Reactions of resorcinols with ketones

Sergei I. Filimonov,*[a] Nikolai G. Savinsky[b] and Elena M. Evstigneeva[c]

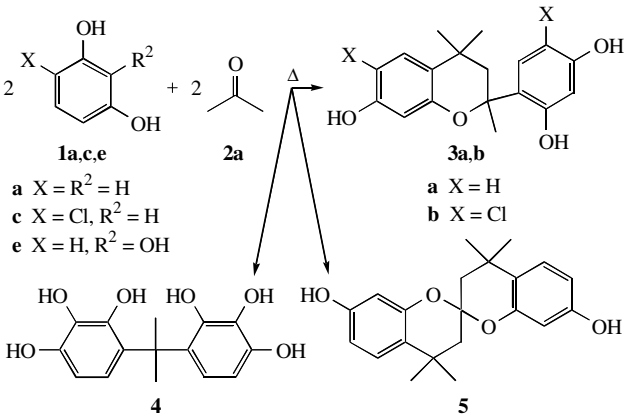
[a] *Yaroslavl State Pedagogical University, 150000 Yaroslavl, Russian Federation. E-mail: filim@nordnet.ru*
[b] *Yaroslavl Institute of Microelectronics, Russian Academy of Sciences, 150007 Yaroslavl, Russian Federation*
[c] *M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, 117571 Moscow, Russian Federation*

10.1070/MC2003v013n04ABEH001687

New products of the condensation of resorcinols with ketones under conditions of mild acid catalysis were studied.

The synthesis of chromans and flavans based on the interaction of di- and trihydroxybenzenes with ketones is of considerable interest.[1,2] Thus, Livant *et al.*[3] studied in detail only the condensation products of acetone and resorcinol. The aim of this work was to study in detail the concentration of various ketones (acetone, cyclopentanone, and substituted cyclohexanones) with substituted resorcinols (4-chloro, 2-methyl, monomethyl ether and pyrogallol) under conditions of mild acid catalysis.

The condensation of ketones with resorcinols under conditions of acid catalysis is a complex multicomponent process, which includes aldol condensation, crotonization and electrophilic alkylation of polyphenol. It can result in the formation of the following products: chromans **3**, bisphenols **4**, spirobichromans **5**, and highly condensed compounds (Schemes 1 and 2).

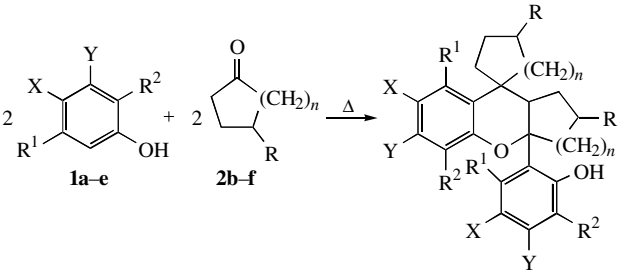


Scheme 1

General reaction conditions were determined based on the studies of the condensation products of acetone and resorcinol. Sulfuric, hydrochloric and toluenesulfonic acids, which are most frequently used for the synthesis of bisphenols, were tested as catalysts. The analysis of reaction mixtures demonstrated that chroman **3** was predominant in all cases; spirobichroman **5** was formed in considerable amounts (20%) only in the catalysis with sulfuric acid. A bisphenol derivative was not isolated. The catalyst concentration strongly affected the formation of highly condensed compounds, and it should be minimum; 0.1–0.3 M per mole of a ketone is sufficient. The solvent plays only an important role; thus, the yield of chroman increased and the reaction time shortened in the order methanol, toluene and chloroform. We found that an optimum temperature for aldol condensation is no higher than 40 °C at the beginning of the synthesis and 60–70 °C at the final stage (condensation processes).

In contrast to published data,[3] we found no detectable effect of an excess of resorcinol on the yield of chroman **3**. Resorcinol was always present as an impurity in the reaction products even at a 1:1 ratio between components. As acetone was replaced with diacetone alcohol, the product yield noticeably decreased, whereas with mesityl oxide chroman **3a** was not formed. This fact may be explained by the difficulty of double bond protonation under these conditions.

We found that acetone, cyclopentanone, cyclohexanone, 4-methylcyclohexanone, 4-*tert*-butylcyclohexanone and 4-phenylcyclohexanone reacted with resorcinol, 4-chlororesorcinol, 2-methylresorcinol, 3-methoxyphenol and pyrogallol with the formation of corresponding compounds **3a–r**† (Schemes 1 and 2). The yields of resulting compounds were no higher than 30–60% except for compound **3a** obtained in 90% yield. The initial components and highly condensed compounds (oligomers) were the main impurities. As a rule, our attempts to improve the yield by increasing reaction time or temperature resulted in an increase in the oligomer content of the reaction mixture; because of this, the main product is difficult to isolate. The pure (> 95%) condensation products are difficult to separate even by chromatography because chroman derivatives are prone to form inclusion compounds[3] (for example, with diethyl ether, up to 20 mol%). Therefore, it is more convenient to analyse them in an acylated form.



1: **a** Y = OH, X = R^1 = R^2 = H
b Y = OMe, X = R^1 = R^2 = H
c Y = OH, X = Cl, R^1 = R^2 = H
d Y = OH, X = R^1 = H, R^2 = Me
e Y = OH, X = R^1 = H, R^2 = OH

2: **b** *n* = 1, R = H
c *n* = 2, R = H
d *n* = 2, R = Me
e *n* = 2, R = Bu^t
f *n* = 2, R = Ph

3: **c** Y = OH, X = R = R^1 = R^2 = H, *n* = 1
d Y = OMe, X = R = R^1 = R^2 = H, *n* = 1
e Y = OH, X = Cl, R = R^1 = R^2 = H, *n* = 1
f Y = OH, X = R = R^1 = H, R^2 = Me, *n* = 1
g Y = OH, X = R = R^1 = R^2 = H, *n* = 2
h Y = OMe, X = R = R^1 = R^2 = H, *n* = 2
i Y = OH, X = Cl, R = R^1 = R^2 = H, *n* = 2
j Y = OH, X = R = R^1 = H, R^2 = Me, *n* = 2
k Y = OH, X = R = R^1 = H, R^2 = OH, *n* = 2
l Y = OH, X = Cl, R = Me, R^1 = R^2 = H, *n* = 2
m Y = OMe, X = R^1 = R^2 = H, R = Me, *n* = 2
n Y = OH, X = R^1 = H, R = Me, R^2 = OH, *n* = 2
o Y = OH, X = R^1 = R^2 = H, R = Bu^t, *n* = 2
p Y = OMe, X = R^1 = R^2 = H, R = Bu^t, *n* = 2
q Y = OH, X = R^1 = R^2 = H, R = Ph, *n* = 2
r Y = OMe, X = R^1 = R^2 = H, R = Ph, *n* = 2

Scheme 2

† *General synthetic procedure*. A solution of 10 mmol of ketone **1**, 15 mmol of di- or trihydroxybenzene **2** and 1 mmol of *p*-toluenesulfonic acid monohydrate in 20–30 ml of chloroform was heated to 40 °C and stirred for 4–6 h until the formation of a viscous oil. Next, the mixture was heated to boiling, refluxed for 0.5–3 h and cooled. The formed precipitate was filtered off. If the product was not crystallised, 30–50 ml of water were added, and the contents were heated with stirring. Next, the aqueous layer was separated; the organic layer was evaporated to dryness, and the residue was crystallised from diethyl ether–hexane.

The structures of compounds **3** were determined based on spectroscopic data and the chemical behaviours of chroman hydroxyl groups in acylation reactions.†,‡ The signals of aliphatic protons in chromans **3c**–**r** are difficult to attribute accurately because they appear as a continuous multiplet in the region 2.5–0.8 ppm. The upfield signals (3.5–2.5 ppm) of protons at C_3 and the CH_2 group closest to C_3 (particularly, for five-membered rings) can be distinguished. The signal due to C–O (90–80 ppm) in the ^{13}C NMR spectra is typical of chromans.

The mass spectra of compounds **3** are characterised by the low-intensity peaks of molecular ions. Scheme 3 illustrates the main direction of molecular fragmentation (the most intense signals) under electron ionisation using compound **3i** as an

† ^1H NMR spectra of the test compounds were recorded on a Bruker DPX 300 spectrometer at 300 MHz using 3–5% solutions in [$^2H_6$]DMSO. The chemical shifts of protons were measured with reference to an internal standard of HMDS (0.055 ppm).

Mass spectra were measured on an MX-1321 mass spectrometer with direct sample injection at 100–150 °C with an ionisation energy of 70 eV.

Reversed-phase high-performance liquid chromatography was performed on a Perkin-Elmer instrument (mobile phase: acetonitrile–water, 70:30; stationary phase: C-18).

‡ **3a**: yield 87%; mp 223–224 °C. ^1H NMR, δ: 9.31 (s, 1H, OH), 9.07 (s, 1H, OH), 8.98 (s, 1H, OH), 6.97 (d, 1H, 6′-H, *J* 8.5 Hz), 6.82 (d, 1H, 5-H, *J* 8.5 Hz), 6.25 (m, 3H), 6.02 (dd, 1H, 5-H′, *J* 8.5 Hz, *J* 2.3 Hz), 2.90 (d, 1H, 3-H_e, *J* 13.9 Hz), 1.64 (d, 1H, 3-H_a, *J* 13.9 Hz), 1.54 (s, 3H, 4-Me), 1.17 (s, 3H, 4-Me), 0.63 (s, 3H, 2-Me).

3b: yield 61%, mp 131–132 °C, M^+ 369.24. ^1H NMR, δ: 9.82 (s, 1H, OH), 9.69 (s, 1H, OH), 9.64 (s, 1H, OH), 7.12 (s, 1H, 6′-H), 6.9 (s, 1H, 5-H), 6.54 (s, 1H, 8-H), 6.48 (s, 1H, 3′-H), 2.9 (d, 1H, 3-H_e, *J* 14.1 Hz), 1.75 (d, 1H, 3-H_a, *J* 14.1 Hz), 1.58 (s, 3H, 4-Me), 1.17 (s, 3H, 4-Me), 0.73 (s, 3H, 2-Me) (inclusion compound with diethyl ether).

3c: yield 27%; mp 193–194 °C. ^1H NMR, δ: 8.88 (s, 1H, OH), 8.61 (s, 1H, OH), 8.56 (s, 1H, OH), 6.92 (d, 1H, 6′-H, *J* 8.5 Hz), 6.83 (d, 1H, H-5, *J* 8.5 Hz), 6.25 (m, 3H), 6.05 (dd, 1H, 5′-H, *J* 8.5 Hz, *J* 2.5 Hz), 3.12 (dd, 1H, 3-H, *J* 14.1 Hz, *J* 6.5 Hz), 2.58 (d, 1H, *J* 14.1 Hz, *J* 3.8 Hz), 1.8–0.8 (m, 13H, CH_2). MS, *m*/*z*: M^+ 352 (29), 309 (4), 295 (8), 281 (3), 242 (4), 213 (8), 201 (7), 187 (4), 177 (100), 176 (69), 161 (17), 147 (21), 123 (23), 115 (6), 91 (5), 77 (4), 41 (3), 28 (9).

3d: yield 24%, mp 150–152 °C. ^1H NMR, δ: 9.12 (s, 1H, OH), 7.06 (d, 1H, 6′-H, *J* 8.6 Hz), 7.01 (d, 1H, 5-H, *J* 8.6 Hz), 6.52 (dd, 1H, 6-H, *J* 2.6 Hz, *J* 8.6 Hz), 6.50 (d, 1H, 8-H, *J* 2.6 Hz), 6.39 (dd, 1H, 5′-H, *J* 8.6 Hz, *J* 2.6 Hz), 6.35 (d, 1H, 3′-H, *J* 2.6 Hz), 3.76 (s, 3H, OMe), 3.74 (s, 3H, OMe), 2.84 (dd, 1H, 3-H, *J* 9.3 Hz, *J* 9.2 Hz), 2.27 (ddd, 1H, 1′′-H, *J* 13.6 Hz, *J* 6.8 Hz, *J* 6.8 Hz), 2.2–1.15 (m, 13H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 158.83 (C-9), 158.04 (C-4′), 155.01 (C-7), 151.33 (C-2′), 126.38 (C-10), 126.31 (C-5), 122.94 (C-6′), 121.62 (C-1′), 106.95 (C-5′), 104.95 (C-6), 101.52 (C-3′), 101.47 (C-8), 92.55 (C-2), 54.39 (OMe), 54.26 (OMe), 51.70 (C-4), 45.06 (C-3), 43.48 (C-11), 39.28 (C-14), 36.03 (C-17), 28.00 (C-12), 23.30 (C-16), 22.86 (C-17), 21.42 (C-13). MS, *m*/*z*: M^+ 380, 366, 337, 323, 257, 227, 215, 191, 175, 161, 159, 137, 115, 103, 91, 77, 28.

3e: yield 21%, mp 185–187 °C, M^+ 421.32. ^1H NMR, δ: 9.35 (s, 1H, OH), 9.25 (s, 2H, OH), 6.95 (s, 1H, H-6′), 6.94 (s, 1H, 5-H), 6.52 (s, 1H, 8-H), 6.49 (s, 1H, 3′-H), 3.35 (dd, 1H, 3-H, *J* 11.0 Hz, *J* 7.9 Hz), 3.18 (d, 1H, H-11, *J* 12.8 Hz, *J* 9.1 Hz), 1.8–0.8 (m, 13H, CH_2).

3f: yield 31%, mp 213–215 °C, M^+ 380.49. ^1H NMR, δ: 8.48 (s, 1H, OH), 8.45 (s, 1H, OH), 8.09 (s, 1H, OH), 6.73 (d, 1H, 6′-H, *J* 8.5 Hz), 6.67 (d, 1H, 5-H, *J* 8.5 Hz), 6.32 (d, 1H, 6-H, *J* 8.5 Hz), 6.20 (d, 1H, 5′-H, *J* 8.5 Hz), 3.16 (dd, 1H, 3-H, *J* 14.1 Hz, *J* 6.5 Hz), 2.61 (d, 1H, CH_2, *J* 14.1 Hz, *J* 3.8 Hz), 2.13 (s, 3H, Me), 2.01 (s, 3H, Me), 1.8–0.8 (m, 13H, CH_2).

3g: yield 55%, mp 233–234 °C. ^1H NMR, δ: 9.23 (s, 1H, OH), 8.95 (s, 1H, OH), 8.83 (s, 1H, OH), 6.92 (d, 1H, 6′-H, *J* 8.5 Hz), 6.75 (d, 1H, 5-H, *J* 8.5 Hz), 6.29 (d, 1H, 8-H, *J* 2.5 Hz), 6.25 (dd, 1H, 6-H, *J* 8.5 Hz, *J* 2.5 Hz), 6.23 (d, 1H, 3′-H, *J* 2.5 Hz), 5.98 (dd, 1H, 5′-H, *J* 8.5 Hz, *J* 2.5 Hz), 3.28 (dd, 1H, 3-H, *J* 14.0 Hz, *J* 3.5 Hz), 2.55 (ddd, 1H, CH_2), *J* 14.0 Hz, *J* 6.8 Hz, *J* 3.8 Hz), 1.8–0.8 (m, 17H, CH_2).

3h: yield 53%, mp 160–162 °C, M^+ 408.5. ^1H NMR, δ: 9.52 (s, 1H, OH), 7.05 (d, 1H, 6′-H, *J* 8.5 Hz), 6.89 (d, 1H, 5-H, *J* 8.5 Hz), 6.50 (d, 1H, 8-H, *J* 2.5 Hz), 6.42 (dd, 1H, 6-H, *J* 8.5 Hz, *J* 2.5 Hz), 6.34 (d, 1H, 3′-H, *J* 2.5 Hz), 6.18 (dd, 1H, 5′-H, *J* 8.5 Hz, *J* 2.5 Hz), 3.74 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.23 (dd, 1H, 3-H, *J* 12.8 Hz, *J* 4.8 Hz), 2.53 (ddd, 1H, CH_2, *J* 12.8 Hz, *J* 12.5 Hz, *J* 4.8 Hz), 1.8–0.8 (m, 17H, CH_2).

3i: yield 43%, mp 263–265 °C. ^1H NMR, δ: 9.62 (s, 1H, OH), 9.54 (s, 1H, OH), 9.47 (s, 1H, OH), 7.06 (s, 1H, 6′-H), 6.81 (s, 1H, 5-H), 6.54 (s,1H, 8-H), 6.48 (s, 1H, 3′-H), 3.23 (dd, 1H, 3-H, *J* 12.4 Hz, *J* 4.5 Hz), 3.48 (ddd, 1H, CH_2, *J* 12.4 Hz, *J* 12.8 Hz, *J* 4.5 Hz), 1.8–0.8 (m, 17H, CH_2). MS, *m*/*z*: M^+ 449 (18), 448 (24), 349 (6), 303 (4), 261 (3), 249 (4), 225 (100), 224 (96), 209 (16), 196 (19), 181 (25), 157 (79), 148 (7), 115 (6), 91 (4), 77 (7), 41 (8), 28 (16).

3j: yield 45%, mp 243–245 °C, M^+ 408.54. ^1H NMR, δ: 8.63 (s, 1H, OH), 8.58 (s, 1H, OH), 7.98 (s, 1H, OH), 6.76 (d, 1H, 6′-H, *J* 8.5 Hz), 6.46 (d, 1H, 5-H, *J* 8.5 Hz), 6.32 (d, 1H, 6-H, *J* 8.5 Hz), 6.10 (d, 1H, 5′-H, *J* 8.5 Hz), 3.32 (dd, 1H, 3-H, *J* 12.1 Hz, *J* 3.8 Hz), 2.62 (ddd, 1H, CH_2, *J* 12.5 Hz, *J* 12.1 Hz, *J* 3.8 Hz), 2.12 (s, 3H, Me), 1.97 (s, 3H, Me), 1.8–0.8 (m, 17H, CH_2).

3k: yield 49%, mp 205–206 °C, M^+ 412. ^1H NMR, δ: 8.82 (s, 1H, OH), 8.45 (s, 1H, OH), 8.18 (s, 1H, OH), 8.12 (s, 1H, OH), 7.75 (s, 1H, OH), 6.39 (d, 1H, 6′-H, *J* 8.8 Hz), 6.24 (d, 1H, 5-H, *J* 8.8 Hz), 6.18 (d, 1H, 6-H, *J* 8.8 Hz), 6.02 (d, 1H, 5′-H, *J* 8.8 Hz), 3.21 (d, 1H, 3-H, *J* 13.9 Hz), 2.49 (d, 1H, CH_2, *J* 13.9 Hz), 0.6–1.8 (m, 16H, CH_2).

3l: yield 20%, mp 158–160 °C (inclusion compound with diethyl ether). ^1H NMR (C_3D_5OD) δ: 8.84 (s, 1H, OH), 8.57 (s, 1H, OH), 8.37 (s, 1H, OH), 7.17 (s, 1H, 6′-H), 7.01 (s, 1H, 8-H), 6.64 (s, 1H, 6′-H), 6.53 (s, 1H, 3′-H), 2.63 (ddd, 1H, 3-H, *J* 4.3 Hz, *J* 13.1 Hz, *J* 13.5 Hz), 1.85–0.85 (m, 16H, CH_2), 0.93 (d, 9H, 4-Me, *J* 6.4 Hz), 0.90 (d, 9H, 4-Me, *J* 6.4 Hz). ^{13}C NMR (C_3D_5OD) δ: 154.05 (C-9), 153.95 (C-2′), 152.87 (C-7′), 152.54 (C-4′), 128.86 (C-10), 128.74 (C-8), 128.02 (C-3′), 124.93 (C-5), 124.52 (C-6′), 108.40 (C-1′), 105.93 (C-5′), 104.90 (C-6), 82.24 (C-2), 40.57 (C-3), 38.87 (C-4), 36.37 (CH_2), 35.00 (CH_2), 34.71 (CH_2), 34.54 (CH_2), 33.30 (CH_2), 32.75 (CH_2), 31.72 (CH_2), 28.34 (CH_2), 23.27 (CH_2), 23.07 (Me), 15.67 (Me).

3m: yield 20%, mp 140–142 °C. ^1H NMR, δ: 9.58 (s, 1H, OH), 7.03 (d, 1H, 6′-H, *J* 8.5 Hz), 6.85 (d, 1H, 5-H, *J* 8.5 Hz), 6.48 (d, 1H, 8-H, *J* 2.5 Hz), 6.39 (dd, 1H, 6-H, *J* 8.5 Hz, *J* 2.5 Hz), 6.31 (d, 1H, 3′-H, *J* 2.5 Hz), 6.16 (dd, 1H, 5′-H, *J* 8.5 Hz, *J* 2.5 Hz), 3.73 (s, 3H, OMe), 3.58 (s, 3H, OMe), 1.85–0.85 (m, 17H, CH_2), 0.82 (d, 3H, 4-Me, *J* 6.5 Hz), 0.80 (d, 3H, 4-Me, *J* 6.5 Hz).

3n: yield 39%, mp 138–140 °C, M^+ 440. ^1H NMR, δ: 8.50 (s, 3H, OH), 7.82 (s, 2H, OH), 6.49 (d, 1H, 6′-H, *J* 8.6 Hz), 6.29 (d, 1H, 5-H, *J* 8.6 Hz), 6.28 (d, 1H, 6-H, *J* 8.6 Hz), 6.07 (d, 1H, 5′-H, *J* 8.6 Hz), 3.22 (dd, 1H, 3-H, *J* 14.1 Hz, *J* 6.1 Hz), 2.53 (dd, 1H, CH_2, *J* 14.1 Hz, *J* 6.1 Hz), 1.1–1.9 (m, 12H, CH_2), 1.1 (m, 2H), 0.97 (d, 3H, Me, *J* 6.8 Hz), 0.88 (d, 3H, Me, *J* 6.8 Hz), 0.75 (m, 2H).

3o: yield 43%, mp 188–190 °C. ^1H NMR (C_3D_5OD) δ: 8.76 (s, 1H, OH), 8.56 (s, 1H, OH), 8.38 (s, 1H, OH), 7.43 (s, 1H, 6′-H), 7.12 (s, 1H, 5-H), 6.70 (s, 1H, 8-H), 6.51 (s, 1H, 3′-H), 2.89 (dd, 1H, 3-H, *J* 4.1 Hz, *J* 12.3 Hz), 2.40 (ddd, 1H, CH_2, *J* 4.3 Hz, *J* 13.5 Hz, *J* 13.6 Hz), 2.0–0.9 (m, 15H, CH_2), 0.86 (s, 9H, Bu^t), 0.83 (s, 9H, Bu^t). ^{13}C NMR (C_3D_5OD) δ: 153.75 (C-9), 53.40 (C-7), 152.86 (C-4′), 152.66 (C-2′), 130.39 (C-10), 129.10 (C-5), 127,52 (C-6′), 124.45 (C-1′), 112.06 (C-6), 111.80 (C-5′), 105.99 (C-8), 105.29 (C-3′), 80.25 (C-O), 48.37 (C-4), 47.17 (C-3), 40.21 (CH_2), 39.79 (CH_2), 37.63 (CH_2), 37.25 (CH_2), 33.16 (CH_2), 33.03 (CH_2), 27.89 (CBu^t), 27.76 (CBu^t), 26.69 (CH_2), 26.48 (CH_2), 23.48 (CH_2), 22.93 (Me), 15.66 (Me).

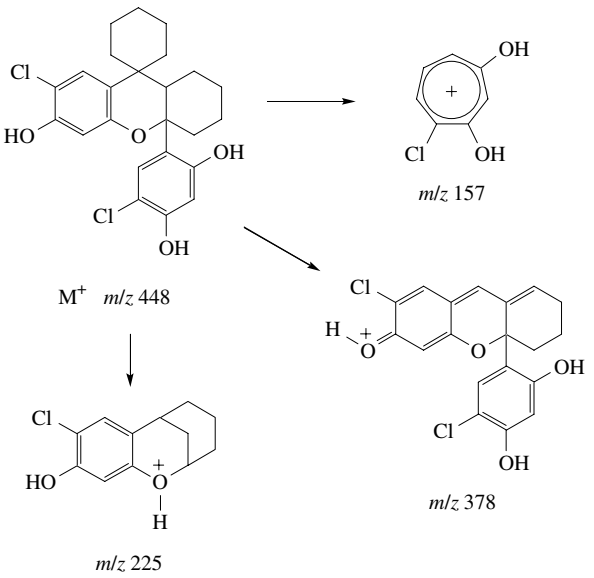
3p: yield 43%, mp 148–150 °C. ^1H NMR, δ: 9.28 (s, 1H, OH), 7.28 (d, 1H, 6′-H, *J* 8.5 Hz), 7.04 (d, 1H, 5-H, *J* 8.5 Hz), 6.53 (d, 1H, 8-H, *J* 2.5 Hz), 6.42 (dd, 1H, 6-H, *J* 8.5 Hz, *J* 2.5 Hz), 6.35 (d, 1H, 3′-H, *J* 2.5 Hz), 6.24 (dd, 1H, 5′-H, *J* 8.5 Hz, *J* 2.5 Hz), 3.76 (s, 3H, OMe), 3.65 (s, 3H, OMe), 2.83 (dd, 1H, CH_2, *J* 12.8 Hz, *J* 4.8 Hz), 2.36 (ddd, 1H, *J* 12.5 Hz, *J* 12.1 Hz, *J* 3.8 Hz), 1.85–0.85 (m, 15H, CH_2), 0.82 (s, 9H, Bu^t), 0.80 (s, 9H, Bu^t).

3q: yield 34%, mp 175–176 °C. ^1H NMR, δ: 8.66 (s, 1H, OH), 8.15 (s, 1H, OH), 8.07 (s, 1H, OH), 7.35–7.1 (m, 10H, 2Ph), 7.10 (d, 1H, 6′-H, *J* 8.5 Hz), 7.02 (d, 1H, 5-H, *J* 8.5 Hz), 6.54 (d, 1H, 8-H, *J* 2.5 Hz), 6.41 (dd, 1H, 6-H, *J* 2.5 Hz, *J* 8.5 Hz), 6.36 (d, 1H, 3′-H, *J* 2.5 Hz), 6.18 (dd, 1H, 5′-H, *J* 2.5 Hz, *J* 8.5 Hz), 3.73 (dd, 1H, 3-H, *J* 12.3 Hz, *J* 4.0 Hz), 2.89 (m, 4H, CH_2), 2.59 (br. s, 1H), 2.2–1.1 (m, 11H, CH_2). MS, *m*/*z*: M^+ 532, 506, 421, 413, 385, 381, 331, 303, 281, 268, 267, 251, 199, 173, 162, 147, 123, 104, 91, 77, 51, 27.

3r: yield 43%, mp 142–144 °C, M^+ 560.7. ^1H NMR, δ: 9.73 (s, 1H, OH), 7.25 (m, 10H, 2Ph), 6.97 (d, 1H, 6′-H, *J* 8.5 Hz), 6.85 (d, 1H, 5-H, *J* 8.5 Hz), 6.57 (d, 1H, 8-H, *J* 2.5 Hz), 6.40 (d, 1H, 3′-H, *J* 2.5 Hz), 6.37 (dd, 1H, 6-H, *J* 8.5 Hz, *J* 2.5 Hz), 6.21 (dd, 1H, 5-H, *J* 8.5 Hz, *J* 2.5 Hz), 3.70 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.46 (dd, 1H, 3-H, *J* 12.8 Hz, *J* 4.8 Hz), 2.8 (m, 3H, CH_2), 2.1–0.9 (m, 13H, CH_2).

4: yield 39%, mp 137–140 °C, M^+ 292. ^1H NMR, δ: 8.35 (s, 2H, OH), 7.7 (s, 2H, OH), 6.83 (s, 2H, OH), 6.49 (d, 2H, H-Ar, *J* 8.8 Hz), 6.21 (d, 2H, H-Ar, *J* 8.8 Hz), 1.65 (s, 6H, Me).

5: yield 20%, mp 195–196 °C. ^1H NMR, δ: 9.0 (s, 2H, OH), 7.14 (d, 2H, 6-H, *J* 8.4 Hz), 6.37 (dd, 2H, 7-H, *J* 8.4 Hz, *J* 2.7 Hz), 5.98 (d, 2H, 8-H, *J* 2.7 Hz), 2.06 (d, 2H, CH_2, *J* 13.8 Hz), 1.91 (d, 2H, CH_2, *J* 13.8 Hz), 1.48 (s, 3H, Me), 1.26 (s, 3H, Me).



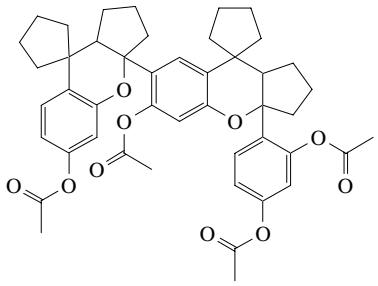
Scheme 3

example. Additional signals due to carbene elimination appear in the mass spectra of acylated chromans (*m*/*z* 42).

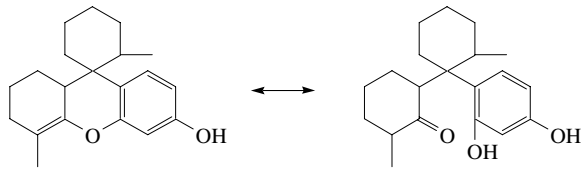
The structure of compounds **3** assumes the occurrence of stereoisomers; however, the presence of stereoisomers was not detected in the isolated products. The methoxy group in compounds **3d**,**h**,**m**,**p**,**r** can occur in either *ortho* or *para* positions with respect to the chroman ring. The fact that these compounds were not acylated with acetic anhydride under mild conditions suggests that the OH group is at the *ortho* position and the OMe group is at the *para* position to the chroman ring (the effect of a sterically hindered group, which is better pronounced in compounds **3f**,**j**). The observed downfield shift of the signal due to the hydroxyl group in compounds **3d**,**h**,**p**,**r**, as compared with the chemical shifts of hydroxyl protons in unmethylated chroman **3c**,**g**,**o**,**q** can be due to the occurrence of a hydrogen bond. This is indirect evidence for the proposed structural formula for compounds **3d**,**h**,**p**,**r**. The results suggest the steroselective and regioselective formation of chromans.

Note that 4-chlororesorcinol reacted with ketones much more slowly than resorcinol, whereas resorcylic acids and resorcylaldehyde almost not reacted with ketones under these conditions. Our attempts to perform the condensation of ketones with monoacylated and monobenzylated resorcinol were unsuccessful, probably, because of steric and deactivating properties of these substituents.

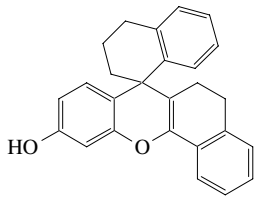
It is beyond the scope of this work to study the structure of highly condensed products (oligomers). However, it is reasonable to assume that their constituents are chroman condensation products because the molecules contained resorcinol units, which can also enter condensation reactions. Thus, the mass spectrum of acylated chroman **3c** exhibited an impurity with M^+ 762, which can be identified as a bichroman (4-acyl groups). According to ^{1}H NMR spectroscopic data, the concentration of this impurity was about 10%.



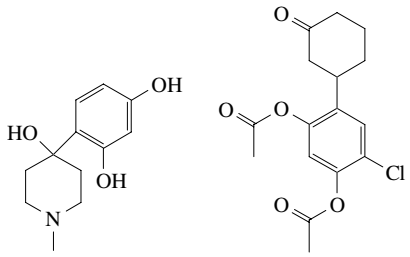
An anomalous result was obtained in the reaction of acetone with pyrogallol: bisphenol **4** was formed. Moreover, ketones with substituents at the α-position (2-methylcyclohexanone and α-tetralone) incompletely condensed with resorcinol to form xanthenes **6a**,**b** as the main products. *N*-methylpiperidone reacted with resorcinol to give 4-(4-hydroxy-1-methyl-4-piperidyl)-1,3-benzdiol **7a** as the main product. The condensation of cyclohexen-2-one with chlororesorcinol afforded 3-(5-chloro-2,4-dihydroxyphenyl)-1-cyclohexanone **7b**.



6a



6b



7a **7b**

Scheme 4 demonstrates the sequence of reactions leading to chromans **3**. These are (i) aldol condensation of two ketone molecules, (ii) addition of a resorcinol molecule to the resulting aldol, (iii) intramolecular condensation to form 2-hydroxychroman, and addition of a second resorcinol molecule to (iv) 2-hydroxychroman or (v) its dehydration product.

The proposed scheme was supported by the condensation products of 2-methylcyclohexanone and α-tetralone with resorcinol: xanthenes **6a**,**b**, which contain only one resorcinol fragment. In the case of 2-methylcyclohexanone, we isolated xanthene

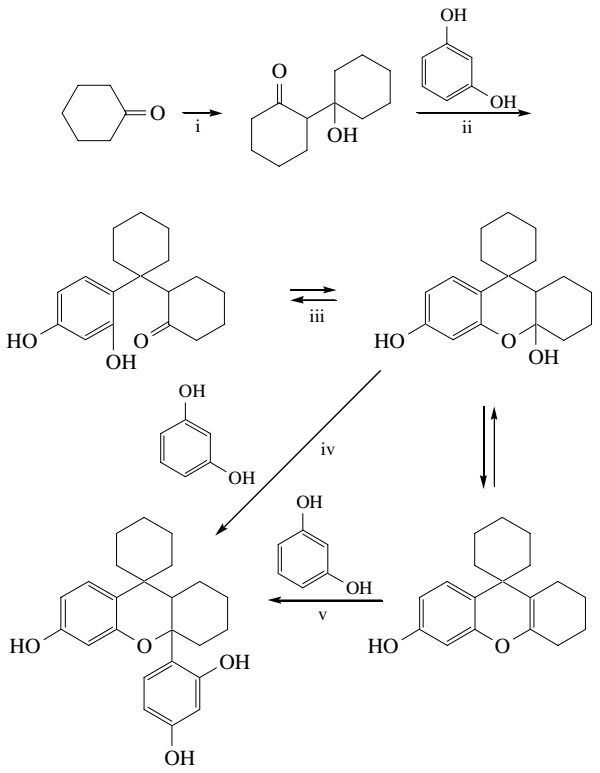
---

6a: separated as a yellow oil by chromatography on silica gel; eluent: ethyl acetate–hexane, 30:70. Yield 20%. ^{1}H NMR, δ: cyclic: 9.08 (s, 1H, OH), 6.86 (d, 1H, 5-H, *J* 8.8 Hz), 6.21 (d, 1H, 6-H, *J* 8.8 Hz, *J* 2.5 Hz), 6.12 (d, 1H, 8-H, *J* 2.5 Hz), 2.92 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 1.8–1.0 (m, 20H, CH_2); acyclic: 8.95 (s, 1H, OH), 8.59 (s, 1H, OH), 6.62 (d, 1H, 5-H, *J* 8.8 Hz), 6.24 (d, 1H, 8-H, *J* 2.8 Hz), 6.14 (d, 1H, 6-H, *J* 8.8 Hz, *J* 2.8 Hz), 2.92 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 1.8–1.0 (m, 20H, CH_2).

6b: mp 138–140 °C, yield 10%, M^+ 408. ^{1}H NMR, δ: 7.55 (d, 1H, H-Ar, *J* 8.8 Hz), 7.50 (d, 1H, H-Ar, *J* 9.0 Hz), 7.25 (m, 6H, H-Ar), 7.13 (t, 1H, H-Ar), 6.75 (dd, 1H, H-Ar, *J* 8.8 Hz, *J* 2.4 Hz), 6.65 (d, 1H, H-Ar, *J* 2.4 Hz), 2.85 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.26 (m, 4H, CH_2 + Ac), 2.0–1.75 (m, 5H, CH_2).

7a: *4-(4-hydroxy-1-methyl-4-piperidyl)-1,3-benzenediol.* ^{1}H NMR, δ: 9.08 (s, 1H, OH), 6.98 (d, 1H, H-Ar, *J* 8.5 Hz), 6.18 (s, 1H, H-Ar), 6.16 (d, 1H, H-Ar, *J* 8.5 Hz), 3.35 (s, 2H, OH), 2.52 (d, 2H, CH_2, *J* 12.5 Hz), 2.32 (t, 2H, CH_2, *J* 12.5 Hz), 2.28 (s, 3H, N–Me), 2.10 (sex, 2H, CH_2, *J* 3.5 Hz, *J* 12.5 Hz), 1.61 (d, 2H, CH_2, *J* 12.5 Hz). MS, *m*/*z*: M^+ 223 (22), 205 (100), 161 (40), 147 (64), 96 (20), 83 (45), 70 (28), 44 (24), 42 (36), 28 (20).

7b: *5-(acetyloxy)-2-chloro-4-(3-oxocyclohexyl)phenyl acetate.* ^{1}H NMR, δ: 7.60 (s, 1H, 3-H), 7.08 (s, 1H, 6-H), 3.18 [m, 1H, 1′-H(C–H)], 2.66 (ddd, 1H, CH_2, *J* 13.3 Hz, *J* 13.2 Hz, *J* 1.0 Hz), 2.44 (1H, ddd, CH_2, *J* 13.3 Hz, *J* 6.0 Hz, *J* 1.0 Hz), 2.31 (s, 6H, Ac), 2.28 (m, 2H, CH_2), 2.11 (ddd, 1H, CH_2, *J* 13.3 Hz, *J* 13.2 Hz, *J* 6.0 Hz), 1.94 (m, 2H, CH_2), 1.77 (m, 1H, CH_2). ^{13}C NMR (C_3D_5OD) δ: 208.9 (C-3′, C=O), 169.67 (Ac), 168.66 (Ac), 148.12 (C-1), 146.49 (C-5), 137.34 (C-4), 129.06 (C-3), 124.9 (C-2), 119.81 (C-6), 47.9 (C-2′), 41.44 (C-4′), 38.38 (C-6′), 32.23 (C-1′), 26.11 (C-5′).



Scheme 4

6 and its acyclic precursor, which was formed at step (ii) (Scheme 2), in a 3:1 ratio from the reaction solution.

Based on the experimental data, we can draw the following conclusions: (1) The formation of chromans **3** was predominant in the condensation of ketones with resorcinols bearing donor substituents under mild acid conditions; the formation of bisphenols **4** was an exception. (2) The formation of chromans **3** was stereoselective and regioselective. (3) Ketones that are prone to self-condensation formed spirochroman **5** under more severe conditions. (4) Ketones that are not prone to self-condensation mainly formed 1:1 alkylation products **7**.

References

1 S. Smolinski, in *Chem. Heterocycl. Comp. Ser. Monograph.*, John Wiley–Interscience, New York, 1981, vol. 36.
2 J. D. Hepworth, in *Comprehensive Heterocycl. Chem.*, ed. A. R. Katritzky, Pergamon, Oxford, 1997, vol. 3, pp. 778–787.
3 P. Livant, T. R. Webb and Weizheng Xu, *J. Org. Chem.*, 1997, **62**, 737.

Received: 12th November 2002; Com. 02/2013