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Tritium Exchange in Specifically Labelled Hydroquinone, Dihydrobenzofuranol and Chromanol Derivatives*

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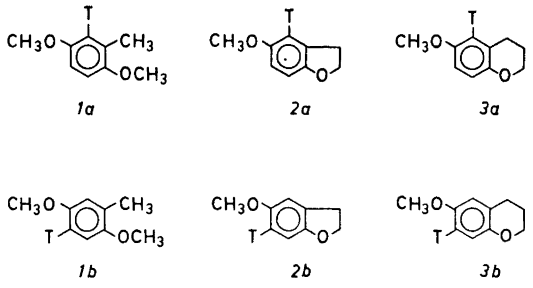
The directing effect of oxygen-heterocyclic annulated rings in aromatic systems has been studied by determining the rate of tritium exchange in anhydrous trifluoroacetic acid from specifically labelled 2-methylhydroquinone dimethyl ether, 2,3-dihydro-5-methoxybenzofuran, and 6-methoxychroman. The results show that the oxygen-containing six-membered annulated ring has a stronger directing effect to the ar-α position of the aromatic ring than the corresponding six-membered carbocyclic ring.

We have previously reported that oxidative coupling of 6-chromanol and its derivatives gives products almost exclusively formed by reaction at the 5-position of the molecule [1] (ar-α position). Similarly, 2,3-dihydro-5-benzofuranol gave coupling products preferentially *via* the 6-position (ar-β position).[2] It was thus apparent that an oxygen-containing annulated ring has a directing effect on the oxidative coupling reaction of these phenols. In a subsequent study we were unable to demonstrate a similar effect in the oxidative coupling of various 5-hydroxyindanes and 6-hydroxytetralins.[3] This indicates that an oxygen-containing ring has a stronger directing effect than an alicyclic annulated ring.

Electrophilic substitution of 5-indanol and 6-tetralol has been studied by numerous investigators.[4–6] These studies show that the ar-α position of 6-tetralol and the ar-β position of 5-indanol are the most reactive sites of these molecules. We have recently published [7] the first order rate constants for detritiation of specifically labelled xylenols, indanols, and tetrahydronaphthols and their methyl ethers. These experiments gave quantitative measurements of the differences in reactivity between the two positions *ortho* to the hydroxy or methoxy groups of the compounds studied, *i.e.* between the ar-α and the ar-β positions. The results were in accordance with the previous quantitative observations. To study if the strong directing effect of oxygen-containing annulated rings observed in oxidative coupling [1,2] could be demonstrated also in

* The directing effect of annulated rings in aromatic systems VIII: Part VII, see Ref. 7.

electrophilic substitution, we have now synthesized the specifically tritiated compounds *1–3* (Scheme 1) and determined the rate of detritiation in anhydrous trifluoroacetic acid.

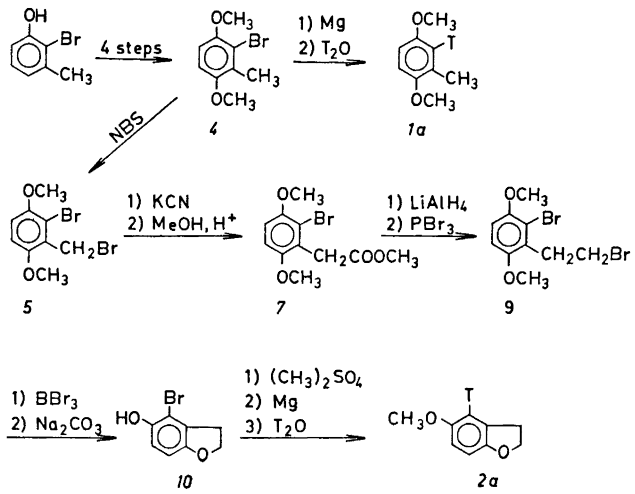


Scheme 1.

SYNTHETIC PROCEDURES

The specifically tritiated compounds used in the kinetic experiments were all obtained from the appropriate bromo compounds which were converted to the Grignard reagents and subsequently hydrolysed with tritiated water.[8] The following discussion will therefore only deal with the preparation of the aromatic bromo compounds.

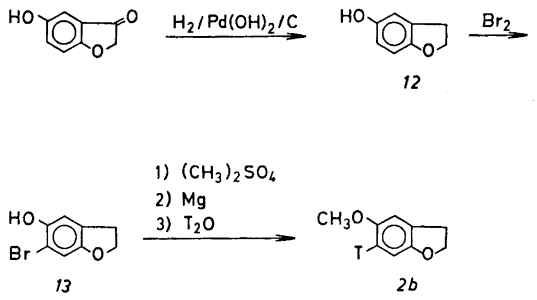
2-Bromo-5-methylhydroquinone dimethyl ether and 5-bromo-6-methoxychroman, used in the synthesis of *1b* and *3a*, respectively were obtained from the corresponding phenols by direct bromination and subsequent *O*-methylation. The tritiated ethers *1a*, *2a*, *2b*, and *3b* were obtained as outlined in



Scheme 2.

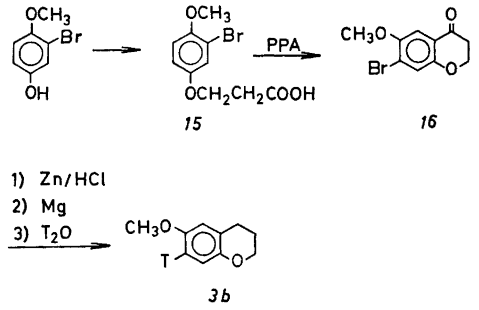
Schemes 2 – 4. 2-Bromo-3-methylphenol was converted to the corresponding hydroquinone and subsequently methylated to *4* (Scheme 2). This compound was used for the preparation of *1a* and also as starting material in the synthesis of *2a*.

Benzylic bromination of *4* yielded *5* which was converted to the ester *7* *via* the nitrile. Reduction of the ester gave the corresponding alcohol together with debrominated material. The mixture was reacted with PBr_3 to form *9*. Demethylation to the hydroquinone, followed by treatment with base, yielded the dihydrofuran *10* after separation from debrominated phenol. The labelled ether *2a* was then obtained as usual. To prepare 2,3-dihydro-5-benzofuranol (*12*) (Scheme 3), 5-hydroxy-3-benzofuranone was hydrogenated over palladium hydroxide on carbon. Bromination of *12* gave *13* as the only product, from which *2b* was obtained as shown in Scheme 3.



Scheme 3.

7-Bromo-6-methoxychroman was prepared by a Clemmensen-type reduction of 7-bromo-6-methoxy-4-chromanone (*16*), prepared as shown in Scheme 4. The tritiated compound *3b* was then prepared as usual. The kinetic studies indicated that the exchange of bromine for tritium *via* the Grignard reagent was specific, and no significant amount of tritium was introduced in any other aromatic position of the molecule (*cf.* Ref. 9).

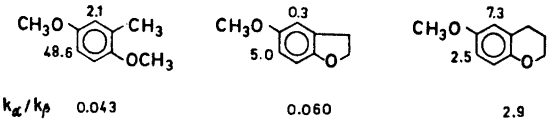


Scheme 4.

RESULTS AND DISCUSSION

The detritiation reactions were carried out in anhydrous trifluoroacetic acid at $20.0 \pm 0.1°$. All the tritiated compounds studied have a methoxy group in the ar-β position. Our previous study [7] of tritium exchange in related hydroxy and methoxy substituted compounds indicate that an ar-β substituent increases the directing effect, particularly of the six-membered annulated ring.

The first-order rate constants obtained for exchange at the appropriate positions are given in Scheme 5. This scheme also shows the ratio between the rate constants (k_α/k_β) for the two positions *ortho* to the methoxy group.



k_α/k_β 0.043 0.060 2.9

Scheme 5. Values of $k \times 10^6$ (sec^{-1}) for detritiation of 2-methylhydroquinone dimethyl ether 2,3-dihydro-5-methoxybenzofuran and 6-methoxychroman.

In our previous study of the detritiation of hydroxy and methoxy substituted *o*-xylene, indane, and tetralin,[7] we found that the methoxy compounds had about 1000 times higher rate of detritiation than the corresponding hydrocarbons. We therefore expected the compounds *1 – 3*, with two alkoxy groups on the aromatic nucleus, to have a considerably higher exchange rate than those with only one alkoxy group. However, we found that the detritiation rate generally was about 1000 times slower than that of the monoalkoxy compounds, and thus of the same order as reported for the hydrocarbons *o*-xylene, indane, and tetralin.[10] The low rate of detritiation for compounds *1 – 3* is probably due to protonation of the alkoxy groups in the reaction medium. This was also indicated by a blue shift in the UV-spectra of the compounds when comparative measurements were carried out in acetic acid and trifluoroacetic acid.

Comparing the exchange rates of 2-methylhydroquinone dimethyl ether *1* and 2,3-dihydro-5-methoxybenzofuran *2* it is apparent that *2*, with a five-membered annulated ring, has about one tenth of the reactivity of *1*, which can be considered as an open analogue of *2*. No similar phenomenon could be observed in the corresponding carbocyclic series.[7]

In our previous study of the bromination of bicyclic phenols,[6] we have shown that only a six-membered annulated ring favours ar-α-substitution; four-, five-, seven-, and eight-membered annulated rings all favour ar-β-substitution in this electrophilic reaction. In the study of the detritiation of hydroxy- and methoxy substituted *o*-xylene, indane, and tetralin,[7] the ratio between the rate constants (k_α/k_β) was used as a measure of the directing effect of the annulated ring. These ratios are of the order of about 0.5 for xylene and indane derivatives, and 5 – 10 times larger for the tetralin derivatives, demonstrating the ar-α directing effect of the six-membered annulated ring of these compounds.

A similar comparsion of the ratios between the rate constants for compounds *1* – *3* (Scheme 1) shows that k_α/k_β for *1* and *2* are of the order of about 0.05 but the ratio for the chroman derivative *3* is 50 – 60 times larger. This is thus an indication that an oxygen-containing six-membered annulated ring has a stronger tendency to favour electrophilic substitution in the ar-α position than the corresponding carbocyclic ring in tetralin. This has previously been observed in oxidative coupling of chromanol and tetralol derivatives, as discussed above.

EXPERIMENTAL

General comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. IR spectra were measured on a Perkin-Elmer 237 spectrophotometer and UV-spectra were measured with a Unicam SP 1800 Ultraviolet spectrophotometer. NMR-spectra were measured in $CDCl_3$-solutions with a Varian A 60 spectrometer. Chemical shifts are expressed in δ ppm relative to tetramethylsilane. Mass spectra were obtained with an LKB 9000 instrument at 70 eV. Thin layer chromatography was performed using silica gel G plates of 0.3 mm (analytical) and 1 mm (preparative) thickness. The plates were activated at 130° for 1.5 h and were stored in a dry cabinet until used. The radioactivity of the synthesized compounds was determined by liquid scintillation counting (Nuclear Chicago, Mark II) after purification to constant specific activity. The chemical identity of each substance was determined by spectral and chromatographic comparison with authentic samples. Exchange-rate measurements were carried out in anhydrous trifluoroacetic acid at 20.0 ± 0.1°, as previously described.[7]

2-Bromo-3-methylhydroquinone. This compound was obtained in 81 % overall yield from 40 g of 2-bromo-3-methylphenol [11] by the method previously used for the preparation of dimethylhydroquinones,[12] m.p. 181 – 184° dec. (from H_2O-ethanol). Mass spectrum shows prominent peaks at *m/e* (rel. int. %) 204 (77), 202 (83 $M^{+\cdot}$), 123 (100), 121 (30), 95 (27), 94 (25), 67 (60), 66 (49), 65 (49), 55 (31), 39 (77). The hydroquinone was rapidly oxidized in air and was therefore methylated to *4* without further purification.

2-Bromo-3-methylhydroquinone dimethyl ether (*4*). 2-Bromo-3-methylhydroquinone (34.0 g; 0.17 mol) was methylated with dimethyl sulphate (63.2 g; 0.5 mol) in alkaline solution [13] affording 28 g (72 %) of *4* m.p. 100 – 102° (from ethanol). (Found: C 47.3; H 4.91. Calc. for $C_9H_{11}BrO_2$: C 46.8; H 4.81.) NMR: δ = 6.81 ppm (s, 2H, Ar*H*), 3.87 and 3.81 ppm (s, 3H each, $-OCH_3$), 2.37 ppm (s, 3H, ArCH_3).

2-Methylhydroquinone-3-[^{3}*H*] *dimethyl ether* (*1a*). 2-Bromo-3-methylhydroquinone dimethyl ether (1.5 g; 6.5 mmol) was converted to the corresponding Grignard reagent and treated with tritiated water (1 ml; 18 mC/ml) as described for 3,4-dimethylanisole-6-[^{3}H] in Ref. 8. The product was purified by preparative TLC affording 0.9 g (90 %) of *1a*. Sp. act. 127 μC/mmol.

2-Methylhydroquinone-5-[^{3}*H*] *dimethyl ether* (*1b*) was similarly obtained from 4-bromo-2,5-dimethoxytoluene [14] (1.5 g; 6 mmol). Sp. act. 104 μC/mmol.

2-Bromo-3-bromomethylhydroquinone dimethyl ether (*5*). This compound was prepared from *4* (14 g; 61 mmol) using *N*-bromosuccinimide (11.3 g; 63 mmol) according to McHale *et al.*,[15] affording 18.3 g (97 %) of *5*, m.p. 75 – 76° (from ethanol). (Found: C 35.4; H 3.25. Calc. for $C_9H_{10}Br_2O_2$: C 34.9; H 3.25.) NMR: δ = 6.95 ppm (s, 2H, Ar*H*), 4.85 ppm (s, 2H, $ArCH_2-$), 3.92 ppm (s, 6H, $-OCH_3$).

2-Bromo-3,6-dimethoxybenzylcyanide (*6*). A mixture of 2-bromo-3-bromomethylhydroquinone dimethyl ether (*5*) (18.3 g; 0.06 mol), KCN (5.8 g; 0.09 mol), acetonitrile (275 ml) and water (45 ml) was refluxed for 1 h. Water (200 ml) was added and the mixture extracted with ether (3 × 100 ml). The combined ether extracts were washed with saturated NaCl-solution, dried (Na_2SO_4) and evaporated. The residue was dissolved in dry ether and passed through a short coloumn of Al_2O_3. Evaporation of the ether extract afforded 13 g (86 %) of *6*, m.p. 82 – 83° (from ethanol-ligroin) ν_{max} (KBr) = 2260 cm^{-1} (C≡N). (Found: C 46.8; H 4.01. Calc. for $C_{10}H_{10}BrNO_2$: C 46.9; H3.93.) NMR: δ = 6.70 ppm (s, 2H, Ar*H*), 3.80 ppm (s, 2H, $ArCH_2-$), 3.75 ppm (s, 6H, $-OCH_2$).

Methyl 2-bromo-3,6-dimethoxyphenylacetate (*7*). A mixture of *6* (12.4 g; 0.05 mol), methanol (75 ml) and concentrated H_2SO_4 (11.9 g; 0.12 mol) was refluxed overnight. Water was added and the precipitate filtered off, washed with water and dried. Crystallisation from ethanol gave 12 g (86 %) of product, m.p. 94 – 96°. ν_{max} (KBr) = 1730 cm^{-1} (C = O). (Found: C 45.8; H 4.56. Calc. for $C_{11}H_{13}BrO_4$: C 45.7; H 4.53.)

2-(2-Bromo-3,6-dimethoxyphenyl)ethanol (*8*). The methyl ester *7* (12 g; 0.04 mol) was reduced with $LiAlH_4$ (15 g; 0.4 mol) in dry THF (150 ml) affording 7.2 g (66 %) of a yellow oil that showed no carbonyl absorption band in the IR-spectrum. Although TLC showed that the crude oil contained debrominated product [2-(3,6-dimethoxyphenyl)ethanol], the mixture was taken to the next step without further purification due to difficulties encountered in separating the two products.

1-Bromo-2-(2-bromo-3,6-dimethoxyphenyl)ethane (*9*). To the above oil (3.7) g), PBr_3 (5.8 g) was added at 0°. The reaction mixture was left at room temperature overnight, poured onto crushed ice and extracted with ether (3 × 30 ml). The combined ether extracts were washed with 1 N NaOH (10 ml), with saturated $NaHCO_3$-solution (10 ml), dried (Na_2SO_4) and evaporated, affording a pale yellow oil (1.9 g; 41 %). The IR-spectrum of the oil showed no OH-stretching band. The crude material was taken to the next step without further purification.

4-Bromo-2,3-dihydro-5-benzofuranol (*10*). To the crude oil *9* (1.9 g; 5.9 mmol) was added dropwise BBr_3 (1.0 g; 4 mmol) causing a vigorous reaction to occur. The mixture was then heated at 70° for 2 min, whereupon a solution of Na_2CO_3 (1.6 g; 0.015 mol) in water (50 ml) was cautiously added. The reaction mixture was then heated to 60°, cooled, acidified with 5 N HCl and extracted with ether (3 × 10 ml). The ether extract was dried (Na_2SO_4), evaporated, and the solid residue, which consisted of a mixture of 4-bromo-2,3-dihydro-5-benzofuranol (*10*) and 2,3-dihydro-5-benzofuranol, was subjected to preparative TLC developed in ether – light petroleum (1 : 5). Crystallisation from ligroin gave 0.92 g (8 %) of *10*, m.p. 80 – 82°. NMR: The two aromatic protons give an AB-pattern centered at $\delta = 6.51$ ppm ($J = 8$ cps, $\delta_A = 6.59$ ppm, $\delta_B = 6.43$ ppm), 4.90 ppm (s broad, 1H, *OH*), 4.6 – 4.3 ppm (t, 2H, OCH_2-), 3.3 – 2.9 ppm (t, 2H, $ArCH_2-$). This spectrum is consistent with structure *10*. Mass spectrum shows prominent peaks at *m/e* (rel. int. %), 217 (10), 216 (96), 215 (13), 214 (100 $M^{+\cdot}$), 136 (15), 135 (40), 134 (31), 107 (87), 79 (68) 78 (36), 77 (73).

4-Bromo-2,3-dihydro-5-methoxybenzofuran (*11*). This compound was obtained by methylation of *10* (0.05 g; 0.23 mmol) with dimethyl sulphate in alkaline solution.[13] Crystallisation from light petroleum gave 0.03 g (57 %) of white needles, m.p. 83 – 84°. NMR: $\delta = 6.62$ ppm (s, 2H, Ar*H*), 4.8 – 4.3 ppm (t, 2H, $-OCH_2-$), 3.77 ppm (s, 3H, $-OCH_3$), 3.4 – 3.0 ppm (t, 2H, $ArCH_2-$). Mass spectrum shows prominent peaks at *m/e* (rel. int. %), 230 (80), 228 (82 $M^{+\cdot}$), 215 (98), 213 (100), 134 (30), 78 (23), 77 (19), These data are consistent with structure *11*.

2,3-Dihydro-5-methoxybenzofuran-4-[^3H] (*2a*). This compound was prepared from *11* (10 mg; 0.044 mmol) as described for *1a via* the Grignard reagent and tritiated water (0.5 ml; 470 mC/ml). Sp. act. 1.0 mC/mmol.

2,3-Dihydro-5-benzofuranol (*12*). 5-Hydroxy-3-benzofuranone[16] (8.0 g; 53 mmol) dissolved in methanol was hydrogenated over 20 % $Pd(OH)_2/C$[17] at atmospheric pressure and room temperature until TLC showed that no ketone remained. The solution was filtered and evaporated, and the product crystallized from toluene, yielding 6.5 g (90 %) of white crystals, m.p. 111 – 112°. (Found: C 70.6; H 5.93. Calc. for $C_8H_8O_2$: C 69.8; H 6.02.) ν_{max} (KBr) 3320 cm^{-1} (OH). NMR: $\delta = 6.9 - 6.4$ ppm (m, 3H, Ar*H*), 4.93 ppm (s, 1H, $-OH$), 4.8 – 4.4 ppm (t, 2H, $-OCH_2-$), 3.4 – 3.0 ppm (t, 2H, $ArCH_2-$).

6-Bromo-2,3-dihydro-5-benzofuranol (*13*). 2,3-Dihydro-5-benzofuranol (*12*) (2.0 g; 0.015 mol) was dissolved in 430 ml ether – CCl_4 (1 : 12) and brominated at 0° by the dropwise addition of bromine (0.8 ml; 0.015 mol) in 80 ml CCl_4. When the reaction was complete the solution was evaporated *in vacuo* yielding an unstable oil (2.6 g, TLC indicated only one product) which rapidly turned brown. The bromophenol was therefore methylated without further purification.

6-Bromo-2,3-dihydro-5-methoxybenzofuran (*14*). The crude product above (2.6 g) was methylated with dimethyl sulphate in alkaline solution[13] affording 1.9 g (68 %) of product, m.p. 63 – 64° (from light petroleum). NMR: $\delta = 7.03$ and 6.87 ppm (s, 1H each Ar*H*), 4.8 – 4.4 ppm (t, 2H, $-OCH_2-$), 3.84 ppm (s, 3H, $-OCH_3$), 3.4 – 2.9 ppm (t 2H, $ArCH_2-$). This spectrum is consistent with structure *14*. Mass spectrum shows

prominent peaks at *m/e* (rel. int. %) 230 (76), 228 (79 $M^+\cdot$), 215 (98), 213 (100), 91 (10), 78 (20), 77 (14), 65 (11), 53 (27).

2,3-Dihydro-5-methoxybenzofuran-6-[^3H] (*2b*) was obtained from *14* (0.5 g; 2.2 mmol) as described for *1a*. Sp. act. 24 μC/mmol.

3-(3-Bromo-4-methoxyphenoxy)propionic acid (*15*). 3-Bromo-4-methoxyphenol [18] (13 g; 0.064 mol in dry DMF (50 ml) was slowly added under nitrogen to a suspension of sodium hydride (10.8 g; 0.22 mol) in dry DMF (50ml) . A solution of 3-bromopropionic acid (24.5 g; 0.16 mol) in dry DMF (50 ml) was then added dropwise, and the reaction mixture was left overnight at room temperature. Water (100 ml) was added and the mixture extracted with ether (3 × 100 ml). The ethereal solution was extracted with saturated $NaHCO_3$ (3 × 100 ml) from which the product precipitated upon acidification. 4.5 g of unreacted phenol was recovered. Crystallisation from toluene gave 9.0 g (50 %) of product, m.p. 112 – 113°. (Found: C 44.1; H 4.06. Calc. for $C_{10}H_{11}BrO_4$: C 43.7; H 4.03.) NMR: $\delta = 9.85$ ppm (s, broad, 1H, $-COOH$), 7.5 – 6.9 ppm (m, 3H, Ar*H*), 4.5 – 4.1 ppm (t, 2H, $-OCH_2-$), 3.92 ppm (s, 3H, $-OCH_3$), 3.1 – 2.7 ppm (t, 2H, $-CH_2-COCH$).

7-Bromo-6-methoxy-4-chromanone (*16*). This compound was obtained by cyclization of *15* (8.5 g; 0.03 mol) with polyphosphoric acid at 80° for 70 min.[19] The crude product was crystallised from ethanol affording 6.7 g (87 %) of yellow needles, m.p. 142 – 144°. (Found: C 46.9; H 3.79. Calc. for $C_{10}H_9BrO_3$: C 46.7; H 3.54.) NMR $\delta = 7.45$ and 7.36 ppm (s, 1H each, Ar*H*), 4.8 – 4.4 ppm (t, 2H, $-OCH_2-$), 3.95 ppm (s, 1H, $-OCH_3$), 3.1 – 2.7 ppm (t, 2H, $-CH_2-CO$). This spectrum is consistent with structure *16* ν_{max} (KBr) = 1700 cm^{-1} (C = O).

7-Bromo-6-methoxychroman (*17*). 7-Bromo-6-methoxy-4-chromanone (0.5 g; 1.9 mmol) was reduced using zinc and hydrochloric acid by the method previously described.[20] The reaction mixture was refluxed for 20 min, cooled, and extracted with ether, and the extract dried (Na_2SO_4) and evaporated *in vacuo*. The residue, which consisted of a mixture of 7-bromo-6-methoxychroman and 6-methoxychroman, as indicated by TLC, was purified by preparative TLC developed in ether – light petroleum (1 : 5). Recrystallisation of the product from ligroin gave 0.2 g (42 %) of white crystals, m.p. 73 – 74°. NMR: $\delta = 7.10$ and 6.67 ppm (s, 1H each, Ar*H*), 4.3 – 4.0 ppm (t, 2H, $-OCH_2-$), 3.86 ppm (s, 3H, $-OCH_3$), 3.0 – 2.6 ppm (t, 2H, $ArCH_2-$), 2.3 – 1.7 ppm (m, 2H, $-CH_2-$). The mass spectrum shows prominent peaks at *m/e* (rel. int. %) 245 (11), 244 (93), 243 (12), 242 (100 $M^+\cdot$) 230 (8), 229 (73), 228 (9), 227 (75), 216 (10), 214 (11), and 120 (31).

6-Methoxychroman-7-[^3H] (*3b*). The above methyl ether (0.1 g; 0.4 mmol) was converted to the Grignard reagent and treated with tritiated water (0.5 ml 470 mC/ml) as described for *1a*. Sp. act. 5.1 mC/mmol.

5-Bromo-6-methoxychroman (*18*). 5-Bromo-6-chromanol [6] (1.3 g; 5.7 mmol) was methylated with dimethyl sulphate (1.07 g, 8.5 mmol) in alkaline solution [13] yielding 1.1 g (80 %) of product, m.p. 93 – 95° (from ligroin). (Found: C 49.6; H 4.42. Calc. for $C_{10}H_{11}BrO_2$: C 49.4; H 4.56.) NMR: $\delta = 6.80$ ppm (s, 2H, Ar*H*), 4.3 – 3.9 ppm (t, 2H, $-OCH_2-$), 3.85 ppm (s, 3H, $-OCH_3$), 3.0 – 2.6 ppm (t, 2H, $ArCH_2-$), 2.3 – 1.7 ppm (m, 2H, $-CH_2-$). This spectrum is consistent with structure *18*.

6-Methoxychroman-5-[^3H] (*3a*). This compound was prepared from *18* (0.5 g; 2 mmol) as described for *1a*. Sp. act. 30μC/mmol.

UV-measurements of the compounds *1 – 3* in trifluoroacetic acid and actic acid gave the following results. 2-Methylhydroquinone dimethyl ether: $\lambda_{max}(CF_3COOH)$ 279 nm; $\lambda_{max}(CH_3COOH)$ 289 nm. 2,3-Dihydro-5-methoxybenzofurane: $\lambda_{max}(CF_3COOH)$ 287 nm; $\lambda_{max}(CH_3COOH)$ 300 nm. 6-Methoxychroman: $\lambda_{max}(CF_3COOH)$ 285 nm; $\lambda_{max}(CH_3COOH)$ 295 nm.

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