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Chlorination of tectochrysin and pinostrobin in methanol

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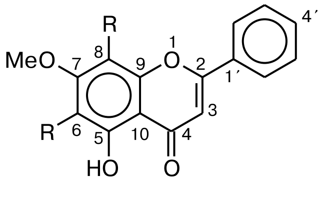
The reactions of the natural flavonoids tectochrysin and pinostrobin with chlorine in methanol afforded for the first time their 6,8-dichloro derivatives. Under the reaction conditions, dichloropinostrobin was transformed further into a tetrachloromethoxy derivative. The molecular structure of the latter was established by X-ray diffraction analysis.

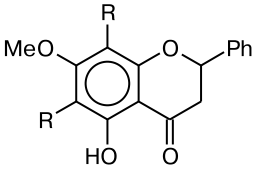
Key words: flavonoids, tectochrysin, pinostrobin, chlorination, X-ray diffraction analysis, 2D NMR spectroscopy.

Tectochrysin (**1**) and pinostrobin (2,3-dihydrotectochrysin) (**2**) are rather readily accessible compounds, which can be isolated from Balsam poplar (*Populus balsamifera* L.)[1] and other plants.[2] Since the introduction of a halogen atom into flavonoid molecules can lead to a change in their biological activities,[3,4] we examined the possibility of the preparation of chloro derivatives of these typical representatives of flavonoids. It should be noted that only one chlorine-containing flavonoid, *viz.*, 6-chloroapigenin (7-demethoxy-6-chloro-4',7-dihydroxytectochrysin), which was found in the aerial part of field horsetail, is presently known.[5]

Like bromination of quercetin in AcOH giving rise to 6,8-dibromoquercetin,[3] chlorination of flavonoid **1** in MeOH at room temperature rapidly afforded 6,8-dichloro derivative **3**. Under the same conditions, chlorination of flavanone **2** gave two products (**4** and **5**), the latter being formed as a result of subsequent transformation of chloride **4**. Actually, chlorination of **4** under the above-mentioned conditions afforded tetrachloromethoxy derivative **5**.

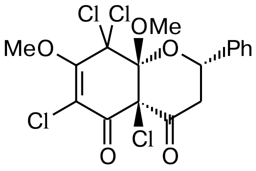


1, **3**



2, **4**

R = H (**1**, **2**), Cl (**3**, **4**)



5

The structures of previously unknown dichlorides **3** and **4** were confirmed by high-resolution mass spectrometry and ^{1}H NMR spectroscopy (Table 1). The structure of tetrachloride **5** was established by X-ray diffraction analysis (Fig. 1).

It should be noted that information on the structures of 1-oxabicyclo[4.4.0]dec-6-ene derivatives structurally

Table 1. Data from ^{1}H NMR spectroscopy of compounds **3**—**5** (acetone-d$_6$, δ, *J*/Hz)

H atom	**3**	**4**	**5**
H(2)	—	5.82 (dd, 1 H, *J* = 13.0, *J* = 3.0)	5.30 (dd, 1 H, *J* = 12.0, *J* = 3.5)
H(3(A))	7.34 (s, 1 H)	3.40 (dd, 1 H, *J* = 17.0, *J* = 13.0)	3.11 (dd, 1 H, *J* = 15.0, *J* = 3.5)
H(3(B))	—	3.07 (dd, 1 H, *J* = 17.0, *J* = 3.0)	2.87 (dd, 1 H, *J* = 15.0, *J* = 12.0)
H(2')—H(6')	7.67—8.20 (m, 5 H)	7.46—7.61 (m, 5 H)	7.40—7.45 (m, 5 H)
OMe	4.04 (s)	3.96 (s)	3.82 (s), 4.38 (s)

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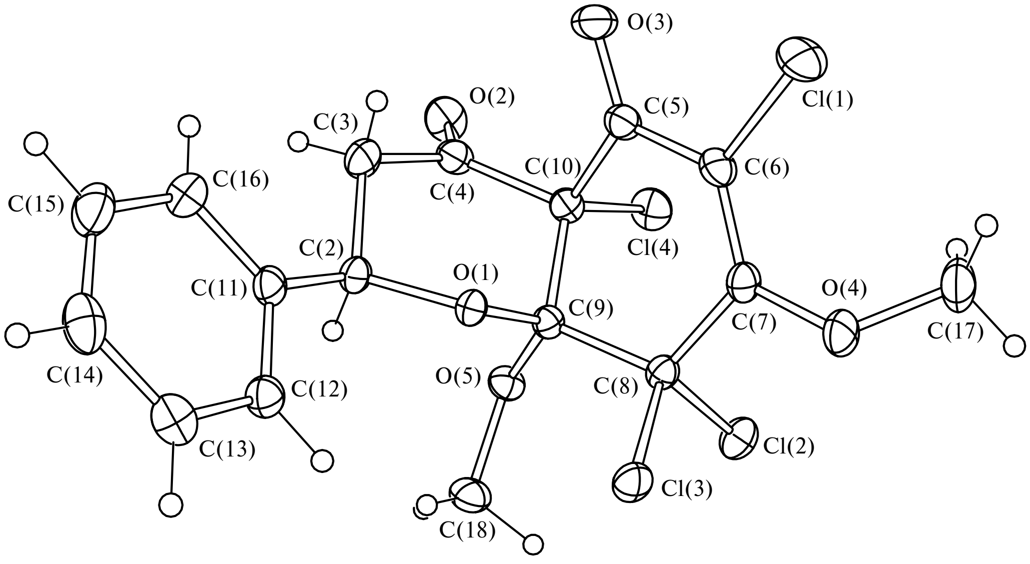

Fig. 1. Molecular structure of **5**.

related to tetrachloride **5** are lacking in the Cambridge Structural Database.[6] The tetrahydropyran ring in compound **5** adopts a chair conformation with the phenyl group in the equatorial position. The orientation of the latter is described by the C(16)—C(11)—C(2)—C(3) torsion angle of 9.8(3)°. The conformation of the carbocycle can be described as a distorted half-chair with the C(9) and C(10) atoms deviating from the plane through the remaining atoms by 0.267(4) and –0.418(4) Å, respectively. Apparently, an increase in the C(4)—C(10) bond length (1.551(3) Å) compared to the average value (1.511(15) Å)[7] is due to steric reasons.

According to the results of calculations (MMX), the energy of molecule **5** with the *cis* arrangement of the methoxy group at the C(9) atom and the chlorine atom at the C(10) atom is 7.1 kcal lower than the energy of its C(9)-epimer (according to the results of calculations by the PM3 method, 2.7 kcal lower).

Experimental

Melting points were determined on a Boetius instrument. The IR spectra were measured on a UR-20 instrument in KBr pellets. The UV spectra were recorded on a Specord UV-VIS instrument in ethanol. The NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13 and 125.76 MHz for ^{1}H and ^{13}C NMR, respectively) in acetone-d_6 with Me_4Si as the internal standard. The high-resolution mass spectra (EI, 70 eV) were obtained on a Finnigan MAT 8200 instrument. Column chromatography was carried out on KSK silica gel. Flash chromatography was performed on silica gels Armsorbsil 100/160 and Chemapol (Czech Republic) 40/100. The TLC analysis was carried out on Silufol-254 plates (Czech Republic) using a 4 : 1 light petroleum—ethyl acetate mixture; visualization was carried out with UV light or 1% aqueous solutions of $FeCl_3$ or $KMnO_4$.

The starting flavonoids **1** and (±)-**2** with m.p. 176—178 °C and 96—99 °C, respectively, were isolated from an extract of buds of Balsam poplar.[1,8] Chlorine was prepared by the reaction of $KMnO_4$ with HCl.[9]

6,8-Dichlorotectochrysin (3). A stream of dry Cl_2 was passed through a solution of tectochrysin **1** (0.20 g, 0.75 mmol) in MeOH (5 mL) at 20 °C until the starting compound was completely consumed (~5 min, TLC control). After evaporation of the solvent and crystallization of the product from a light petroleum—ethyl acetate mixture, dichloride **3** was obtained in a yield of 0.23 g (92%) as yellow crystals, m.p. 259—260 °C, R_f = 0.53. IR (KBr), ν/cm^{-1}: 3072 (CH arom.), 3033, 2997, 2955, 2926, 1655 (C=O), 742 (C—Cl), 727 (C—Cl). MS, m/z (I_{rel} (%)): 340 [M$^+$, ^{37}Cl, ^{37}Cl] (12), 338 [M$^+$, ^{35}Cl, ^{37}Cl] (65), 336 [M$^+$, ^{35}Cl, ^{35}Cl] (100.00), 295 (8), 293 (12), 272 (6), 236 (13), 234 (20), 191 (14), 102 (5), 77 (5). Found: m/z: 335.99423 [M]$^+$. $C_{16}H_{10}Cl_2O_4$. Calculated: M = 335.99561. The ^{1}H NMR spectroscopic data are given in Table 1.

Chlorination of pinostrobin (2). A stream of dry Cl_2 was passed through a solution of compound **2** (0.5 g, 1.85 mmol) in MeOH (10 mL) at 20 °C until the starting compound was completely transformed into the reaction products (~5 min, TLC control). The solvent was removed *in vacuo* and the residue was chromatographed. From the appropriate fractions, compounds **4** and **5** were obtained by crystallization from a light petroleum—ethyl acetate mixture in yields of 0.21 g (34%) and 0.53 g (65%), respectively.

6,8-Dichloropinostrobin (4), yellow needle-like crystals, m.p. 145—147 °C, R_f = 0.58. IR (KBr), ν/cm^{-1}: 3069, 3035 (CH arom.), 2989, 2949, 2917, 2874, 1637 (C=O), 1621 (C=C), 751(C—Cl), 721 (C—Cl). UV (EtOH), λ_{max}/nm: 208 (4.32), 283 (3.98), 356 (3.51). MS, m/z (I_{rel} (%)): 342 [M$^+$, ^{37}Cl, ^{37}Cl] (7), 340 [M$^+$, ^{37}Cl, ^{35}Cl] (38), 338 [M$^+$, ^{35}Cl, ^{35}Cl] (59), 263 (12), 261 (19), 239 (11), 237 (7), 236 (64), 235 (12), 234 (100), 206 (6), 193 (7), 191 (11), 163 (6), 131 (5), 104 (8), 103 (12), 78 (6), 77 (9). Found: m/z 338.01213 [M]$^+$. $C_{16}H_{12}O_4Cl_2$. Calculated: M = 338.01126. The ^{1}H NMR spectroscopic data are given in Table 1.

(2*S,4a*S**,8a*R**)-4a,6,8,8-Tetrachloro-7,8a-dimethoxy-2-phenyl-8,8a-dihydro-2*H*-chromene-4,5(3*H*,4a*H*)-dione (5),** colorless crystals, m.p. 179—181 °C, $R_f = 0.52$. IR (KBr), ν/cm^{-1}: 3032 (CH arom.), 2994, 2953, 2913, 1759 (C(4)=O), 1688 (C(5)=O), 1593 (C=C), 747, 723, 714, 700 (C—Cl). UV (EtOH), λ_{max}/nm: 206 (3.95), 276 (3.81). ^{13}C NMR, δ: 46.44 (t, C(3)); 53.64 (q, OCH_3); 65.49 (q, OCH_3); 74.07 (d, C(2)); 76.09 and 87.47 (both s, C(Cl)); 101.16 (s, C(9)); 115.57 (s, C(6)); 126.85 (d, C(2´) and C(6´)); 129.53 (d, C(3´) and C(5´)); 139.00 (d, C(4´)); 164.65 (s, C(7)); 183.25 (s, C(5)); 190.49 (s, C(4)). The ^{1}H NMR spectroscopic data are given in Table 1.

Chlorination of dichloride 4. A stream of dry Cl_2 was passed through a solution of compound **4** (0.20 g, 0.59 mmol) in MeOH (10 mL) at 20 °C until the starting compound was completely consumed (~12 min, TLC control). After evaporation of the solvent and crystallization of the product from a light petroleum—ethyl acetate mixture, tetrachloride **5** was obtained in a yield of 0.29 g (89%), m.p. 179—181 °C. According to the IR spectrum, this product is identical with the sample prepared from pinostrobin (**2**).

X-ray diffraction study of compound 5 was carried out on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator). Crystals of compound **5** are monoclinic: $a = 10.9527(4)$, $b = 11.9409(4)$, $c = 13.8650(7)$ Å, $\beta = 93.836(4)°$, $V = 1809.3(1)$ Å^3, $C_{17}H_{14}Cl_4O_5$, $M = 440.08$, $Z = 4$, space group $P2_1/n$, $d_{calc} = 1.616$ g cm^{-3}, $\mu = 0.681$ mm^{-1}, the crystal dimensions were 0.58×0.50×0.38 mm. The intensities of 3169 independent reflections were measured using the $\theta/2\theta$ scan technique in the angle range $2\theta < 50°$. The absorption correction was applied by an integration method taking into account the crystal habitus (transmission was 0.73—0.81). The structure was solved by direct methods and refined by the least-squares method with anisotropic thermal parameters for nonhydrogen atoms and isotropic thermal parameters for H atoms using the SHELX97 program package. The refinement converged to $wR_2 = 0.0789$, $S = 1.098$ for all F^2 ($R = 0.0297$ for 2862 $F > 4\sigma$). The atomic coordinates and equivalent isotropic thermal parameters of molecule **5** were deposited with the Cambridge Structural Database.

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