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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 (*1*) 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-xylose. The MS spectra of compounds *1*, *2* and 3,8-dihydroxy-2-methylchromone (*6*) [1,2] are discussed. The former two (*1*, *2*) seem to be new compounds.

In previous papers [1,2] the isolation and identification of a series of phenolic compounds, furanes 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-trihydroxycyclohexanone (*3*), 5,6,7,8-tetrahydro-3,5-dihydroxy-2-methyl-8-oxo-benzopyrone (*5*) and two unidentified chromones.[2] 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 reaction product). The yields of *5* and *6* from D-glucuronic acid, were 1.7 and 3.4 %, respectively. Based upon these findings, tentative mechanisms were later presented [3] for the formation of *4* and *6* (see DISCUSSION).

This paper describes the identification of the prevously [1,2] isolated chromones *1* 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-xylose.

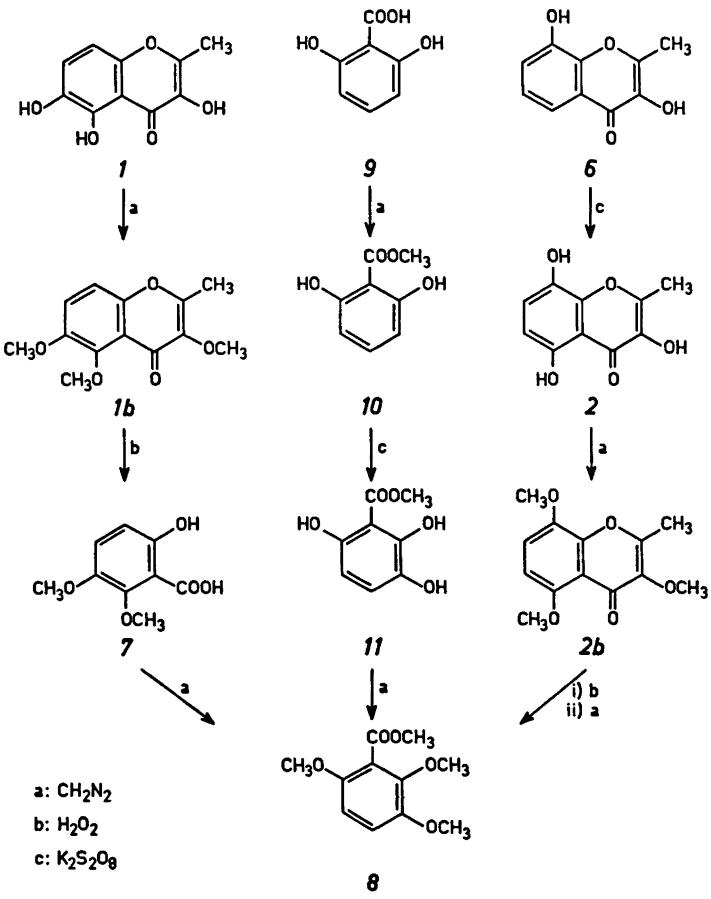
* Part III. See Ref. 14.

RESULTS

Compound *1* gave green and compound *2* reddish-violet colour with acidic ferric chloride. Both compounds corresponded to the formula $C_{10}H_8O_5$ 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 (*1a* and *2a*) indicated three acetyl groups. NMR spectra (Table 1) of *1* and *2* showed that each had two adjacent aromatic protons. Both substances gave a positive reaction to Wilson's boric acid test,[4] indicating a hydroxyl group at position 5.

Compound *1* was methylated with diazomethane, and the tri-*O*-methyl ether (*1b*) oxidized according to Aso [5] 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 [6] 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 *1* and *2*



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.

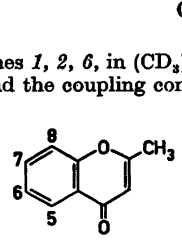
The structures of compounds *1* and *2* are fully established by the data and reactions presented above. Some results from the NMR spectral and MS studies of compounds *1*, *2*, *6* and their derivatives, which are of general interest to the chemistry of chromones and related compounds are discussed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

DISCUSSION

The ^1H NMR spectra of 2-methylchromones have been discussed previously.[7] 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.[12,13] 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 appearence of metastable peaks. We found

Table 1. ^{1}H NMR spectral data for chromones *1*, *2*, *6*, in $(CD_3)_2SO$ and for their derivatives in $CDCl_3$. The chemical shifts (δ) are given in the table and the coupling constants (J; without sign) as footnotes.



Compounds	5-H	6-H	7-H	8-H	CH_3	OCH_3	OAc
1 [a]			7.26	6.89	2.41		
2 [b]		6.55	7.09		2.40		
6 [c]	7.50	7.22	7.17		2.44		
1a [a]			7.48	7.34	2.51		2.31; 2.33; 2.34
2a [b]		6.98	7.40		2.40		2.32; 2.35; 2.39
6a [d]	8.08	7.37	7.41		2.41		2.41; 2.37
1b [a]			7.25	7.04	2.34	3.84; 3.87; 3.91	
2b [b]		6.61	7.02		2.41	3.85; 3.87; 3.88	
6b [e]	7.80	7.28	7.12		2.50	3.91; 3.98	
1c [a]			7.21	6.83	2.43	3.88; 3.92	
2c [b]		6.68	7.11		2.50	3.88; 3.90	

[a] $J_{7,8}$ 9.0 Hz. [b] $J_{6,7}$ 8.5 Hz. [c] $J_{5,6}$ 6.5, $J_{5,7}$ 3.3 and $J_{6,7}$ 7.5 Hz. [d] $J_{5,6}$ 8.3, $J_{5,7}$ 1.1 and $J_{6,7}$ 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 etherified. This is in agreement with previous results on flavones.[13] The methoxychromones also gave fragmentation patterns similar to methyoxyflavones,[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.

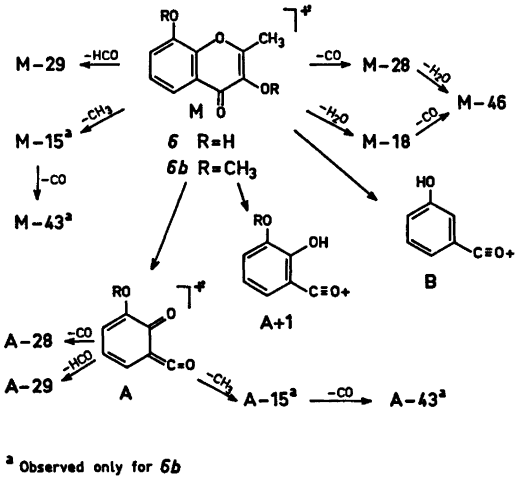


Fig. 1. Fragmentation on electron impact of compounds *6* and *6b*.

In the present and the previous studies[1,2] 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_{10}-intermediates. The formation of monocyclic γ-pyrones from D-fructose or D-glucose *via*

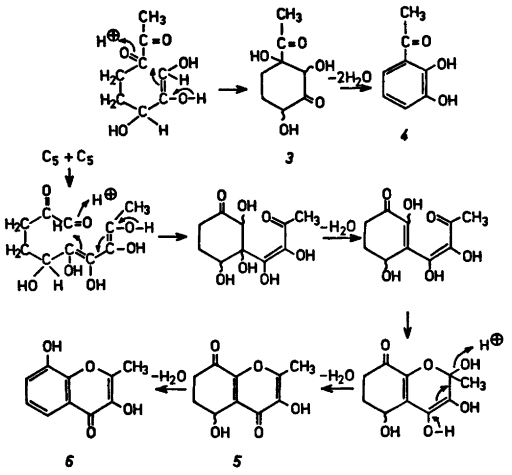


Fig. 2. Tentative mechanisms for the formation of compounds *4* and *6*.

closure of dicarbonyl sugars has been discussed previously.[15]

Anderegg and Neukom have studied the formation of *6* from ascorbic acid and pentoses,[16,17] and a mechanism for its formation from D-ribose was suggested,[17] based on our findings of *5* as a precursor. The suggested acyclic intermediate is somewhat different from ours, but many equally probable mechanisms may be constructed. Aso, who first isolated the chromone *6* (named alginetin) from treatment of alginic acid in aqueous solution at 160 °C,[5] suggested a mechanism for its formation,[18] which in the light of our isolation of *5* may be discarded or be considered to be a less likely alternative.

The formation of the cyclic intermediates *3* and *5* under weakly acidic conditions and their rapid transformation into the phenolic compounds *4* and *6* in high yields resembles the biosynthesis of phenolic compounds.[19,20] There are also many biogenetically modelled syntheses related to our findings. These studies have mainly been concerned with cyclization of poly-β-carbonyl compounds (see Ref. 21 for a summary), but the synthesis of a 2,6-diketodeoxyheptonic acid and its ready cyclization to 3-dehydroquinic acid provide an example from the shikimate route.[22]

EXPERIMENTAL

Melting points are corrected. TLC was performed on Silica Gel HF_{254} (Merck) 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) [1,2] was recrystallized from ethanol, m.p. 223 – 224 °C. Found: C 57.2; H 3.9. Calc. for $C_{10}H_8O_5$: 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(6,[M – 46]), 153(33,[A + 1]), 137 (27,[B]), 124(6,[A – 28]), 57(12), 55(14), 43(20). IR (KBr): 1640 (s), 1620 (s), 1600(s), 1560 (s), 1470 (broad), 1370 (m), 1310 (broad), 1265 (s,) 1215 (broad), 1155 (w), 1105 (s), 1050 (s), 995 (s), 830 (s), 790 (s) cm^{-1}. UV [abs. ethanol (log ε)]: 238(4.17), 255(4.24), 295(sh, 363), 367 (3.62). (NaOH/ethanol): 235(4.07), 500(3.25) nm.

Acetylation of *1* (Ac_2O/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 $C_{16}H_{14}O_8$: 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), 179(14), 163(7), 137(9), 136(5),121(8), 107(6), 63(6), 55(6), 51(7), 43(61). Methylation (CH_2N_2) 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-acetontrile 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 $C_{13}H_{14}O_5$: 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 dimethyl ether 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 [23] that 5-hydroxyflavones 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. $C_{12}H_{12}O_5$: C, H. MS [IP 70 eV; *m/e* (% rel. int.)]: 237(20), 236(100, M), 235(16), 221(52,[M – 15]), 218(13, [M – 18]), 208(13, [M – 28]), 207(12,[M – 29]), 203(10), 194(12), 193(90,[M – 43]), 190(12,[M – 46]), 178(22), 166(19,[A]), 151(15,[A – 15]), 150(18), 123(18, [A – 43]), 79(22), 67(10), 55(10), 51(11), 43(26).

3,5,8-Trihydroxy-2-methylchromone (2) was synthesized in 28 % yield from *6* by oxidation

with $K_2S_2O_8$ in the same way previously reported [23] 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 $C_{10}H_8O_5$: C 57.7; H 3.9.[MS IP 70 eV; *m/e* (% rel. int.)]: 209(12), 208(100, M), 180(10, [M–28]), 179(13, [M–29]), 162(6,[M–46]), 153(60,[A+1]), 137(22, [B]), 124(4,[A–28]), 123(4,[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), 1095 (m), 1035 (m), 1005 (m), 960 (m), 800 (m), 745 (m) cm^{-1}. UV[abs. ethanol (log ε)]: 248(4.35), 370 (3.65) and (NaOH/ ethanol): 235(sh, 3.23), 365(3.79) nm.

Acetylation (Ac_2O/pyr.) yielded the *triacetate* (*2a*), recrystallized from benzene, m.p. 175.5–179.5 °C (dec.). Anal. $C_{16}H_{14}O_8$: C, H. MS[IP 70 eV; *m/e* (% rel. int.)]: 334 (1, M), 292(20), 250(25), 209(14), 208(100), 207(13), 179(7), 153(6), 43(90).

Methylation (CH_2N_2) of compound *2* yielded a mixture of the di- and tri-methyl ether in ratio 3:1. Separation was effected in the same way as for compounds *1b* and *1c*.

3,5,8-Trimethoxy-2-methylchromone (*2b*) crystallized on storage, m.p. 106–110 °C. Found: C 62.9; H 5.8. Calc. for $C_{13}H_{14}O_5$: C 62.4; H 5.6. MS [IP 70 eV; *m/e* (% rel. int.)]: 251(15), 250(100, M), 249(14), 235(84,[M–15]), 233(17), 232(13,[M–18]), 221(19,[M–29]), 220(16), 217(30), 207(24,[M–43]), 206(25), 205(14), 204(15,[M–46]), 192(17), 191(12), 180(26,[A]), 177(12), 165(12,[A–15]), 151(20, [A–29]), 137(28,[A–43]), 123(14), 122(18), 78(13), 77(15), 55(10), 53(14), 51(12), 43(59).

For the reasons given for *1c* the dimethyl ether was assigned *5-hydroxy-3,8-dimethoxy-2-methylchromone* (*2c*), recrystallized from aqueous ethanol, m.p. 100–102.5 °C. Anal. $C_{12}H_{12}O_5$: C, H. MS [IP 70 eV; *m/e* (% rel. int.)]: 237(22), 236(83, M), 222(39), 221(85,[M–15]), 207(8, [M–29]), 206(27), 203(17), 193(13), 190(4, [M–46]), 178(24), 166(13,[A]), 151(21,[A–15]), 138(6,[A–28]), 137(10,[A–29]), 135(12), 133(12), 123(23,[A–43]), 79(19), 77(12), 69(18), 67(18), 55(35), 54(17), 53(31), 51(25), 43(100).

3,8-Dihydroxy-2-methylchromone (*6*).[1,2] MS [IP 70 eV; *m/e* (% rel.int.)]: 193(13), 192(100, M), 174(3,[M–18]), 164(16,[M–28]), 163(21, [M–29]), 146(15,[M–46]), 137(56,[A+1]), 136(21,[A]), 121(50,[B]), 118(16), 108(11,[A–28]), 107(15,[A–29]), 81(14), 80(13), 79(16), 77(12), 65(19), 63(24), 55(28), 53(30), 52(32), 51(27), 50(15), 43(46). IR(KBr): 1640 (m), 1620 (m), 1600 (s), 1550 (broad), 1480 (s), 1435 (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 ε)]: 238(sh, 441), 242(4.46), 331(3.85) and (NaOH/ ethanol). 255(4.37) nm.

Acetylation (Ac_2O/pyr.) yielded the *diacetate* (*6a*), recrystallized from benzene–light petroleum (b.p. 60–80 °C), m.p. 126.5–127 °C (lit. value [5,18] 125 °C). Anal $C_{14}H_{12}O_6$: C,H. MS [IP 70 eV; *m/e* (% rel. int.)]: 276(3, M), 235(4), 234(26), 193(12), 192(100), 163(7), 137(9), 136(5), 121(8), 107(6), 63(6), 55(6), 51(7), 43(88).

Methylation (CH_2N_2) of compound *6* yielded the *dimethyl ether* (*6b*) recrystallized from hexane, m.p. 105–106 °C (lit. value [5,18] 105 °C). Anal. $C_{12}H_{12}O_4$: C, H. MS [IP 70 eV; *m/e* (% rel. int.)]: 220(100, M), 219(25), 205(40, [M–15]), 202(37,[M–18]), 191(12,[M–29]), 190(20), 177(24), 174(10,[M–46]), 151(20, [A+1]), 150(49,[A]), 135(4,[A–15]), 122(64, [A–28]), 121(21,[A–29]), 120(14), 119(11), 107(23,[A–43]), 91(15), 77(15), 76(17), 67(12), 65(15), 53(11), 51(20), 50(14), 43(34).

6-Hydroxy-2,3-dimethoxybenzoic acid (*7*). Compound *1b* was oxidized with H_2O_2 in the same way as previously reported [5] for *6b*. To *1b* (250 mg) were added aqueous Na_2CO_3 (1 %, 175 ml) and aqueous H_2O_2 (3 %, 50 ml), and the mixture left at room temperature overnight. After acidification, extraction with ethyl acetate (3 × 50 ml), drying (Na_2SO_4) and evaporation, the compound (80 mg) was purified by silicic acid column chromatography (9:1 chloroform-acetic acid), yielding 60 mg *7* (30 %). After sublimation the crystals melted at 79–80.5 °C. (lit. value [24] 77–79 °C). Found: C 55.2; H 5.1. Calc. for $C_9H_{10}O_5$: C 54.6; H 5.1.

Methyl-2,6-dihydroxybenzoate (*10*) [25] was oxidized to *methyl-2,3,6-trihydroxybenzoate* (*11*) in analogy with a previous related synthesis;[6] recrystallized from benzene, m.p. 136–139 °C (lit. value [26] 139–140.5 °C).

Methyl-2,3,6-trimethoxybenzoate (*8*) was obtained in an amorphous state from compound *11* by methylation (CH_2N_2). It was identical (NMR, MS) with methylated (CH_2N_2) compound *7*, and with oxidized and methylated *2b*. (Lit. value [27] m.p. 57.0–57.5 °C). MS [IP 70 eV; *m/e* (% rel. int.)]: 227(19), 226(100, M), 211(55), 195(55), 183(38), 180(18), 179(20), 164(14), 137(40), 45(18). ^1H NMR, δ ($CDCl_3$): 3.73 (3 H, s), 3.78 (3 H, s), 3.85 (3 H, s), 3.87 (3 H, s) 6.59 (1 H, d, *J* 9.3 Hz), 6.88 (1 H, d, *J* 9.3 Hz).

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