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ISOMERIZATION OF DIHYDROQUERCETIN

EBERHARD KIEHLMANN* and EDMOND P.M. LI

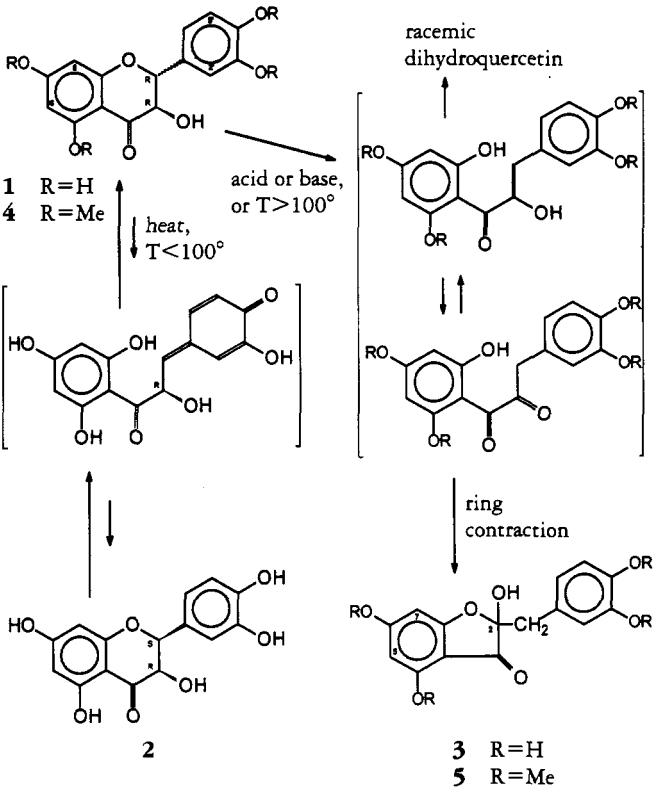
Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada V5A 1S6

ABSTRACT.—(+)-*trans*-Dihydroquercetin (taxifolin, **1**) equilibrates with approximately 10% of its less stable (+)-*cis* diastereomer (epitaxifolin, **2**) in hot aqueous or alcoholic solution by C-2 epimerization. The reaction is postulated to proceed through an optically active quinone methide formed by heterocyclic ring opening. Racemization and isomerization to alphitonin (2-benzyl-2,3′,4,4′,6-pentahydroxy-3-coumaranone, **3**) at elevated temperatures or with acid/base catalysts are attributable to slow deprotonation at C-3 and formation of an achiral α-diketone intermediate. Dibasic sodium phosphate converts dihydroquercetin to the dihydrate of a hemi-sodium salt.

Douglas fir bark is one of the major waste products of the forest industry in the Pacific Northwest. It contains relatively large quantities of dihydroquercetin (taxifolin, **1**), an antioxidant (1) and fungicide, which is readily extracted with Et_2O from the hot-H_2O-soluble fraction (11%) of dry bark (2). The adhesive properties of bark extracts, utilized in plywood manufacture, are attributed mainly to oligomeric flavanoids (condensed tannins) which are believed to be formed by enzymatic reduction of dihydroquercetin and interflavanoid coupling. A better understanding of the chemistry of dihydroquercetin may lead to further applications of this abundant renewable resource. Recent papers on the isolation and structure determination of several dihydroflavonols and their glycosides from acacia heartwood (3), cypress leaves (4), pine needles (5), and Douglas fir bark (6) prompt us to report the results of our studies of the isomerization of dihydroquercetin.

The first paper on the isolation of dihydroquercetin from Douglas fir heartwood (7) was followed by a thorough investigation of its chemistry (2). Dihydroquercetin has since been found in many other plants (8–10), and its 2,3-*trans*-dihydroflavonol structure and (2*R*,3*R*) absolute configuration have been verified by nmr spectroscopy (11,12) and by chemical correlation with (+)-catechin (13), respectively.

However, a careful examination of the physical properties of dihydroquercetin, especially its melting point (from 218° to 253°) and optical rotation, reveals rather wide variations. Pew (7) reported premature browning, depressing the melting point, on using soft glass capillaries. Neither repeated recrystallization from H_2O or aqueous EtOH nor chromatographic purification significantly diminish the melting point range. To determine the purity of a melted sample of dihydroquercetin, we examined its ^1H- and ^{13}C-nmr spectra and detected the presence of a large proportion of alphitonin (2-benzyl-2,3′,4,4′,6-pentahydroxy-3-coumaranone, **3**). The rearrangement of dihydroflavonols to 2-benzyl-2-hydroxy-3-coumaranones in alkaline solutions is well-known (14–17) and constitutes a major side reaction when dihydroquercetin is methylated with Me_2SO_4 and K_2CO_3 in Me_2CO (18,19), but the ready occurrence of this reaction in the absence of base is new (Scheme 1). Alphitonin [**3**] was formed in 78% yield (together with 14% quercetin) on heating an aqueous solution of dihydroquercetin in a sealed tube at 115° for four days. The most characteristic features of the nmr spectra of alphitonin, distinguishing the compound clearly from its flavanone precursor, are the signals due to the benzylic carbon (41.6 ppm) and hydrogens (3.01 and 3.05 ppm). The chemical shifts agree well with those reported



SCHEME 1

for 2-benzyl-4-methoxy-2,4′,6-trihydroxy-3-coumaranone (carpusin) except for C-3, C-4, and C-7a which were incorrectly assigned by Mathew and Subba Rao (20). The physical and spectral properties of penta-*O*-methylalphitonin, obtained by methylation with dimethyl sulfate, also agree with those in the literature (15).

Dihydroquercetin was obtained approximately 95% pure and free of alphitonin (^{1}H-nmr and hplc analysis) by boiling Douglas fir bark for 40 min with H_2O, extraction of the concentrated black aqueous filtrate with toluene (dewaxing) and Et_2O, and evaporation of the solvent and recrystallization of the beige solid residue from H_2O. Extraction of the aqueous mother liquor with Et_2O yielded a second crop of crystals which was found to contain, besides (+)-*trans*-dihydroquercetin [**1**] as major component, 45% of the diastereomeric (+)-*cis*-dihydroquercetin (epitaxifolin, **2**) with nmr chemical shifts (H-2 at 5.42, H-3 at 4.62, OH-5 at 11.87 ppm) identical to those reported by Nonaka *et al.* (4) and Lundgren and Theander (5). *cis*-Dihydroquercetin was first isolated and described by Tominaga *et al.* (21), who obtained it by acidic hydrolysis of its 3-*O*-rhamnoside (neoastilbin). The specific rotation of our 45/55 *cis/trans* mixture ($[\alpha]^{25}D$ +36.2° in MeOH, c=0.5) was higher than that of *trans*-dihydroquercetin (22.9°). Contrary to previous observation (5), in our hands the composition of the mixture of diastereomers, as monitored by hplc and polarimetry, remained constant over a period of two months, that is, at room temperature the less stable *cis*-dihydroquercetin [**2**] did not epimerize to the more stable *trans* structure in MeOH solution. We actually used aqueous MeOH as eluent in gel permeation chromatography to raise the *cis/trans* ratio of an isomer mixture

from 70:30 to 85:15 (see Experimental).

However, equilibrium mixtures with the two isomers in the approximate molar ratio of 9:1 (*trans/cis*), the same value quoted by Lundgren and Theander (5), and with a specific rotation of +25.5° were formed on refluxing pure (+)-*trans*-dihydroquercetin for 24 h in MeOH, on simple recrystallization (95°/10 min) from H_2O, or on heating (75°/12 h) a 1:2 mixture in 0.5 M HCl in 50% aqueous MeOH. This equilibration, which is analogous to the epimerization of 2,3-*cis*- to 2,3-*trans*-3′,4′,7,8-tetrahydroxydihydroflavon-3-ol observed by Foo (3) under similar conditions, can be used to advantage to prepare *cis*-dihydroquercetin [**2**] from the *trans*-isomer. More drastic experimental conditions, for example, refluxing in strong aqueous HCl, result in complete racemization (1,7) which also accompanies salt formation in alkaline medium (22). The attempted purification of *trans*-dihydroquercetin via its sodium salt led to the formation of a dihydrate, $C_{15}H_{11}O_7Na \cdot C_{15}H_{12}O_7 \cdot 2H_2O$, in only 40% yield instead of the expected high yield of $C_{15}H_{11}O_7Na$ reported in the literature (22).

The results of our experiments show that most of the (+)-*cis*-dihydroquercetin isolated from the hot-H_2O-soluble fraction of Douglas fir bark is formed by C-2 epimerization of the abundant *trans*-diastereomer during the extraction. Clark-Lewis and Korytnyk (13,19) have proved the (2*R*,3*R*)-*trans*-stereochemistry of natural (+)-dihydroquercetin by chemical correlation of the configuration of its tetramethyl ether with that of (2*R*,3*S*)-catechin and explained its greater stability relative to the *cis*-isomer on the basis of the more favorable diequatorial arrangement of the two large substituents at C-2 (3,4-dihydroxyphenyl) and C-3 (OH group). Nonaka *et al.* (4) and Lundgren and Theander (5) verified these assignments by recording the cd spectra of all four stereoisomers and found the two (3*S*)-structures to be levorotatory. Consequently, inversion at C-3 of (+)-*trans*-dihydroquercetin [**1**] by deprotonation and formation of an enediol (3) or inversion at both asymmetric carbons (23) would be expected to reduce the angle of rotation or lead to racemization, which is contrary to our results. The observed increase in the specific rotation on partial conversion of (+)-*trans*-dihydroquercetin [**1**] to the less stable *cis*-isomer indicates a mechanism which involves heterocyclic ring opening to an intermediate quinone methide, as suggested previously (5). Thus, C-2 epimerization, with retention of configuration and chirality at C-3, is relatively fast, and C-3 epimerization is slow (Scheme 1). However, in the presence of enzymes such a pathway may well lead to the in vivo formation of (−)-*cis*-dihydroquercetin [**3**] and, if followed by reduction of the carbonyl group and interflavanoid coupling (3,24), be responsible for the predominance of epicatechin (with 2,3-*cis*-stereochemistry) as an extending unit in the condensed tannins of Douglas fir bark.

Acid/base catalysis and high temperature (>100°) accelerate both C-2 and C-3 epimerization leading to racemization and/or ring contraction to alphitonin [**3**] via an achiral α-diketone intermediate (Scheme 1). *trans*-3′,4′,5,7-Tetra-*O*-methyldihydroquercetin [**4**], a compound incapable of quinone methide formation, has been found to undergo the same rearrangement to the more stable coumaranone ring system (3′,4,4′,6-tetra-*O*-methylalphitonin, **5**) on prolonged treatment with acid (13,19) or base (18) or on heating (195°) above its melting point, without concomitant formation of the *cis*-isomer of **4**. We are presently exploring methods for the purification of (+)-*cis*-dihydroquercetin and study of its chemical reactivity.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps (uncorrected) were recorded on a Fisher-Johns

melting-point apparatus, optical rotations on a Perkin-Elmer 241 polarimeter, uv spectra on a Perkin-Elmer 8720 spectrometer, ir spectra on a Perkin-Elmer 1600 Ft-ir instrument, mass spectra on an HP-5985 quadrupole instrument, and nmr spectra on a Bruker spectrometer (400 MHz). Chemical shifts are reported relative to the Me_2CO-d_6 peaks centered at δ 2.04 (^{1}H nmr) and 29.80 ppm (^{13}C nmr), or to the $CHCl_3$ peak at δ 7.26 (^{1}H nmr). Analytical tlc was performed on Merck Kieselgel 60F-254 (0.2 mm) DC-Plastikfolien, and prep. tlc on Merck Si Gel 60HF-254/366 (1.0 mm). Elemental analyses were run on a Carlo Erba elemental analyzer model 1106. Hplc was carried out on reversed-phase analytical columns with C_8 or C_{18} bonded to the Si gel stationary phase, using aqueous MeOH as eluent.

PLANT MATERIAL.—The bark of Douglas fir [*Pseudotsuga menziesii* (Mirbel) Franco] was collected from the University Research Forest, Haney, British Columbia, in May 1987.

EXTRACTION AND ISOLATION.—The bark sample (2.0 kg) was initially extracted with boiling H_2O (24 liters; 40 min) followed by extraction of the concentrated black filtrate with Et_2O (4 liters). Solvent evaporation gave a fluffy, beige solid which was washed free of wax with toluene. Crude *trans*-dihydroquercetin (**1**, 20 g) was obtained by recrystallization from H_2O and purified by crystallization from 25% aqueous MeOH; mp 224–226° [lit. 218–220° (4), 240–242° (7)]; $[\alpha]^{25}D$ +23° (*c*=2.5, MeOH) (lit. (5) +19.4°, *c*=0.5); ^{1}H nmr (Me_2CO-d_6) δ 4.60 (1H, dd, *J*=11.3 and 3.9 Hz, H-3), 4.73 (1H, d, *J*=3.9 Hz, OH-3), 5.01 (1H, d, *J*=11.3 Hz, H-2), 5.93, 5.98 (2H, 2 × d, *J*=2.1 Hz, H-6, -8), 6.85 (1H, d, *J*=8.2 Hz, H-5′), 6.90 (1H, dd, *J*=2.0 and 8.2 Hz, H-6′), 7.06 (1H, d, *J*=2.0 Hz, H-2′), 8.07, 8.12 (2H, br s, OH-3′, -4′), 9.83 (1H, br s, OH-7), and 11.71 (1H, s, OH-5); ^{13}C nmr (Me_2CO-d_6) δ 73.0 (d, ^1J=142 Hz, C-3), 84.3 (d, ^1J=147 Hz, C-2), 96.0 (d, ^1J=164 Hz, C-8), 97.0 (d, ^1J=162 Hz, C-6), 101.4 (C-4a), 115.7 (d, ^1J=158 Hz, C-2′, -5′), 120.8 (d, ^1J=160 Hz, C-6′), 129.6 (C-1′), 145.6, 146.4 (C-3′, -4′), 164.0 (C-8a), 164.8 (C-5), 167.8 (C-7), and 198.0 (C-4).

Dihydroquercetin sodium salt.—In an attempt to purify dihydroquercetin by initial salt formation (1,22), beige, Me_2CO-insoluble crystals (86 mg, 40% yield) were obtained from a hot aqueous solution of dihydroquercetin (213 mg) and excess dibasic sodium phosphate (230 mg) after 25 min stirring. *Anal.*, C 54.05, H 4.18, Na 3.69 (Atomic Absorption Spectrometer PE 1100B, sodium lamp current 10 mA); calcd for $C_{30}H_{27}O_{16}Na$, C 54.06, H 4.08, Na 3.45. After drying *in vacuo* over KOH (110°/72 h): *anal.*, C 56.74, H 3.82, calcd for $C_{30}H_{23}O_{14}Na$: C 57.15, H 3.68. The ^{1}H-nmr spectrum of the sodium salt was similar to that of *trans*-dihydroquercetin [**1**] except for the expected upfield position of the aromatic proton signals.

(+)-cis-*Dihydroquercetin* (*epitaxifolin*, **2**).—Extraction using Et_2O of the aqueous mother liquor from the recrystallization of 2.50 g of crude *trans*-dihydroquercetin [**1**] gave 0.40 g of a brown, amorphous solid containing **1** and *cis*-dihydroquercetin [**2**] in an approximate ratio of 11:9, together with small amounts (<5%) of methoxylated impurities (δ 3.9–4.0) from Douglas fir bark. The two diastereomers were readily distinguished by the characteristically different chemical shifts of the H-2, H-3, and OH-5 signals in their ^{1}H-nmr spectra (see below), and by their different hplc retention volumes (17.6 ml for *trans* vs. 22.2 ml for *cis*, on a 25×0.4 cm Versapak C_8 column eluted with 1.0 ml/min 30% aqueous MeOH). The composition of this mixture, dissolved in MeOH at 25° and monitored by hplc and polarimetry ($[\alpha]^{25}D$ +36°, *c*=0.5, 1-ml cell of 10-cm pathlength) remained constant over a period of sixty days. Repeated recrystallizations from 25% aqueous MeOH and evaporation of the filtrates yielded pure (+)-*trans*-dihydroquercetin ($[\alpha]^{25}D$ +23°, MeOH, *c*=0.5) and a mixture substantially enriched in the more soluble cis-isomer (*cis*/*trans* ratio, 7:3). Gel permeation chromatography of the latter (0.60 g) on a MCI CHP-20P (46×2.5 cm column, 476 12-ml fractions eluted with 30–40% MeOH in 72 h) did not completely separate the two isomers, but afforded a small sample (50 mg 7:1 *cis*/*trans*, eluted with 40% MeOH in fractions 287–311) sufficiently pure for analysis by nmr, hplc, and polarimetry ($[\alpha]^{25}D$ +45°, MeOH, *c*=0.9; $[\alpha]^{25}D$ +48° calculated for pure **2**; lit. (5) +30.5°, *c*=0.4). Further purification by preparative cc on Florisil (eluent EtOAc) and on Lichroprep C-18 (30×2.5 cm, eluent 35% aqueous MeOH) was unsuccessful. ^{1}H-nmr data of **2** (Me_2CO-d_6): δ 4.27 (1H, dd, *J*=2.8 and 5.7 Hz, H-3), 5.18 (1H, d, *J*=5.7 Hz, OH-3), 5.42 (1H, d, *J*=2.8 Hz, H-2), 5.96, 6.00 (2H, 2 × d, *J*=2.1 Hz, H-6, -8), 6.81 (1H, d, *J*=8.2 Hz, H-5′), 6.90 (1H, dd, *J*=1.9 and 8.2 Hz, H-6′), 7.10 (1H, d, *J*=1.9 Hz, H-2′), 11.85 (1H, s, OH-5); ^{13}C nmr (Me_2CO-d_6) δ 72.5 (C-3), 82.2 (C-2), 95.7, 96.7 (C-6, -8), 101.4 (C-4a), 115.4, 115.6 (C-2′, -5′), 119.9 (C-6′), 128.4 (C-1′), 145.4, 145.8 (C-3′, -4′), 163.8 (C-8a), 165.4, 167.4 (C-5, -7), and 196.1 (C-4).

On heating (75°/12 h) with an equal volume of aqueous 1 M HCl, the *cis*/*trans* ratio of a 1% (w/v) MeOH solution changed from 7:1 to 1:9. The same equilibrium ratio was measured after heating solutions of pure *trans*-dihydroquercetin in MeOH (60°/24 h) or H_2O (95°/10 min).

Alphitonin [**3**] *and its pentamethyl ether.*—To determine the position of the equilibrium between *trans*- and *cis*-dihydroquercetin at 115°, a solution of 495 mg **1** in 10 ml hot H_2O was heated at this temperature in a sealed pressure vial for 93

h. The air was replaced by nitrogen to minimize oxidation. A small quantity (62 mg, 13% yield) of a greenish-yellow solid precipitated that was filtered, dried, and identified as quercetin. On solvent evaporation *in vacuo*, the red-brown aqueous filtrate afforded a yellow solid (365 mg, 78% yield) with nmr signals characteristic of alphitonin monohydrate as exclusive product. ^{1}H nmr of **3** (Me_2CO-d_6): δ 3.01, 3.04 (2H, 2 × d, J=13.9 Hz, CH_2), 5.82, 5.85 (2H, 2 × d, J=2.1 Hz, H-5, -7), 6.45 (1H, s, OH-2), 6.53 (1H, dd, J=2.0 and 8.1 Hz, H-6'), 6.60 (1H, d, J=8.1 Hz, H-5'), 6.71 (1H, d, J=2.0 Hz, H-2'), 7.68, 7.73 (2H, br s, OH-3', -4'), 8.84 (1H, br s, OH-6), and 9.69 (1H, br s, OH-4); ^{13}C nmr (Me_2CO-d_6) δ 41.6 (CH_2), 91.3, 96.7 (C-5, -7), 102.5 (C-2), 106.9 (C-3a), 115.5, 118.4 (C-2', -5'), 122.8 (C-6'), 126.1 (C-1'), 144.4, 145.0 (C-3', -4'), 158.6 (C-7a), 169.6, 172.6 (C-4,6), and 195.5 (C-3); *anal.*, C 56.59, H 4.24, calcd for $C_{15}H_{14}O_8$, C 55.90, H 4.38. When the reaction time and temperature were reduced to 21 h and 110°, respectively, hplc (30×0.4 cm MicroPak C-18, 2 ml/min, 30% aqueous MeOH) revealed the presence of **3** (retention volume 7.2 ml), **1** (23.6 ml) and **2** (29.0 ml) in the peak area ratio (5.5:5.4:1). A sample (10 mg) of dihydroquercetin kept for 10 min at 260° in a melting point capillary was shown by integration of its ^{1}H-nmr spectrum (in Me_2CO-d_6) to contain approximately equal amounts of **1** and **3**.

Because alphitonin [**3**] does not readily crystallize, its structure was verified by methylation with Me_2SO_4 and K_2CO_3 in Me_2CO, as described in the literature (15). The pentamethyl ether was obtained in 35% yield after purification by prep. tlc (toluene-Me_2CO-MeOH, 8:1:1, R_f 0.41) and recrystallization from EtOH, mp 112–113° [lit. (15) 119–120°]; eims (70 eV) *m/z* $[M]^+$ 374 (14), $[M^+-(MeO)_2C_6H_4CH_2]$ 223 (100), 195 (13), 152 (11), $[(MeO)_2C_6H_4CH_2]^+$ 151 (72); ir (nujol mull) 1708 cm^{-1} (C=O); uv λ max (95% EtOH) (log ε) 292 nm (4.21); (MeCN) 233 (4.12) and (4.23) 288 nm; ^{1}H nmr (Me_2CO-d_6) δ 3.00, 3.08 (2H, 2 × d, J=13.9 Hz, CH_2), 3.18 (3H, s, MeO-2), 3.68–3.85 (12H, 4×s, MeO-3', -4, -4', -6), 6.02, 6.19 (2H, 2 × d, J=2.2 Hz, H-5, -7), 6.67 (1H, dd, J=1.9 and 8.2 Hz, H-6'), 6.71 (1H, d, J=8.2 Hz, H-5'), and 6.79 (1H, d, J=1.9 Hz, H-2'); ^{13}C nmr (Me_2CO-d_6) δ 41.4 (CH_2), 51.9 (MeO-2), 55.5–56.5 (MeO-3', -4, -4', -6), 89.5, 93.3 (C-5, -7), 105.4 (C-2), 109.8 (C-3a), 112.4, 115.6 (C-2', -5'), 123.8 (C-6'), 126.9 (C-1'), 149.4, 149.7 (C-3', -4'), 159.7 (C-7a), 171.4, 174.3 (C-4, -6), and 192.5 (C-3); *anal.*, C 63.94, H 5.89, calcd for $C_{20}H_{22}O_7$, C 64.16, H 5.92.

Isomerization of 3',4',5,7-tetra-O-methyldihydroquercetin [**4**].—A small sample (10 mg) of pure racemic *trans*-3',4',5,7-tetra-*O*-methyldihydroquercetin [**4**], mp 170–171°, prepared by methylation of **1** with Me_2SO_4/K_2CO_3 in Me_2CO as described in the literature (18), was heated at 195° for 2 h. After cooling and dissolution in $CDCl_3$, the pale yellow product was analyzed by ^{1}H nmr and found to contain starting material [**4**] and 3',4,4',6-tetra-*O*-methylalphitonin [**5**] in the approximate ratio 3:2. No *cis*-3',4',5,7-tetra-*O*-methyldihydroquercetin (no ^{1}H-nmr signals in the region δ 4.2–5.8 other than the two doublets due to H-2 and H-3 of **4**) was detected in the mixture. ^{1}H-nmr data ($CDCl_3$) of **5**: δ 3.11, 3.19 (2H, 2 × d, J=14.0 Hz, CH_2), 3.84, 3.85, 3.86 (12H, 3 × s, MeO-3', -4, -4', -6), 5.93, 6.05 (2H, 2 × d, J=1.6 Hz, H-5, -7), 6.77 (1H, d, J=7.8 Hz, H-5'), 6.85 (1H, br s, H-2'), and 6.86 (1H, dd, J=7.5 and 1.5 Hz, H-6').

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