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NMR of a series of novel hydroxyflavothiones

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Alkylated hydroxyflavothiones, namely flavothione, 5-hydroxyflavothione, 5,7-dihydroxyflavothione (chrysinthione), 7-dodecyloxy-5-hydroxyflavothione, 7-butyloxy-5-hydroxyflavothione, 2′,3,4′,7-tetramethoxy-5-hydroxyflavothione, 3,3′,4′,7-tetramethoxy-5-hydroxyflavothione, 7-butyloxy-4′,5-dihydroxyflavothione and 7-butyloxy-4′,5-hydroxyflavanonethione have been synthesized from the corresponding hydroxyflavones in two steps, alkylation of the non-hydrogen-bonded hydroxyl groups by bromoalkanes or dimethyl sulfate followed by conversion of the carbonyl group to a thione using Lawesson's Reagent under microwave irradiation and solvent-free conditions. Part of the alkylated flavanone, 7-butyloxy-4′,5-dihydroxyflavanone, was oxidized during the treatment with Lawesson's reagent to yield a second product 7-butyloxy-4′,5-dihydroxyflavothione in addition to the target product butyloxy-4′,5-hydroxyflavanonethione. Deuterium isotope effects on 13C chemical shifts have been measured in hydroxyflavones, isoflavones, flavanones and the thio analogs. Formal four-bond deuterium isotope effects on 13C chemical shifts, nΔC═S(OD) are very sensitive to variations in structures and substitution patterns. Density functional theory (DFT) calculations are carried out to obtain geometries. Correlations relating distances around the hydrogen bond system to the deuterium isotope effects on 13C chemical shifts are discussed. 13C chemical shifts are calculated by DFT methods. Effects of thiocarbonyl anisotropies are suggested.

Keywords: hydroxyflavothiones; hydroxyisoflavothiones; deuterium isotope effects; thiocarbonyl anisotropy; intramolecular hydrogen bonding; alkylflavonoids; DFT calculations

Introduction

Flavonoids are a well-known class of natural products that have been thoroughly examined because of their diverse physiological and pharmacological properties such as estrogenic, antitumor, antimicrobial, antiallergic and anti-inflammatory effects.[1–3] Flavothiones (FT) have also received attention because of their rich photophysical and photochemical characteristics. These are described by absorption and emission spectroscopy, triplet yield and life times. They are used as oxygen photosensitizes[4,5] and photobiological activities and also as green pesticides as they inhibit the growth of fungi, bacteria and mammalian cells.[6,7]

In the mid-1950s, Baker synthesized FTs and isoflavothiones using phosphorus pentasulfide in dry benzene or xylene under reflux.[8] FT and eight hydroxy-substituted flavone and FT were made by solid-phase synthesis.[9]

In the present investigation, we report the synthesis of alkylated hydroxyflavothiones and hydroxyisoflavothiones with a variety of alkoxy substituents in two steps: alkylation of the hydroxyl group first by bromoalkane (except FT and 5-hydroxyflavothione) and then converting the carbonyl functional group to a thione using Lawesson's reagent under microwave irradiation under solvent-free conditions[10–12] (Scheme 1). The present compounds provide an important new kind of thioketones.

A series of *o*-hydroxythioketones have previously been synthesized.[13,14] These, together with β-thioxoketones,[15] form the basis for the present understanding of the properties of intramolecularly hydrogen-bonded thioketones. The study focuses on the hydrogen bonds between OH and C═S groups (Fig. 1). The intramolecular hydrogen bonds can be studied by deuterium isotope effects on ^{13}C chemical shifts with advantage.[16,17] The mechanism for isotope effects involving hydrogen bonds is discussed.

In addition to experimental data also, density functional theory (DFT) calculations are performed to test the reliability of calculated nuclear shieldings, especially of C═S-bonded carbons.

Assignment of NMR Spectra

The assignments have been based on HMBC and HMQC spectra of **4b**. The starting point for this analysis is the down-field shifted ^{1}H peak at 13.60 ppm, which was assigned to 5-OH owing to the strong intramolecular hydrogen bond it is involved in. For the protons H-3,H-6,H-8, H-2′, H-3′ and H-4′ correlations over two and three bonds could be observed. Combined with the assumption that the oxygen-carrying carbons fall in the range 150–170 ppm, a full assignment of all carbons and proton signals could be done. A comparison of the chemical shifts of **4a** (a flavone) with that of **4b** (a FT) reveals that C-2, C-3, C-4, C-9 and C-10 change markedly going from the flavone to the FT (Table 3a). For the ^{1}H spectrum, the H-3 resonance is markedly changed (Table 2b). Using these differences, the remaining FTs and isoflavones can be assigned on the basis of the assignments of the flavones[18–21] and isoflavones.[22] For **2b**, the assignment was aided by unintentional

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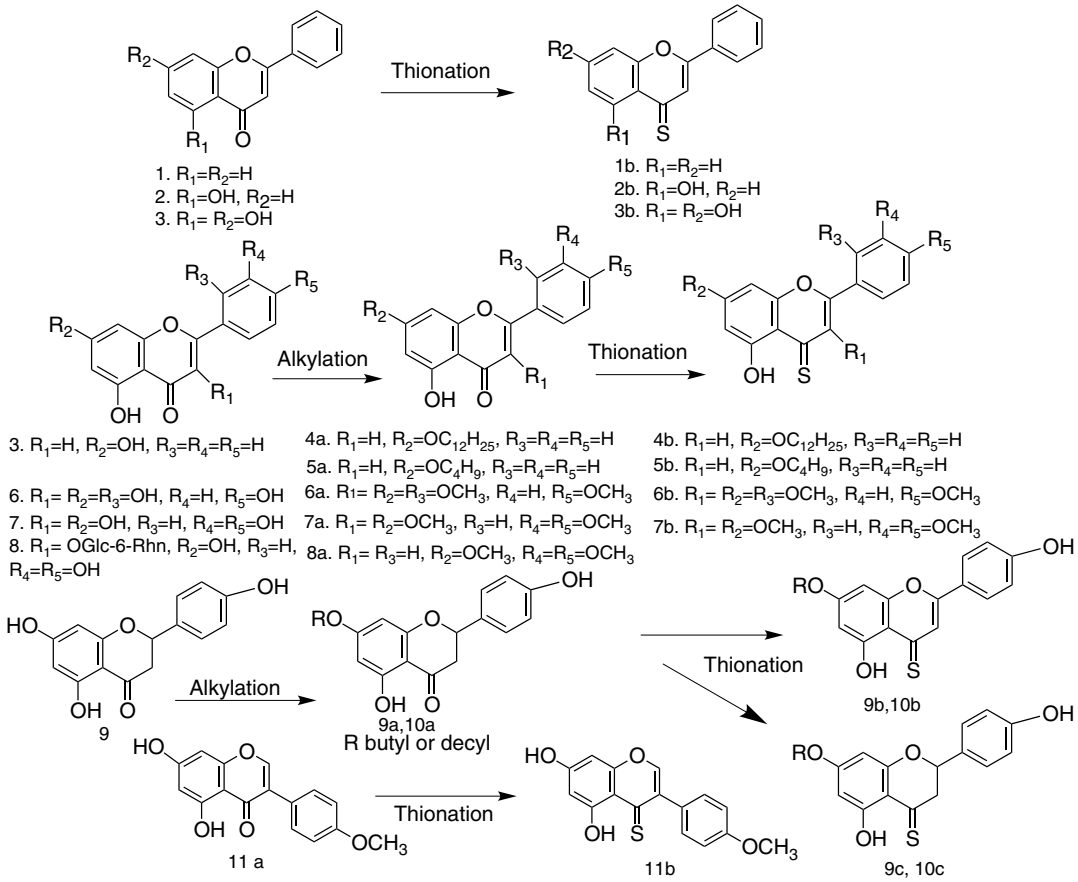


Scheme 1. Synthesis of hydroxyflavothiones from the corresponding hydroxyflavones.

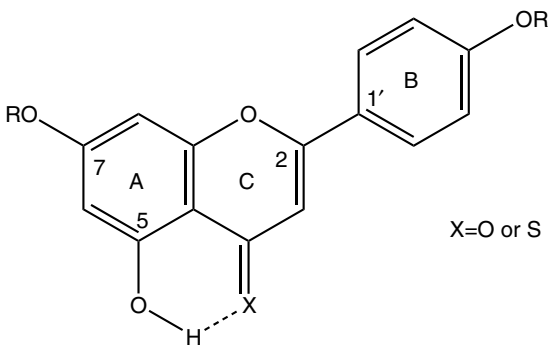


Figure 1. Structure and numbering of hydroxyflavones and thioflavones.

partial proton decoupling. The assignment of the 3,7-dimethoxy-3′,4′-O-CH_2O- derivative of **7** is given in Refs. [23–25] and the chemical shifts are very similar to those of compound **7a**.

For **8a**, the ^{13}C chemical shifts are similar to those given in Ref. [24], but the assignment is different.

The HMBC spectrum of **9a** confirmed that the substituent is at O-7.

The assignment of **11a** is taken from Ref. [26].

Deuteriation is carried out by dissolving the compounds in CH_3OD followed by evaporation under vacuum. This leads to exchange of all OH protons. In the spectra, no isotope effects are seen on carbon chemical shifts for OH(D) groups at ring B. In order to observe isotope effects, a slow exchange of OH protons is a prerequisite. Presumably, the OH groups at ring B are in fast exchange at the NMR time scale. This is further supported by the fact that these OH resonances are often not observed in the ^1H spectra of flavonoids. The finding that isotope effects are not seen at carbons of ring B ensures that the isotope effects observed for **9a, 9b** and **10c** are due to deuteriation at OH-5.

For **11b**, both OH-5 and OH-7 are deuteriated and two isotope effects are observed for carbons 4, 5 and 7. For C-5, the large effect is due to deuteriation at OH-5 as similar effects are seen for all others compounds. For C-4, the negative effect can be ascribed to deuteriation at OH-5 as again a negative effect is found in all other compounds. For C-7, the larger isotope effect is due to deuteriation at OH-7, as a three-bond isotope effect is to be expected.[27]

Results

Experiments showed that flavonoids containing one or more hydroxyl groups in addition to the OH group at position-5 are generally sparingly soluble in dichloromethane or chloroform but soluble in dimethyl sulfoxide or methanol. The solubility in the former two solvents is best for the NMR measurements of deuterium isotope effects on chemical shifts. Therefore, it was useful to modify the solubility of the hydroxyflavone and hydroxyflavanone by inserting an alkyl chain to make soluble alkoxy derivatives. Furthermore, the yield of the thionation reaction was very low for molecules with multi hydroxyl groups in the molecule.

Table 1. Bond lengths of hydroxyflavothiones and isoflavothiones

Bonds and angle/compounds[a]	1b	2b	3b	4b & 5b[b]	6b[c]	6b[d]	6b[e]	7b[f]	7b[g]	9b[b]	11b
O1–C2	1.35997	1.35399	1.35830	1.35743	1.35580	1.35478	1.35568	1.35978	1.35947	1.35801	1.39520
C2–C3	1.36415	1.36272	1.36045	1.36054	1.37063	1.37199	1.37155	1.37480	1.37599	1.36259	1.35670
C3–C4	1.43491	1.43264	1.43571	1.43536	1.45122	1.45016	1.44730	1.44755	1.44627	1.43310	1.46228
C═S	1.67232	1.69420	1.69593	1.69618	1.69813	1.69938	1.69779	1.69784	1.69932	1.69763	1.69385
C4–C10	1.46852	1.45170	1.44502	1.44525	1.44561	1.44490	1.44554	1.44521	1.44454	1.44617	1.44883
C10–C5	1.40901	1.43539	1.44030	1.44094	1.44519	1.43897	1.44393	1.44363	1.43735	1.44046	1.44625
C5–O	–	1.33360	1.33216	1.33355	1.33397	1.33321	1.3337	1.33320	1.33238	1.33372	1.33085
O–H	–	0.99910	1.00022	0.99933	1.00049	1.00269	1.00143	1.00135	1.00377	0.99973	1.00265
H···S	–	2.01542	2.01298	2.01701	1.99327	1.98475	1.99553	1.99553	1.98662	2.01543	1.97598
O···S	–	2.94311	2.94368	2.94690	2.92613	2.92003	2.93056	2.93018	2.92403	2.94615	2.91118
C5–C6	1.38494	1.40108	1.39852	1.39178	1.39062	1.39779	1.39103	1.39138	1.39873	1.39206	1.39453
C6–C7	1.40477	1.38985	1.39466	1.39887	1.40003	1.39795	1.39979	1.39936	1.39713	1.39855	1.39418
C7–C8	1.38678	1.39355	1.39910	1.39930	1.39666	1.39986	1.39710	1.39816	1.40041	1.39975	1.39760
C8–C9	1.39908	1.38859	1.38678	1.38897	1.39160	1.38420	1.39150	1.39060	1.38319	1.38920	1.38690
C9–C10	1.40656	1.41950	1.41865	1.41704	1.41606	1.42106	1.41585	1.41407	1.41926	1.41634	1.42081
C9–C1	1.37069	1.37273	1.37011	1.37110	1.36220	1.36349	1.36326	1.36506	1.36616	1.37118	1.36775

[a] The methoxy group is pointing toward C-8 in the calculations except for 6b for with both conformations have been calculated.
[b] Calculated as the methoxy derivative.
[c] The methoxy group is pointing towards C-8.
[d] The methoxy group is pointing towards C-6. This conformer is more stable by 1.2 kJ.
[e] This conformer is 8 kJ lower in energy than that given in c.
[f] 3′OCH_3 bond approximately perpendicular to the phenyl ring.
[g] Both OCH_3 groups in the ring plane OCH_3 bonds pointing away form each other. This rotamer is more stable than that in f by 7 KJ.

The hydroxy groups seemed to interfere with the thionation agent.

For morin **6**, quercetin **7** and rutin **8**, the methylation was performed using dimethyl sulfate. The methylation of morin and quercetin with four equivalents of dimethyl sulfate gave a good yield (91%). On the other hand, methylation of rutin under the same condition gave the unexpected product **8a** (Scheme 1), which means that the sugar moiety was removed. For naringenin **9,** alkylation resulted in only monoalkylation at O-7 irrespective of the excess of alkylating reagent. Naringenin was alkylated both with butylbromide, resulting in **9a**, and with decylbromide, giving **10a**. The thionation reaction not only resulted in conversion to the C═S group but also partially to oxidation of the methylene groups to a double bond (see Scheme 1).

Calculations

Data for the calculated structures are given in Table 1. The twist angle of the B-ring (Fig. 1) is rather small (~14–22°) for the FTs (**1b**–**5b, 7b**), whereas for **6b** and the isoflavothione (**11b**) the twist angles are 45–60°. The latter can be compared with biochanine A (52°). For **6b**, the twist angle depends on the conformation of the methoxy groups as well as the mutual orientation of the phenyl ring and the methoxy group at C-3 (Table 1). A comparison between FTs and *o*-hydroxythioketones[14] shows that the C═S bond is on the long end of the *o*-hydroxythioketones. The heavy atom distance O···S is seen to be shorter in the isoflavothione (**11b**) than in the FTs probably caused by steric interaction with the phenyl ring in the isoflavothione. The OH bond length is rather moderate for the FTs.

^{13}C chemical shifts are calculated. For the compounds with long alkyl chains, these are calculated as methoxy groups. However, as the compounds contain alkylated oxygens and, as these groups have conformationally different orientation, the fit between experimental and calculated values could be slightly worse. This is illustrated for **7b** for which the C ring can take up different orientations. The rotamer that is calculated to have the lowest energy (Table 1) is also the one with the best fit for the ^{13}C NMR data. Another reason for a less good fit is that the ^{13}C chemical shifts could be concentration dependent as shown for genestein.[26] However, combining with the ^{13}C NMR data of Ref. [14] and taking the above-mentioned problems into account leads to the equation: $\delta^{13}C = -0.9942 \times \sigma^{13}C + 195.23$, $R^2 = 0.995$. Rather promising is the good prediction of the C═S chemical shifts.

Isotope effects on chemical shifts can be calculated using the equation given by Jameson:[27]

$$\langle\sigma\rangle - \langle\sigma^*\rangle = \sum_i \left(\frac{\delta\sigma}{\delta r_i}\right)_e \left[\langle\Delta r_i\rangle - \langle\Delta r_i\rangle^*\right] + \sum_{ij} \left(\frac{\delta^2\sigma}{\delta r_i \delta r_i}\right)_e \left[\langle\Delta r_i \Delta r_j\rangle - \langle\Delta r_i \Delta r_j\rangle^*\right] + \sum_{ij} \left(\frac{\delta\sigma}{\delta\alpha_{ij}}\right) \left[\langle\Delta\alpha_{ij}\rangle - \langle\Delta\alpha_{ij}\rangle^*\right] + \ldots$$

Only the first term is important and the first part of that can be obtained by calculating the ^{13}C nuclear shielding as a function of the OH bond length.[17,28]

Table 2a. ^{1}H-NMR chemical shift of the parent, alkylated hydroxyflavones and the hydroxyflavothiones

Carbon/ compound Solvent	1[a] $CDCl_3$	1b $CDCl_3$	2[a] DMSO-d_6	2b $CDCl_3$	3[b] DMSO-d_6	3b $CDCl_3$	10a $CDCl_3$	11[d] DMSO-d_6	11b CD_3Cl
2			–	–	–	–	5.33[c]	8.33 (s)	7.58 (s)
3	6.84 (s)	7.78 (s)	7.12 (s)	7.49 (s)	6.97 (s)	7.58 (s)	3.08,2.77[c]	–	–
5	8.26 (dd, 1.5, 7.6 Hz)	8.59 (dd, 1.5, 8.1 Hz)	12.65 (s)	13.49 (s)	12.83 (s)	13.62(s)	12.00 (s)	12.98 (s)	14.14 (s)
6	7.43 (ddd, 0.9, 6.9 Hz)	7.41 (ddd, 0.9, 8.1 Hz)	6.82 (dd, 8.4 Hz)	6.88 (d, 8.4 Hz)	6.33 (d, 2.1 Hz)	6.37 (d, 1.2 Hz)	6.06[e] (d, 2.4 Hz)	6.39 (d, 2.0 Hz)	6.34 (d, 2.4 Hz)
7	7.71 (ddd, 1.8, 7.2 Hz)	7.71 (ddd, 1.5, 6.9, 7.2Hz)	7.73 (d, 7.8 Hz)	7.69 (dd, 8.4, 8.4 Hz)	10.92 (s)	–	–	10.91 (s)	–
8	7.60 (m)	7.60 (dd, 0.9, 7.2 Hz)	7.19 (dd, 0.9, 8.4 Hz)	7.12 (d, 8.4 Hz)	6.23 (d, 2.1 Hz)	6.63 (d, 1.2)	6.02[e] (d, 2.4 Hz)	6.23 (d, 2.0 Hz)	6.30 (d, 2.4 Hz)
2′	7.94 (m)	7.98 (dd, 1.5, 7.5 Hz)	8.17 (dd, 1.8, 7.8 Hz)	8.12 (dd, 1.2, 7.8 Hz)	8.06 (dd, 1.8, 8.1 Hz)	8.10 (dd, 1.8, 8.1 Hz)	7.31 (d, 8.4 Hz)	7.39 (d, 8.0 Hz)	7.31 (d, 8.7 Hz)
3′	7.54 (m)	7.51 (m)	7.59 (m)	7.52 (m)	7.56 (m)	6.97 (m)	6.8 (d, 8.4 Hz)	6.81 (d, 8.0 Hz)	6.97 (d, 8.7 Hz)
4′	7.57 (m)	7.56 (m)	7.62 (m)	7.61 (m)	7.62 (m)	7.04 (m)	–	9.63 (s)	–
5′	7.54 (m)	7.51 (m)	7.59 (m)	7.52 (m)	7.56 (m)	6.97 (m)	6.8 (d, 8.4 Hz)	6.81 (d, 8.0 Hz)	6.97 (d, 8.7 Hz)
6′	7.94 (m)	7.98 (dd, 1.5, 7.5 Hz)	8.17 (dd, 1.8, 7.8 Hz)	8.12 (dd, 1.2, 7.8 Hz)	8.06 (dd, 1.8, 8.1 Hz)	8.10 (dd, 1.8, 8.1 Hz)	7.31 (d, 8.4 Hz)	7.39 (d, 8.0 Hz)	7.31 (d, 8.7 Hz)
OCH_3	–	–		–	–	–	f	–	3.80 (s)

[a] Similar to Ref. [19].
[b] Similar to Ref. [18].
[c] ABX system.
[d] Taken from Ref. [22].
[e] May be interchanged.
[f] Signals from long chain of **10a**, 3.95 (t, 6.3 Hz), 1.76, 1.41, 1.27, 0.88 (t, 6.6 Hz).

Magnetic Resonance in Chemistry

NMR

The alkyl flavonoids have ^{1}H and ^{13}C chemical shifts very similar to those for the nonalkylated ones (Tables 2a, 2b, 2c, 2d, 3a, 3b and 3c).

It is well known that the C═O chemical shifts of flavones are very low (~180 ppm) for a carbonyl group. Similarly, the C═S chemical shifts of the investigated thioflavones (~198 ppm) are much lower than those of the investigated *o*-hydroxythioketones (~230 ppm)[13,14] and **10c**. This can, in both cases, be related to the conjugative effects of O-1 (See Scheme 2), which will lead to a longer C═O or C═S bond length. This is also confirmed by the DFT calculations (see above). Most of the ^{13}C chemical shifts of the C-ring are likewise changed upon thionation (Tables 3a, 3b and 3c).

The OH chemical shifts of the thio derivatives are about 1 ppm larger than those in the corresponding oxygen analogs. For the *o*-hydroxythioketones, a similar difference was found.[13]

Upon deuteriation of the OH group, deuterium isotope effects can be seen at the carbon signals. The isotope effects on chemical shifts are defined as $^{n}\Delta C{-}x(OD) = \delta C{-}x(OH){-}\delta C{-}x(OD)$. The effects of FTs and flavones can be compared. The two-bond deuterium isotope effects, $^{2}\Delta C(OD)$, are only marginally larger in the thio-derivatives than in the oxygen analogs. This is in contrast to the *o*-hydroxythioketones.[14] The deuterium isotope effect over formally four bonds, $^{n}\Delta C{=}S(OD)$, are found to be negative in all the investigated compounds, but much less negative for the thioflavones than those found in *o*-hydroxythioketones.[14] The four-bond isotope effect for **10c** falls between these two groups. From the DFT calculation, it is seen that the O···S distance is long. It was obvious from plots of e.g. $^{n}\Delta C{=}S(OD)$ *versus* R···S or RC═C that neither of these plots gave very good fits (plots not shown) as would not be expected from Eqn 1 (see below).

A comparison between $^{n}\Delta C{=}O(OD)$ and $^{n}\Delta C{=}S(OD)$ should take into account the much higher sensitivity of the 'CS' chemical shift compared to the 'CO' one. This can roughly be estimated from β-thioxoketones by comparing $\delta C{=}S{-}\delta C{-}SH$ *versus* $\delta C{=}O{-}\delta C{-}OH$. The ratio is found to be 52/14.[15] In all the cases, DFT calculations of $^{2}\Delta C(OD)$ and $^{n}\Delta C{=}S(OD)$ give a ratio very close to 1 between the two isotope effects for 2-hydroxythioacetophenone, **6b** and **9b**, showing that $^{n}\Delta C{=}S(OD)$ is very strongly correlated to $^{2}\Delta C(OD)$ and therefore to hydrogen bonding. The isotope effects are calculated as described above, taking into account that the second term will cancel out calculating the ratio between the two isotope effects. $^{n}\Delta C{=}S(OD)$ is seen to become more negative with oxygen substitution at position 7, whereas a methoxy group at C-3 leads to slightly more positive values. This is similar to what is found for $^{n}\Delta C{=}O(OD)$ of the oxygen analogs (see Schemes 3 and 4).

Despite the limited number of carbon NMR data, an analysis of the four bond isotope effects, $^{n}\Delta C{=}S(OD)$, from the present investigation combined with those of Ref. [14] has been attempted involving all the distances around the hydrogen bond system, this means $R_{O\cdots S}$, R_{OH}, R_{C-O}, $R_{C=C}$, $R_{C-C(S)}$ and $R_{C=S}$. From a partial least squares analysis, it could be seen that the RC═S distances were of little importance. The following equation can be formulated:

$$^{n}\Delta C{=}S(OD) = 4.7 \times R_{O\cdots S} - 4.7 \times R_{OH} - 1.2 \times R_{CO} - 2.4 \times R_{C=C} - 3.0 \times R_{CC(S)} \text{ in parts per million.} \quad (1)$$

The correlation coefficient, *R*, is equal to 0.95. This confirms that the shorter the O···S distance, the more positive is the isotope effect, whereas the longer the OH distance (strong hydrogen bond) the more negative are the four-bond isotope effects.

The ^{1}H chemical shift of the chelated OH group is found to be 1 ppm larger in the thioketones than in the ketones.[13] This finding can possibly be related to the anisotropy of the thiocarbonyl group. The anisotropy is not known in detail but is found to be larger for thiocamphor than for camphor.[29] For the present compounds, an interesting difference in the OH chemical shifts is seen when comparing **2** and **2b** (diff. 0.84 ppm), **4a** and **4b** (diff. 0.94 ppm), **5a** and **5b** (diff. 0.96 ppm) compared to **6a** and **6b** (diff. 1.40 ppm) and **7a** and **7b** (diff. 1.45 ppm). The difference between the two group of compounds is the number of OR groups in conjugation with the C═S group leading to a higher $C{-}S^{-}$ contribution (Scheme 2) and possibly to a higher anisotropy. The higher contribution of $C{-}S^{-}$ is reflected in the C═S chemical shift variations, **2b** > **4b** ~ **5b** > **6b** ~ **7b** (Tables 3a–c). This difference in the C═S chemical shifts and the higher $C{-}S^{-}$ also explains the higher stability of the multi hydroxyl compounds, as this makes the compounds less prone to oxidation at sulfur.

Conclusions

The FTs and isoflavothiones show rather long C═S bond lengths, indicating extensive conjugation with oxygens. This is reflected in the C═S ^{13}C chemical shifts. The long C═S bonds lead to stability of the FTs as compared to simple thiocarbonyl compounds. The C═S chemical shifts can be calculated quite well. The anisotropy of the C═S double bond can be judged from the OH chemical shifts of the chelated proton. The formal four-bond deuterium isotope effect on carbon chemical shifts, $^{n}\Delta C{=}S(OD)$, can be related to the geometry around the hydrogen bond system.

Experimental

Materials: The parent flavonoids, flavone **1,** premuletin **2,** chrysin **3,** morin **6,** quercetin **7,** rutin **8,** naringenin **9** and biochanin A **11a** were commercial samples. Lawesson's reagent, alkyl bromide, anhydrous potassium carbonate, dimethyl sulfate, acetone, dichloromethane, hexane and ethyl acetate were purchased from Aldrich. Solvents were used as received. Silica gel 60A for column chromatography was purchased from Sigma.

Deuteriation: The deuterations were performed by dissolving the compounds in 1 ml $CDCl_3$. The solution was stirred continuously with 1-ml D_2O for 30 min and then the D_2O was sucked off. The $CDCl_3$ solution was dried with anhydrous Na_2SO_4, filtered and used for the NMR measurements.

NMR: The NMR spectra were recorded on a Varian Mercury 300 instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C at ambient temperature. TMS was used as reference. Solvents are given in Table 3. Recording ^{13}C spectra for measurements of isotope effects, an acquisition time of 4 s was used.

2D ^{1}H-^{13}C HMQC and HMBC NMR spectra were recorded on a Varian Unity-Inova 600 MHz spectrometer, with a 5-mm triple-resonance gradient probe. A series of ^{1}H-^{13}C HMBC spectra were recorded with a varying spin echo delay time to emphasize different multibond couplings.

IR: The IR spectra were recorded in KBr on a Perkin Elmer Spectrum 2000 FT-IR Spectrometer.

Table 2b. ^{1}H-NMR chemical shift of the parent hydroxyflavones, alkylated hydroxyflavones and the hydroxyflavothiones

Carbon/ compound Solvent	4 DMSO-d_6	4a[a] CD_3Cl	4b[b] CD_3Cl	5 DMSO-d_6	5a[a] CD_3Cl	5b[b] CD_3Cl
3	6.97 (s)	6.66 (s)	7.34 (s)	6.97 (s)	6.57 (s)	7.37 (s)
5	12.83 (s)	12.66(s)	13.60 (s)	12.83 (s)	12.66(s)	13.62 (s)
6	6.33 (d, 2.1 Hz)	6.49 (d, 2.1 Hz)	6.48 (d, 2.4 Hz)	6.33 (d, 2.1 Hz)	6.40 (d, 2.1 Hz)	6.51 (d, 2.1 Hz)
8	6.23 (d, 2.1 Hz)	6.36 (d, 2.1 Hz)	6.42 (d, 2.4 Hz)	6.23 (d, 2.1 Hz)	6.28 (d, 2.1 Hz)	6.44 (d, 2.1 Hz)
2′	8.06 (dd, 1.8, 8.1 Hz)	7.81(dd, 1.5, 7.5 Hz)	7.88 (dd, 1.5, 7.8 Hz)	8.06 (dd, 1.8, 8.1 Hz)	7.80 (dd, 1.8, 7.8 Hz)	7.90 (dd, 1.8, 7.8 Hz)
3′	7.56 (m)	7.51 (m)	7.50 (m)	7.56 (m)	7.51 (m)	7.52 (m)
4′	7.62 (m)	7.53 (m)	7.53 (m)	7.62 (m)	7.53 (m)	7.55 (m)
5′	7.56 (m)	7.51 (m)	7.50 (m)	7.56 (m)	7.51 (m)	7.52 (m)
6′	8.06(dd, 1.8, 8.1 Hz)	7.81(dd, 1.5, 7.5 Hz)	7.88 (dd, 1.5, 7.8 Hz)	8.06(dd, 1.8, 8.1 Hz)	7.80 (dd, 1.8, 7.8 Hz)	7.90(dd, 1.8, 7.8 Hz)

[a] Chemical shifts of the long chains of **4a**: 0.81 (3H, t), 1.83–1.20 (18H, m), 3.40 (2H, t), 4.03 (2H, t); **5a**: 0.81 (3H, t), 1.43 (2H, m), 1.76 (2H, m), 3.95 (2H, t).
[b] Chemical shifts of the long chains of **4b**: 0.88 (3H, t), 1.83–1.20 (18H, m), 3.39 (2H, t), 4.02 (2H, t); **5b**: 0.99 (3H, t), 1.65 (2H, m), 1.81 (2H, m), 4.05 (2H, t).

Table 2c. ^{1}H-NMR chemical shift of the parent hydroxyflavones, alkylated hydroxyflavones and the hydroxyflavothiones

Carbon/ compound Solvent	6 DMSO-d_6	6a $CDCl_3$	6b $CDCl_3$	9 $CDCl_3$	9a[a] $CDCl_3$	9b[b] $CDCl_3$	9c[d] $CDCl_3$
2	–	–	–	5.42 (dd, 3.0, 9.9 Hz)	5.36 (dd,, 3.0, 9.9 Hz)	–	5.23[c]
3	–	–	–	3.21, 2.71 (dd, 3.0, 9.9 Hz)	3.08, 2.78 (dd, 3.0, 9.9 Hz)	7.31 (s)	3.38, 3.35[c]
5	–	12.68 (s)	14.08 (s)	12.15 (s)	12.05 (s)	13.67 (s)	13.50(s)
6	6.23 (d, 2.2 Hz)	6.35 (d, 2.4 Hz)	6.46 (d, 2.4 Hz)	5.89 (d, 2.1Hz)	6.06 (d, 2.1 Hz)	6.50 (d, 2.4 Hz)	6.05 (d, 2.7Hz)
7	–	–		10.80 (s)	–	–	–
8	6.17 (d, 2.2 Hz)	6.31 (d, 2.4 Hz)	6.42 (d, 2.4 Hz)	5.89 (d, 2.1Hz)	6.03 (d, 2.1 Hz)	6.45 (d, 2.4 Hz)	6.12 (d, 2.7 Hz)
2′	–	–	–	7.31 (dd, 2.1, 6.9 Hz)	7.33 (dd, 2.1, 6.6 Hz)	7.83 (d, 9 Hz)	7.32 (d, 8.7 Hz)
3′	6.41 (d, 2.1 Hz)	6.59 (d, 2.4 Hz)	6.61, d, 2.1 Hz)	6.80 (dd, 2.1, 6.9 Hz)	6.89 (dd, 2.1, 6.6 Hz)	6.97 (d, 9Hz)	6.87(d, 8.7 Hz)
4′	–	–		9.60 (s)	–	–	–
5′	6.36 (dd, 2.1, 1.9 Hz)	6.56 (dd, 2.1, 4.2 Hz)	6.58 (dd, 2.1, 4.5 Hz)	6.80 (dd, 2.1, 6.9 Hz)	6.89 (dd, 2.1, 6.6 Hz)	6.97 (d, 9Hz)	6.87(d, 8.7 Hz)
6′	7.24 (d, 8.5 Hz)	7.35 (d, 8.4 Hz)	7.47 (d, 8.4 Hz)	7.31 (dd, 2.1, 6.9 Hz)	7.33 (dd, 2.1, 6.6 Hz)	7.83 (d, 9 Hz)	7.32 (d, 8.7 Hz)
OCH_3-C3	–	3.86 (s)	3.59 (s)	–			
OCH_3-C7	–	3.77 (s)	3.84 (s)	–	–	–	
OCH_3-C2′	–	3.82 (s)	3.89 (s)	–	–	–	
OCH_3-C4′	–	3.82 (s)	3.87 (s)	–	–	–	

[a] Chemical shifts of the long chains of **9a**, 0.95 (3H, t), 1.44 (2H, m), 1.75 (2H, m), 3.97 (2H, t).
[b] Chemical shifts of the long chains of **9b**, 0.99 (3H, t), 1.47 (2H, m), 1.81 (2H, m), 4.06 (2H, t).
[c] ABX system.
[d] Chemical shifts of the long chain of **9c**, 4.00 (3H, t), 1.78, 1.40, 0.99 (3H, t).

MS: The mass spectra were measured on a LCQ-Deca ion trap instrument from Thermo-Finnigan, equipped with an atmospheric pressure chemical ionization interface (APCI) running in both negative and positive mode using the infusion technique.

Calculations: The molecular geometries were optimized using the Gaussian03 suite of programs and density functional[30] theory (DFT) (Beckes exchange[31] and Lee, Yang, Parr correlation term,[32] B3LYP and basis set 6–31G(d,p) was used. The nuclear shieldings were calculated using the GIAO approach.[33,34]

7-Dodecyloxy-5-hydroxyflavone 4a

A solution of chrysin (**3**) (2.0 g; 7.86 mmol) in dry acetone (50 ml) was treated with anhydrous K_2CO_3 (1.62 g; 11.6 mmol) and 1-bromododecane (1.96 g; 7.86 mmol). The mixture was refluxed under nitrogen atmosphere over night with continuous stirring and monitored by TLC. The mixture was cooled to room temperature and filtered. The solid was washed with acetone. Evaporation of the combined organic solvent under reduced pressure furnished a residue, which was purified by silica gel column chromatography, using dichloromethane–ethyl acetate

Table 2d. ^{1}H-NMR chemical shift of the parent hydroxyflavones, alkylated hydroxyflavones and the hydroxyflavothiones

Carbon/compound Solvent	7 DMSO-d_6	7a $CDCl_3$	7b $CDCl_3$	8[a] DMSO-d_6	8a $CDCl_3$
5	12.51 (s)	12.62 (s)	14.07 (s)	12.60 (s)	11.78 (s)
6	5.91 (d, 2.1 Hz)	6.37 (d, 2.4 Hz)	6.49 (d, 2.7 Hz)	6.39 (d, 2.0 Hz)	6.49 (d, 2.1 Hz)
8	5.69 (d, 2.1 Hz)	6.27 (d, 2.4 Hz)	6.46 (d, 2.7 Hz)	6.20 (d, 2.0 Hz)	6.37 (d, 2.1 Hz)
2′	7.18 (d, 2.1 Hz)	7.69 (d, 2.1 Hz)	7.81 (d, 2.1 Hz)	7.56 (d,2.0)	7.79 (d, 2.1 Hz)
5′	6.39 (d, 8.7 Hz)	6.93 (d, 8.4 Hz)	7.00 (d, 9.3 Hz)	6.85 (d, 8.0 Hz)	7.00 (d, 8.7 Hz)
6′	7.04 (dd, 8.4, 2.1Hz)	7.65 (dd, 8.4, 2.1Hz)	7.79 (dd, 8.9, 2.4 Hz)	7.54 (dd, 8.0, 2.0 Hz)	7.82 (dd, 8.7, 2.1 Hz)
OCH_3-C3	–	3.92 (s)	3.89 (s)	–	–
OCH_3-C7	–	3.92 (s)	3.74 (s)	–	3.89 (s)
OCH_3-C3′	–	3.82 (s)	3.98 (s)	–	3.98 (s)
OCH_3-C4′	–	3.82 (s)	3.95 (s)	–	3.97 (s)

[a] Chemical shifts for rhamnose: 0.99 (3H, d, 6.0 Hz), 3.04–3.39 (4H, m), 4.35 (1H, s); glucose: 3.04–3.39 (5H, m), 5.35 (1H, d, 7.5 Hz).

Table 3a. ^{13}C-NMR of the parent hydroxyflavones, alkylated hydroxyflavones and the hydroxyflavothiones

N_0	1[a,b]	1b	2[a]	2b	3[b]	3b	4a[c]	4b[d]
2	163.45	151.53	164.12	152.50	163.15	161.14	163.90	154.23
3	107.66	120.15	105.68	119.55	105.20	117.30	105.89	118.41
4	178.49	202.25	183.27	200.74	181.85	195.96	183.46	197.81
5	125.25	128.65	159.85	161.06	161.46	161.65	162.15	162.75
6	126.33	126.02	111.03	113.49	99.00	100.78	98.62	99.50
7	133.80	134.16	136.03	135.17	164.44	163.14	165.25	164.77
8	118.11	118.42	107.58	107.35	94.11	94.73	93.10	93.80
9	156.32	154.21	155.98	154.72	157.45	154.12	157.80	154.11
10	124.01	131.10	110.10	118.07	103.96	112.54	105.58	114.01
1′	131.85	129.95	130.56	130.23	130.71	130.69	131.40	131.89
2′	125.76	126.56	126.65	126.66	126.39	126.56	126.28	126.48
3′	129.28	129,20	129.21	129.23	129.11	129.19	129.08	129.15
4′	131.62	131.85	132.37	132.24	131.98	131.98	131.79	131.89
5′	129.28	129.20	129.21	129.23	129.11	129.19	129.08	129.15
6′	125.76	126.56	126.65	126.66	126.39	126.56	126.28	126.48

[a] In agreement with Ref. [19].
[b] In agreement with Ref. [18].
[c] Chemical shifts for the long chains, 14.12, 22.70, 25.94, 28.20, 28.80, 28.96, 29.45, 29.63, 32.86, 31.93, 34.06, 68.73.
[d] Chemical shifts for the long chains, 14.13, 22.71, 25.94, 28.20, 28.80, 28.96, 29.45, 29.63, 32.86, 31.93, 34.06, 68.90.

(10 : 1 v/v) as eluent to give **4a** as pale yellow crystals, yield 51%, mp 86–87 °C, APCI-MS, 421 (M-1). IR KBr (γ, cm^{-1}), ~3400 (vw, br), 2917 (s), 2851 (s), 1667 (s), 1623 (s), 1509 (w), 1452 (m), 1384 (m), 1335 (m), 1274 (m), 1171 (s), 1103 (w), 822 (m), 767 (w), 674 (w). For ^{1}H and ^{13}C NMR data, see Tables 2b and 3a.

7-Butyloxy-5-hydroxyflavone 5a

The synthesis was carried out analogously to **4a**, using a mixture of chrysin (**3**) (2.0 g; 7.86 mmol), 1-bromobutane (1.08 g; 7.86 mmol) and anhydrous K_2CO_3 (1.62 g; 11.6 mmol) in dry acetone (50 ml) to give **5a** as pale yellow crystals, yield 86%, mp 142–143 °C, APCI-MS, 309 (M-1). IR KBr (γ, cm^{-1}), 2952 (w), 2869 (w), 1667 (s), 1619 (s), 1508 (w), 1451 (m), 1380 (m), 1335 (m), 1275 (m), 1172 (s), 1099 (w), 825 (m), 766 (m), 675 (w). For ^{1}H and ^{13}C NMR data, see Tables 2b and 3b.

2′,3,4′,7-Tetramethoxy-5-hydroxyflavone 6a

This compound was synthesized by a modified method of Manthey and Guthrie.[35] Morin **6** (3.0 g, 0.01 mol) was added to a solution of acetone (150 ml), water (75 ml) and 30% aqueousKOH (6 ml) in 1-l three necks round bottom flask. The reaction mixture was heated to reflux for 10 min. Dimethyl sulfate (DMS) (2.4 ml) was added, and the mixture was left under reflux for 20 min. KOH solution (3 ml) was added, producing a dark brown solution. An additional 2.4 ml of DMS was added, and the solution was again refluxed for 20 min. KOH (3.0 ml) was added, followed by DMS (0.6 ml). An additional aliquot of DMS (3.0 ml) was added and the mixture was refluxed for 1.5 h and allowed to cool. Evaporation of the acetone furnished a dark yellow residue. The crude product was purified by column chromatography on silica gel, using hexane-ethyl acetate (1 : 3) as eluent to give **6a** as pale yellow crystals, yield 85%, mp 130–131 °C, APCI-MS, 357 (M-1). IR KBr (γ, cm^{-1}), ~2980 (vw), 2838 (vw), 1655 (s), 1621 (s), 1598 (s), 1502 (s), 1442 (w),

Table 3b. ^{13}C-NMR of the parent hydroxyflavones, alkylated hydrodroxyflavones and hydroxyflavothiones

Compound/carbon	5a[a]	5b[b]	9	9a[a]	9b[b]	10a	10c[b]	11	11b
2	163.79	154.29	78.48	78.93	154.18	78.92	77.63	153.80	144.97
3	105.71	118.46	42.03	43.19	117.24	43.12	53.14	122.20	132.80
4	183.40	197.86	196.38	196.01	197.05	196.16	218.86	180.10	198.03
5	162.09	162.74	163.56	164.09	162.59	164.05	165.46	161.90	162.58
6	98.66	100.07	95.88	95.59	99.98	95.61	96.45	98.70	101.18
7	165.23	164.82	166.70	167.69	164.60	167.78	167.51	164.20	164.07
8	93.00	93.55	95.03	94.63	93.48	94.69	95.11	93.60	94.33
9	157.74	154.25	162.98	162.89	154.58	162.93	156.33	157.50	153.98
10	105.53	113.89	101.83	103.01	113.50	103.00	113.51	104.40	114.91
1′	131.27	130.46	128.91	130.60	122.38	130.47	130.26	121.10	126.10
2′	126.23	126.23	128.37	127.96	128.58	127.96	127.89	130.10	131.44
3′	129.07	129.31	115.23	115.69	116.31	115.70	115.66	115.00	113.57
4′	131.82	131.96	157.79	156.17	159.63	156.23	159.1	157.50	159.43
5′	129.07	129.31	115.23	115.69	116.31	115.70	115.66	115.00	113.57
6′	126.23	126.23	128.37	127.96	128.58	127.96	127.89	130.10	131.44
$-OCH_3$	–	–	–	–	–	–	–	–	55.23

[a] Chemical shifts for the long chains of **5a**: 13.86, 19.23, 31.06, 68.45; **9a**: 13.71, 19.11, 30.92, 68.29.
[b] Chemical shifts for the long chains of **5b**: 13.69, 19.14, 31.31, 68.50; **9b**: 13.78, 19.14, 31.95, 68.50; **10a**, 68.63, 31.88, 29.53, 29.30, 29.28, 28.88, 25.88, 22.67, 14.12; **10c**, 68.63, 32.00, 29.64, 29.41, 28.97, 25.97, 22.80, 14.23.

Table 3c. ^{13}C-NMR of the parent hydroxyflavones, alkylated hydroxyflavones and the hydroxyflavothiones

N_0	6	6a	6b	7	7a	7b	8[a]	8a
2	149.63	156.43	153.74	146.74	155.21	151.81	156.60	150.83
3	136.49	139.94	148.50	135.68	138.77	147.05	133.30	136.02
4	176.71	178.70	193.18	175.78	178.52	192.52	177.36	175.40
5	161.31	162.86	162.99	160.67	161.79	162.73	161.22	160.65
6	99.57	97.66	99.22	98.13	97.65	99.35	98.67	97.89
7	164.10	165.14	164.88	163.79	165.25	164.77	164.08	165.73
8	94.99	92.05	92.73	93.30	91.98	92.51	93.68	92.26
9	156.94	157.32	151.16	156.09	156.49	149.81	156.42	156.82
10	104.97	104.69	115.28	102.98	105.81	114.41	103.96	104.07
1′	111.19	112.31	112.06	121.93	122.72	122.86	121.17	123.49
2′	158.09	158.64	159.41	115.01	110.68	111.55	116.26	110.97
3′	104.97	104.69	105.06	144.97	148.58	148.95	144.74	145.86
4′	160.97	161.95	163.24	147.61	151.22	152.98	148.41	148.84
5′	109.25	106.40	105.06	115.55	111.07	111.04	115.22	110.72
6′	132.31	131.55	132.27	119.95	122.01	122.30	121.58	121.52
OCH_3-C3	–	60.44	60.44	–	59.98	59.17	–	–
OCH_3-C7	–	55.43	55.43	–	55.65	55.83	–	56.08
OCH_3-C2′	–	55.63	55.63	–			–	
OCH_3-C3′	–	–	–	–	55.89	56.09	–	56.01
OCH_3-C4′	–	55.63	55.63	–	55.84	56.02	–	55.90

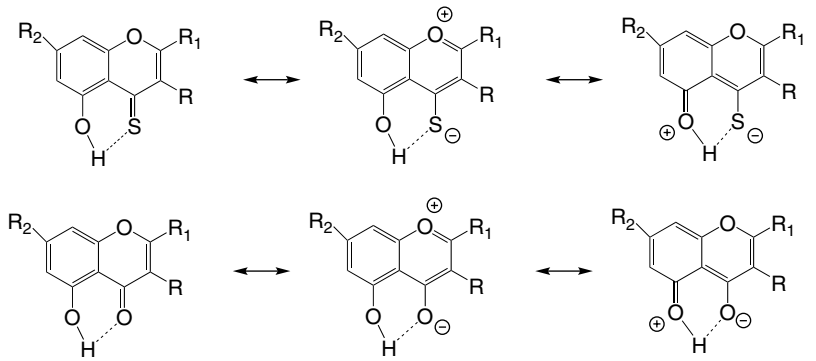
[a] Chemical shifts for the long chains, glucose: 66.98, 75.90, 69.99, 76.45, 74.07, 101.18, rhamnose: 17.72, 68.23, 71.85, 70.56, 70.73, 100.74.

1355 (s), 1312 (vw), 1278 (m), 1159 (s), 1088 (m), 822 (m), 786 (vw), 675 (vw). For ^{1}H and ^{13}C NMR data, see Tables 2c and 3c.

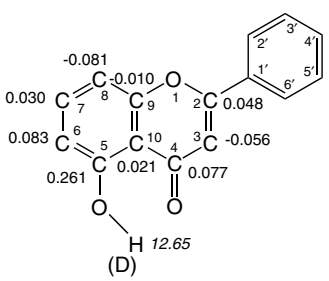
3,3′,4′,7-Tetramethoxy-5-hydroxyflavone 7a

The synthesis was carried out analogously to **6a**, using, quercetin (**7**) (3.0 g, 10.0 mmol) to give compound **7a** as pale yellow crystals, yield 86%, mp 157–158 °C, APCI-MS, 357 (M-1). IR KBr (γ, cm^{-1}), 2946 (vw), 2839 (vw), 1655 (s), 1589 (s), 1513 (s), 1431 (s), 1326 (s), 1310 (s), 1272 (s), 1157 (m), 1094 (w), 822 (s), 771 (w), 667 (vw). For ^{1}H and ^{13}C NMR data, see Tables 2c and 3c.

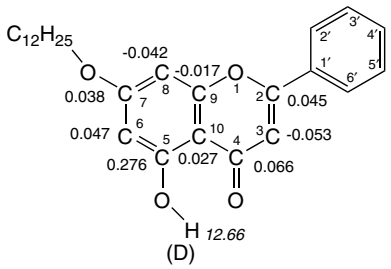
Methylation of rutin **8** by the same method described for **6a** gave an unexpected compound due to the cleavage of the sugar moiety. The physical and spectral data of this compound were identical to those reported in Refs. [24,25].



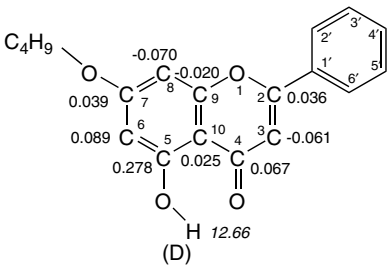
Scheme 2. Resonance forms of hydroxyflavones and hydroxyflavothiones.



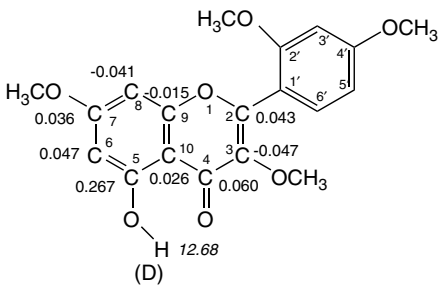
2



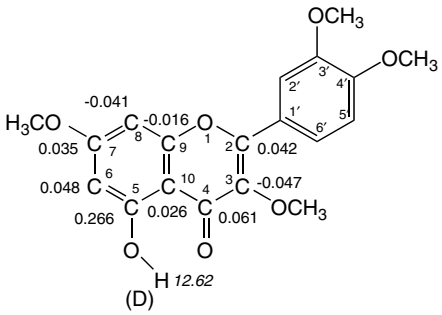
4a



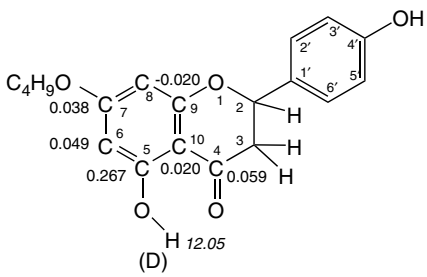
5a



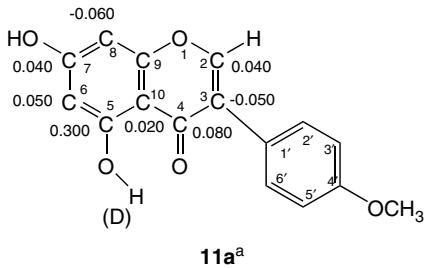
6a



7a

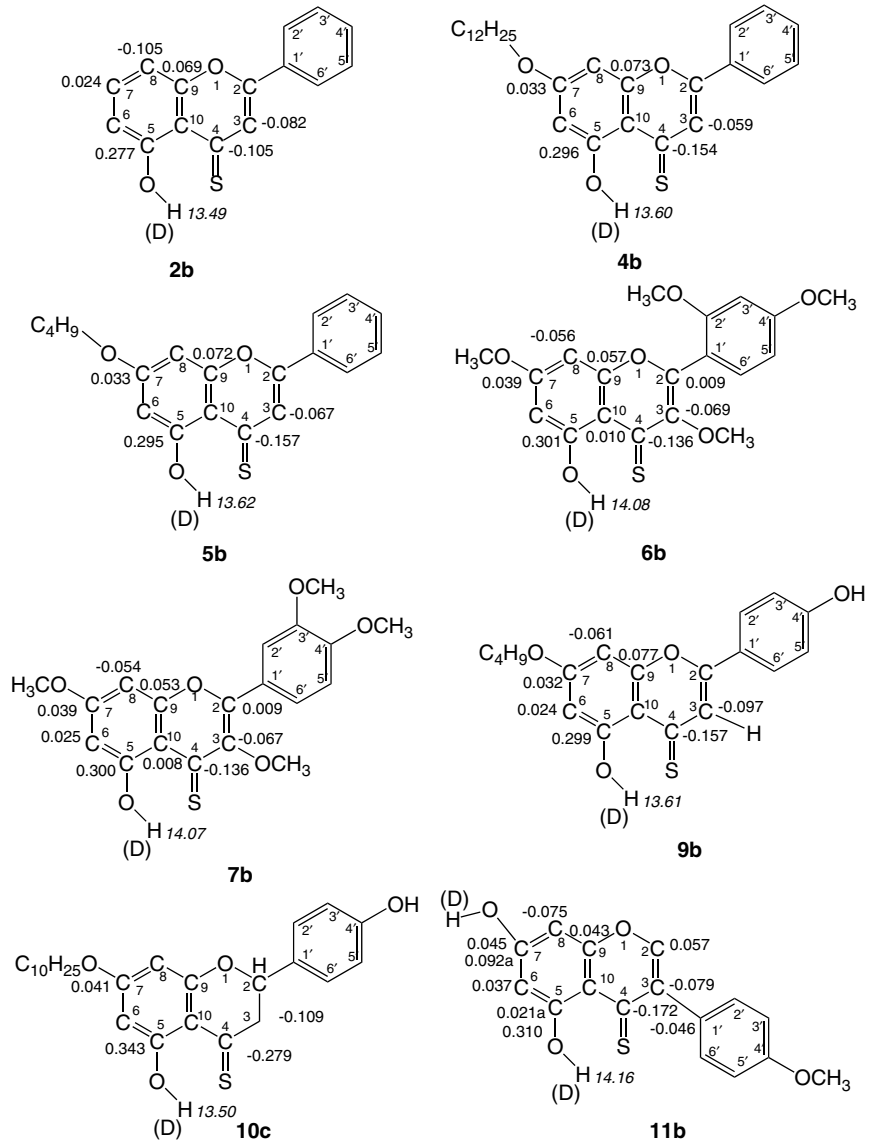


9a



11a[a]

Scheme 3. Deuterium isotope effect on ^{13}C chemical shifts (in ppm) of flavones and isoflavones. OH chemical shifts are given in italics. [a]Taken from Ref. [26].



Scheme 4. Deuterium Isotope effect on ^{13}C chemical shifts (in ppm) of seven flavothiones and isoflavothiones. OH chemical shifts are given in italics. [a]Due to deuteriation at OH-7.

7-Butyloxy-4′,5-dihydroxyflavanone 9a

The synthesis was carried out analogously to **4a**, using a mixture of naringenin (**9**) (2.14 g; 7.86 mmol), 1-bromobutane (2.16 g; 15.72 mmol) and anhydrous K_2CO_3 (2.77 g; 20.0 mmol) in dry acetone (50 ml) to give **9a** as pale yellow crystals, yield 21%, mp 145–146 °C, APCI-MS, 327 (M-1). IR KBr (γ, cm^{-1}), 3313 (s, br), 2958 (m), 2872 (w), 1634 (s), 1596 (s), 1519 (s), 1471 (m), 1377 (s), 1304 (m), 1271 (m), 1166 (s), 1096 (s), 829 (s), 767 (w), 670 (vw). For ^1H and ^{13}C NMR C NMR data, see Tables 2c and 3b.

7-Decyloxy-4′,5-dihydroxyflavanone 10a

The synthesis was carried out analogously to **4a**, using a mixture of naringenin (**9**) (2.14 g; 7.86 mmol), 1-bromodecane (3.48 g; 15.72 mmol) and anhydrous K_2CO_3 (2.77 g; 20.0 mmol) in dry acetone (50 ml) to give **10a** as pale yellow crystals, yield 26%, mp 106–107 °C, APCI-MS, 411 (M-1). IR KBr (γ, cm^{-1}), 3335 (s,br), 2943 (m), 2919 (s), 2851 (s), 1631 (s), 1595 (s), 1518 (s), 1472 (m), 1375 (s), 1351 (m), 1296 (s), 1164 (s), 1097 (s), 839 (s), 829 (s), 732 (m), 629 (w). For ^1H and ^{13}C NMR C NMR data, see Tables 2c.

Flavothione 1b

The synthesis was carried out using a method similar to that of Varma and Kumar[12] Flavone **1** (238 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol) were mixed well in a Pyrex test tube. The test tube was then placed in an alumina bath and irradiated in a microwave oven (650 W) for 4 min. The dark orange solid material was dissolved in dichloromethane and the crude product was purified by column chromatography on silica gel, using hexane: ethyl acetate (9 : 1 v/v) as eluent. Evaporation of the solvent afford a yellow solid, which on recrystallization from methanol–hexane (1 : 1 v/v) gave compound **1b** as yellow crystals, yield 71%, mp 84–85 °C, APCI-MS, 237 (M-1). IR KBr (γ, cm^{-1}), ~2980 (vw), 1638 (m), 1599 (s), 1550 (s), 1492 (s), 1459 (m), 1368 (m), 1319 (m), 1243 (vw), 1172 (m), 1059 (w), 873 (m), 764 (s), 685 (m). For ^1H and ^{13}C NMR data, see Tables 2a and 3a.

5-hydroxyflavothione 2b

The synthesis was carried out analogously to **1b** using a mixture of primuletin (**2**) (238 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol), and gave after column chromatography on silica gel, using hexane-ethyl acetate (9 : 1 v/v) as eluent, and recrystallization from methanol–hexane (1 : 1 v/v) compound **2b** as a yellow crystal, yield 90%, mp 136–137 °C, APCI-MS, 253 (M-1). IR, KBr (γ, cm^{-1}), 3057 (vw), 1630 (s), 1598 (s), 1575 (m), 1497 (w), 1460 (s), 1343 (w), 1306 (vw), 1249 (m), 1166 (w), 1028 (w), 874 (w), 769 (m), 683 (m). For ^{1}H and ^{13}C NMR data, see Tables 2a and 3a.

5,7-dihydroxyflavothione 3b

The synthesis was carried out analogously to **1b** using a mixture of chrysin (**3**) (254 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). After column chromatography on silica gel, using dichloromethane-ethyl acetate (10 : 1 v/v) as eluent gave compound **3b** as yellow crystals, yield 8%, mp 218 °C, APCI-MS, 269 (M-1). IR KBr (γ, cm^{-1}), ~3400 (vw, br), 3057 (vw), 1630 (s), 1598 (s), 1575 (m), 1497 (w), 1460 (s), 1343 (w), 1306 (vw), 1249 (m), 1166 (w), 1028 (w), 874 (w), 769 (m), 683 (m). For ^{1}H and ^{13}C NMR data, see Tables 2a and 3a.

7-Dodecyloxy-5-hydroxyflavothione 4b

The synthesis was carried out analogously to **1b** using a mixture of **4a** (422 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). Column chromatography on silica gel, using dichloromethane as eluent gave compound **4b** as yellow crystals, yield 52%, mp 104–105 °C, APCI-MS, 438 $(M-1)^{+}$. IR KBr (γ, cm^{-1}), 2922 (s), 1645 (m), 1598 (m), 1574 (w), 1492 (vw), 1467 (w), 1380 (w), 1303 (w), 1262 (vw), 1178 (w), 1028 (w), 874 (w), 769 (m), 683 (m). For ^{1}H and ^{13}C NMR data, see Tables 2b and 3a.

7-Butyloxy-5-hydroxyflavothione 5b

The synthesis was carried out analogously to **1b** using a mixture of **5a** (310 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). Column chromatography on silica gel, using dichloromethane as eluent gave compound **5b** as yellow crystals, yield 82%, mp 121–122 °C, APCI-MS, 325 (M-1). IR KBr (γ, cm^{-1}) 2954 (s), 1648 (s), 1599 (s), 1575 (m), 1492 (w), 1450 (w), 1382 (m), 1305 (s), 1265 (m), 1177 (s), 1032 (w), 873 (vw), 767 (m), 681 (w). For ^{1}H and ^{13}C NMR data, see Tables 2b and 3b.

2′,3,4′,7-Tetramethoxy-5-hydroxyflavothione 6b

The synthesis was carried out analogously to **1b** using a mixture of **6a** (358 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). Column chromatography on silica gel, using dichloromethane–ethyl acetate (10 : 1 v/v) as eluent gave compound **6b** as yellow crystals, yield 48%, mp 157–158 °C, APCI-MS, 373 (M-1). IR KBr (γ, cm^{-1}), 2925 (m), 1646 (s), 1584 (s), 1497 (m), 1456 (s), 1339 (w), 1306 (w), 1282 (m), 1221 (m), 1162 (s), 1024 (m), 837 (m), 790 (w), 670 (vw). For ^{1}H and ^{13}C NMR data, see Tables 2c and 3c.

3,3′,4′,7-Tetramethoxy-5-hydroxyflavothione 7b

The synthesis was carried out analogously to **1b** using a mixture of **7a** (358 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). Column chromatography on silica gel, using dichloromethane-ethyl acetate (10 : 1 v/v) as eluent gave compound **7b** as yellow crystals, yield 49%, mp 168–169 °C APCI-MS, 373 (M-1). IR KBr (γ, cm^{-1}), 2934 (w), 1646 (s), 1584 (s), 1499 (s), 1448 (s), 1346 (w), 1318 (s), 1275 (s), 1247 (s), 1221 (s), 1159 (s), 1021 (s), 876 (w), 772 (m), 667 (w). For ^{1}H and ^{13}C NMR data, see Tables 2c and 3c.

7-Butyloxy-4′,5-dihydroxyflavothione 9b and 7-butyloxy-4′,5-dihydroxyflavanonethion 9c

The synthesis was carried out analogously to **1b** using a mixture of compound **9a** (328 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). Column chromatography on silica gel using dichloromethane as eluent the early fractions gave compound **9b** as yellow crystals, yield 15%, mp 144–145 °C, APCI-MS, 340 (M-1). IR KBr (γ, cm^{-1}), 3446 (br,s), 2959, 2930, 2873 (w), 1639 (s), 1579 (m), 1501 (m),1464 (m), 1379 (m), 1288 (m), 1271 (w), 1203 (w) 1174 (m), 1124 (m), 1074 (m), 836 (m), 743 (w), 700(w). The later fractions gave product **9c** as yellow crystals, yield 26%, mp 128–129 °C, APCI-MS, 342 (M-1). IR KBr (γ, cm^{-1}), 3423 (br,s), 2955, 2931, 2875 (w), 1627 (s), 1556 (m), 1455 (m), 1349 (m), 1286 (m), 1256(w), 1204 (m) 1166 (m), 1117 (m), 1061(m), 831(m), 700(w). For ^{1}H and ^{13}C NMR data, see Tables 2c and 3b.

10b and **c** were synthesized as described above using decylbromide. None of the products were fully purified.

4′-Methoxy-5,7-dihydroxyisoflavothione 11b

The synthesis was carried out analogously to **1b** using a mixture of biochanin A (**11a**) (284 mg, 1.0 mmol) and Lawesson's reagent (202 mg, 0.5 mmol). Column chromatography on silica gel, using dichloromethane as eluent gave compound **11b** as yellow crystals, yield 29%, mp 162–163 °C, APCI-MS, 300 (M-1). IR KBr (γ, cm^{-1}), ~3450 (w, br), 2929 (w), 1611 (s), 1594 (s), 1509 (s), 1459 (w), 1409 (w), 1295 (m), 1252 (s), 1179 (m), 1025 (m), 890 (w), 803 (w), 707 (w). For ^{1}H and ^{13}C NMR data, see Tables 2a and 3b.

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