopyrone (5) and two unidentified chromones. The former two compounds (3 and 5) were shown to be precursors of, respectively, 2,3-dihydroxyacetophenone (4) and 3,8-dihydroxy-2-methylchromone (6) (the predominant phenolic reduction product). The yields of 5 and 6 from D-glucuronic acid, were 1.7 and 3.4 %, respectively. Based upon these findings, tentative mechanism were later presented for the formation of 4 and 6 (see DISCUSSION).

This paper describes the identification of the previously isolated chromones I and 2, isolated from D-glucuronic acid in 0.7 and 0.2 % yields, respectively, in smaller amounts from D-galacturonic acid and 2 also from D-xylene.

RESULTS

Compound I gave green and compound 2 redish-violet colour with acidic ferric chloride. Both compounds corresponded to the formula C_{14}H_{10}O_{5} as shown by elemental analysis and they resembled the chromone 6 closely in their MS fragmentation pattern as well as in their UV and IR spectra, indicating 3-hydroxy-2-methylchromones. NMR spectroscopy and MS of their acetates (Ia and 2a) indicated three acetyl groups. NMR spectra (Table 1) of I and 2 showed that each had two adjacent aromatic protons. Both substances gave a positive reaction to William's boric acid test, indicating a hydroxyl group at position 5.

Compound I was methylated with diazomethane, and the tri-O-methyl ether (1b) oxidized according to Aso with hydrogen peroxide to acid 7. This was further converted to methyl-2,3,6-trimethoxybenzoate (8) with diazomethane. The latter compound was shown to be identical (IR, NMR and MS) with an authentic sample prepared from 2,6-dihydroxybenzoic acid (9) via oxidation of the methyl ester (10) to 11 with potassium persulfate followed by methylation.

Authentic 2 was synthesized from compound 6 by oxidation with potassium persulfate in a yield of 26 % calculated on reacted 6 and the identity with the isolated sample shown by IR, NMR, MS, melting points and chromatographic properties. It was further shown that compound 2 could be converted to the ester 8 via methylation, oxidation and treatment with diazomethane. Treatment of I and 2

* Part III. See Ref. 14.
with diazomethane gave, in addition to 1b and 2b, 3,6-dimethoxy-5-hydroxy-2-methylchromone (1c) and 3,8-dimethoxy-5-hydroxy-2-methylchromone (2c), respectively, which were chromatographically separated.

The structures of compounds 1 and 2 are fully established by the data and reactions presented above. Some results from the NMR spectral and MS studies of compounds 1, 2, 6 and their derivatives, which are of general interest to the chemistry of chromones and related compounds are discussed below.

DISCUSSION

The 1H NMR spectra of 2-methylchromones have been discussed previously. 1 The 1H NMR spectral data for compounds 1, 2, 6, their methyl ethers and acetates are collected in Table 1. The proton H-7 was localized in the spectra of the dimethyl ethers 1c, 2c and 6b by its long range coupling to the adjacent methoxyl group. 8a The mutual assignment of H-7 and H-8 in compound 1a was confirmed by the addition of the shift reagent “Eu(fod)₃”, which shifted the signal at δ 7.48 (H-7) most (cf. Ref. 8b). In compound 6 and its acetate 6a the aromatic protons form an ABC-system, which was analyzed by computer simulation.

MS spectra of 2-methylchromones have been previously 9-11 reported, and give fragmentation patterns similar to those of flavones. 10,11 Thus, the most prominent peaks correspond to the molecular ions, to losses of 28 and 29 mass units and to retro-Diels-Alder reactions (exemplified by fragment A and A+1 in Fig. 1). The fragmentation of compounds 6 and 6b, as well as of 1 and 2 and their methoxy derivatives, was supported by the appearance of metastable peaks. We found

Table 1. $^1$H NMR spectral data for chromones 1, 2, 6, in (CD$_3$)$_2$SO and for their derivatives in CDCl$_3$. The chemical shifts ($\delta$) are given in the table and the coupling constants ($J$; without sign) as footnotes.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>5-H</th>
<th>6-H</th>
<th>7-H</th>
<th>8-H</th>
<th>CH$_3$</th>
<th>OCH$_3$</th>
<th>OAc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6$^c$</td>
<td>7.50</td>
<td>7.22</td>
<td>7.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a$^a$</td>
<td></td>
<td>7.48</td>
<td>7.34</td>
<td>2.61</td>
<td>2.31; 2.33; 2.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a$^b$</td>
<td>7.98</td>
<td>7.40</td>
<td></td>
<td>2.40</td>
<td>2.32; 2.35; 2.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6a$^d$</td>
<td>8.08</td>
<td>7.37</td>
<td>7.41</td>
<td>2.41</td>
<td>2.41; 2.37</td>
<td></td>
<td></td>
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<tr>
<td>6b$^e$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.84; 3.87; 3.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c$^a$</td>
<td></td>
<td>7.21</td>
<td>6.83</td>
<td>2.43</td>
<td>3.88; 3.92</td>
<td></td>
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</tr>
<tr>
<td>2c$^b$</td>
<td>6.68</td>
<td>7.11</td>
<td></td>
<td>2.50</td>
<td>3.88; 3.90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ $J_{5,6}$ 9.0 Hz. $^b$ $J_{5,6}$ 8.5 Hz. $^c$ $J_{5,6}$ 6.5, $J_{5,7}$ 3.3 and $J_{5,7}$ 7.5 Hz. $^d$ $J_{5,6}$ 8.3, $J_{5,7}$ 1.1 and $J_{4,7}$ 8.0 Hz. $^e$ $J_{5,6}$ 8.0, $J_{5,7}$ 2.0 and $J_{6,7}$ 8.0 Hz.

that peak A + 1 is more intense than peak A in the spectra of the 3-hydroxychromones, while peak A predominates when the hydroxyl group at C-3 is esterified. This is in agreement with previous results on flavones.$^{13}$ The methoxychromones also gave fragmentation patterns similar to methoxyflavones,$^{13}$ exhibiting strong peaks for M − 15, M − 43, A − 15 and A − 43. The strong peak B was found for all 3-hydroxychromones, in agreement with previous results$^{12}$ for flavones. In methoxychromones, however, A − 15 and B are isobaric, but no metastable peak could be found confirming the formation of the latter. Peak M − 46 seems to be characteristic for all 3-hydroxy- and 3-methoxychromones and A − 29 for chromones having a hydroxyl or methoxyl group at C − 8.

In the present and the previous studies,$^{1,4}$ on the formation of aromatic compounds from reaction of hexuronic acids or pentoses under slightly acidic conditions, the only precursors isolated so far are compounds 3 and 5. The following tentative mechanisms are suggested$^3$ for the formation of the corresponding phenolic compounds 4 and 6 from these precursors (Fig. 2). We are fully aware that the acyclic intermediates may be different and that other alternatives are possible for the subsequent reactions. Both 5 and 6 are formed from pentoses or hexuronic acids, but not from hexoses according to our recent investigations,$^{14}$ which strongly suggest that $C_5$-fragments are involved in the formation of the acyclic $C_{16}$-intermediates. The formation of monocyclic $\gamma$-pyrones from D-fructose or D-glucose via

Fig. 1. Fragmentation on electron impact of compounds 6 and 6b.

EXPERIMENTAL

Melting points are corrected. TLC was performed on Silica Gel HF_6 (Merek) with 9:1 dichloromethane-acetonitrile as solvent. Silicic acid (100 mesh Mallinckrodt) was used for column chromatography. The plates were studied in UV-light before treatment with (a) diazotized sulfanilic acid or (b) ferric chloride as spray reagents. Sublimations (or distillations) were performed at 0.5 mmHg in an electrically heated tube. NMR spectra were recorded at 100 MHz.

3,5,6-Trihydroxy-2-methylchromone (1) was recrystallized from ethanol, m.p. 223–224°C. Found: C 57.2; H 3.9. Calc. for C_{17}H_{18}O_{4}: C 57.7; H 3.9. MS [IP, 70 eV; m/e (% rel. int.): 209(11), 208(100, M), 180(14, [M – 28]), 179(15, [M – 29]), 162(26, [M – 46]), 153(33, [A + 1]), 137 (27, [B]), 124(6, [A – 28]), 117(55, 20), 112(15), 110(15). IR (KBr): 1640 (s), 1620 (s), 1600 (s), 1560 (s), 1470 (broad), 1370 (m), 1310 (broad), 1285 (s), 1215 (broad), 1155 (w), 1105 (w), 1050 (s), 995 (s), 830 (s), 790 (s) cm⁻¹. UV (abs. ethanol, 1 log ε): 238(4.17), 253(4.24), 295(3.83), 367 (3.62). (NaOH/ethanol): 235(4.07), 500(3.25) nm.

Acetylation of 1 (Ac₂O/pyr.) yielded the triacetate (1a) recrystallized from benzene-light petroleum (b.p. 40–60°C), m.p. 165–166°C. Found: C 58.1; H 4.3. Calc. for C_{19}H_{24}O_{5}: C 57.5; H 4.2. MS [IP, 70 eV; m/e (% rel. int.): 334(1, M), 292(14), 250(32), 209(13), 208(100), 178(14), 163(7), 137(9), 126(5), 121(8), 107(6), 65(6), 55(6), 51(7), 45(8). Methylation (CH₃I) of compound 1 yielded a mixture of the di- and tri-methyl ethers in ratio 1:5, which were separated on a silicic acid column with 9:1 dichloromethane-acetonitrile as solvent.

3,5,6-Trimethoxy-2-methylchromone (1b) was recrystallized from carbon tetrachloride, m.p. 130.5–132°C. Found: C 62.9; H 5.6. Calc. for C_{17}H_{18}O_{4}: C 62.4; H 5.6. MS [IP, 70 eV; m/e (% rel. int.): 250(63, M), 236(16), 235(100, [M – 15]), 233(10), 221(12, [M – 29]), 220(11), 217(16), 207(18, [M – 43]), 204(5, [M – 46]), 203(12), 192(32), 180(18, [A]), 165(19, [A – 15]), 137(21, [A – 43]), 78(17), 77(15), 55(12), 53(11), 50(12), 43(56).

The dimethylether was positive towards Wilson’s boric acid test 4 and towards spray b, indicating a free hydroxyl at C-5. Since it is previously known 28 that 5-hydroxydihydroflavones are difficult to methylate with diazomethane, the compound was assigned 5-hydroxy-3,6-dimethoxy-2-methylchromone (1c). It was recrystallized from aqueous ethanol, m.p. 80.5–82.5°C. Anal. C_{17}H_{18}O_{4}: C, H, MS [IP, 70 eV; m/e (% rel. int.): 237(20), 236(100, M), 235(16), 221(52, [M – 15]), 218(13, [M – 19]), 208(13, [M – 28]), 207(12, [M – 29]), 206(10), 194(12), 193(10, [M – 43]), 190(12, [M – 46]), 178(22), 175(19, [A]), 151(15, [A – 15]), 150(18), 123(18, [A – 43]), 79(22), 76(10), 55(10), 51(11), 43(26).

3,5,6-Trihydroxy-2-methylchromone (2) was synthesized in 28% yield from 6 by oxidation.
with \( \text{K}_2\text{S}_2\text{O}_8 \) in the same way previously reported \(^{22} \) for 5-hydroxy-3,7-dimethoxyflavone, and recrystallized from ethanol.\(^*\) M.p. 254—256°C (dec.). Found: C 57.2; H 3.7. Calc. for \( \text{C}_6\text{H}_4\text{O}_3\): C 57.7; H 3.8. \( \text{MS} \) [IP 70 eV; \( \text{m/e} \) (% rel. int.)]: 200(12), 208(100), 180, (19, \( \text{M} - 28 \)), 179(13, \[ \text{M} - 29 \]), 162(6, \[ \text{M} - 46 \]), 153(60, [\text{A} + 1]), 137(22, [B]), 124(4, \[ \text{A} - 28 \]), 123(4, \[ \text{A} - 29 \]), 126(40, [\text{A} - 29]), 57(18), 55(15), 43(20]). IR (KBr): 1645 (w), 1620 (s), 1560 (s), 1470 (broad), 1420 (w), 1360 (w), 1270 (s), 1215 (s), 1165 (w), 1005 (m), 1055 (m), 1005 (m), 960 (m), 800 (m), 745 (m) cm\(^{-1}\). UV [abs. ethanol (log e)]: 248(3.35), 370 (3.65) and (\text{NaOH/ ethanol}): 233(sh, 3.25), 365(3.79) nm.

Acetylation (\( \text{Ac}_2\text{O/pyr} \)) yielded the triacetate (2a), recrystallized from benzene, m.p. 175.5—179.5°C (dec.). Anal. \( \text{C}_6\text{H}_4\text{O}_3\cdot \text{C}_2\text{H}_5\text{OH} \cdot \text{NaOH} \): C, H, MS [IP 70 eV; \( \text{m/e} \) (% rel. int.):] 334 (1, M), 292(20), 250(25), 209(14), 208(100), 207(13), 179(7), 153(6), 43(99).

Methylation (\( \text{CH}_3\text{N}_2 \)) of compound 2 yielded a mixture of the di- and tri-methyl ether in ratio 3:1. Separation was achieved in the same way as for compounds Ib and Ic.

3,5,8-Trime thoxy-2-methylchromone (2b) crystallized on storage, m.p. 106—110°C. Found: C 62.9; H 5.8. Calc. for \( \text{C}_8\text{H}_10\text{O}_3 \): C 62.4; H 5.6. MS [IP 70 eV; \( \text{m/e} \) (% rel. int.):] 251(15), 250(100, M), 249(14), 235(4, \[ \text{M} - 15 \]), 233(17), 232(13, \[ \text{M} - 18 \]), 221(19, \[ \text{M} - 29 \]), 220(16), 217(30), 207(24, \[ \text{M} - 43 \]), 206(25), 205(14), 204(15, \[ \text{M} - 46 \]), 192(17), 191(12), 180(26, [A]), 177(15), 165(12, \[ \text{M} - 15 \]), 151(20, \[ \text{A} - 29 \]), 137(28, \[ \text{A} - 43 \]), 123(14), 122(18), 78(13), 77(15), 55(10), 53(14), 51(12), 43(59).

For the reasons given for Ic the dimethyl ether was assigned 5-hydroxy-3,5-dimethoxy-2-methylchromone (2e), recrystallized from aqueous ethanol, m.p. 100—105.5°C. Anal. \( \text{C}_6\text{H}_4\text{O}_3\cdot \text{C}_2\text{H}_5\text{OH/NaOH} \): C, H, MS [IP 70 eV; \( \text{m/e} \) (% rel. int.):] 237(22), 236(53, M), 229(30), 228(6), 206(8), 205(14), 204(5, \[ \text{M} - 46 \]), 192(17), 191(12), 180(26, [A]), 177(15), 165(12, \[ \text{M} - 15 \]), 151(21, \[ \text{A} - 15 \]), 138(6, \[ \text{A} - 28 \]), 137(10, \[ \text{A} - 29 \]), 135(12), 133(12), 123(23, \[ \text{A} - 43 \]), 79(19), 77(12), 69(18), 67(18), 55(35), 54(17), 53(31), 51(25), 43(100).

3,8-Dihydroxy-2,5-methylchromone (6), \(^{1,2} \) MS [IP 70 eV; \( \text{m/e} \) (% rel. int.):] 206(3), 193(13), 192(100, M), 174(5, \[ \text{M} - 18 \]), 164(16, \[ \text{M} - 28 \]), 163(21, \[ \text{M} - 29 \]), 146(55, \[ \text{M} - 46 \]), 137(66, \[ \text{M} + 1 \]), 136(21, [A]), 121(50, [B]), 113(16), 108(11, \[ \text{M} - 28 \]), 107(15, \[ \text{A} - 29 \]), 81(14), 80(13), 79(16), 77(12), 65(19), 63(4, \[ \text{M} - 28 \]), 55(28), 53(30), 52(32), 51(27), 50(15), 43(46). IR (KBr): 1640 (m), 1620 (m), 1600 (s), 1550 (broad), 1480 (s), 1455 (m), 1390 (m), 1325 (w), 1290 (s), 1245 (s), 1220 (broad), 1150 (w), 1095 (m), 1025 (s), 980 (s), 890 (w), 830 (w), 750 (s) cm\(^{-1}\). UV [abs. ethanol (log e):] 238(sh, 4.41), 242(4.40), 331(3.86) and (\text{NaOH/ ethanol}): 255(4.37) nm.

* The synthesized and the isolated \(^1\) sample were found to be identical in all respects.

REFERENCES


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