THE JOURNAL OF Organic Chemistry

VOLUME 50, NUMBER 2

JANUARY 25, 1985

Hypervalent Iodine Oxidation of Flavanone. Synthesis of *cis*- and *trans*-3-Hydroxyflavanones

Robert M. Moriarty* and Om Prakash

Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60680

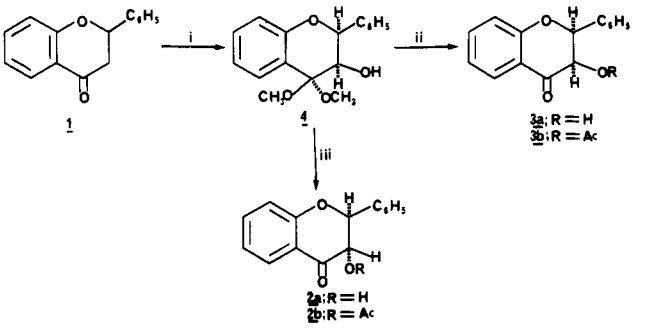
Received August 1, 1984

The synthesis of *cis*-3-hydroxyflavanone (**3a**) from flavanone (1) via acid-catalyzed hydrolysis of dimethyl acetal **4** formed by $C_6H_5I(OAc)_2$–KOH/CH_3OH oxidation is described. Under more vigorous hydrolytic conditions isomerization accompanies hydrolysis of **4** with the formation of *trans*-3-hydroxyflavanone (**2a**). The ^1H NMR spectra and mass spectra of **2a** and **3a** are discussed, as well as the mechanism of formation of **4** and isomerization of **3a** to **2a**.

Flavonoids affect the human liver microsomal hydroxylation of benzo[*a*]pyrene. Certain flavonoids such as flavanone, apigenin, chrysin, and myricetin inhibit the enzymic hydroxylation, while others such as flavanone and 7,8-benzoflavone cause significant stimulation in the hydroxylation of benzo[*a*]pyrene as well as aflatoxin B (to 2,3-dihydro-2,3-dihydroxyaflatoxin B) and the metabolic activation of aflatoxin B_1 to mutagenic products.[1,2] The mechanism by which these inhibitors and stimulators influence cytochrome P-450 is unknown.[1] These effects are of particular importance because flavonoids are a significant component of human diet.[3] Accordingly we have undertaken a study of the synthesis of flavanones hydroxylated in the C(3) position. It is possible that the stimulatory and inhibitory activity may be linked with metabolic hydroxylation of the flavanone, and it then becomes of importance to have such potential metabolites in hand. Furthermore, the hydroxylation of flavanones is not a well developed synthetic area and it is of interest to make available such compounds for the study of their effects upon human liver microsomal systems to establish oxygenase induction or inhibition.

Methods for the C_3-hydroxylation of flavanone (1) yield the trans product.[4] Thus alkaline hydrogen peroxide oxidation of 1 gives *trans*-3-hydroxyflavanone (**2a**) together with flavonol.[5] Lead tetraacetate oxidation of 1 gives *trans*-3-acetoxyflavanone (**2b**) along with flavone and isoflavone.[6a,b] *cis*-3-Hydroxyflavanone (**3a**) is not well described in the literature.[7,8] We report now a straight-

Scheme I[a]



[a] (i) $C_6H_5I(OAc)_2$, KOH/MeOH, 0 °C; (ii) 3 N HCl/EtOH, 30 min, or 50% HOAc, 50–70 °C, 6 h, or *p*-TsOH, acetone-H_2O, 3 days; (iii) concentrated HCl–acetone, 2 h.

(1) Buening, M. K.; Chang, R. L.; Huang, M-T.; Fortner, J. G.; Wood, A. W.; Conney, A. H. *Cancer Res.* **1981**, *41*, 67.

(2) Buening, M. K.; Fortner, J. G.; Kappas, A.; Conney, A. H. *Biochem. Biophys. Res. Commun.* **1978**, *82*, 348.

(3) Conney, A. H.; Pantuck, E. J.; Pantuck, C. B.; Buening, M.; Jerina, D. M.; Fortner, J. G.; Alvarez, A. P.; Anderson, K. E.; Kappas, A. "The Induction of Drug Metabolism Symposia Medica Hoechst"; Estabrook, R. W., Lindenlaub, E., Eds.; F. K. Schattauer Verlag: Stuttgart–New York, 1979; Vol. 14, pp 583–605.

(4) (a) Wagner, H. "The Flavanoids"; Harborne, J. B., Mabry, T. J., Mabry, H., Eds.; Academic Press: New York, 1975; Vol. I, pp 146–152 and references there in. (b) Whalley, W. B. "The Chemistry of Flavonoid Compounds"; Geissman, T. A. Ed.; The Macmillan Company: New York, 1962; pp 452–455 and references therein.

(5) Murakami M.; Irie, T. *Proc. Imp. Acad.* (*Tokyo*) **1935**, *11*, 229; *Chem. Abstr.* **1935**, *29*, 6598.

(6) (a) Oyamada, T. J. *J. Chem. Soc.*, **1943**, *64*, 331; *Chem. Abstr.* **1947**, *41*, 3797. (b) Cavill, G. W. K.; Dean, F. M.; McGookin, A. A.; Marshall, B. M.; Robertson, A. *J. Chem. Soc.* **1954**, 4573.

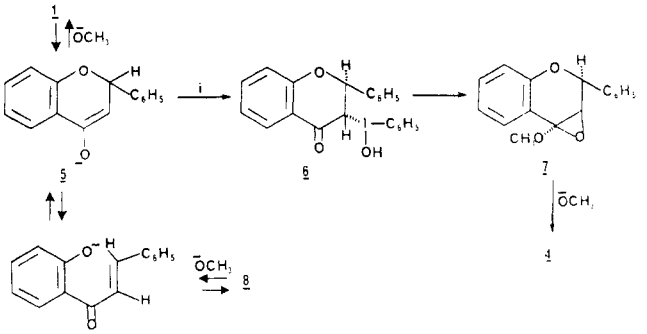
(7) Donnelly et al. [Donnelly, D. M. X.; Keenan, A. K.; Leahy, T.; Philibin, E. M. *Tetrahedron Lett.* **1970**, 1335] succeeded in making *cis*-3-methylflavanones by oxidation but could not prepare *cis*-3-hydroxyflavanone (**3a**).

0022-3263/85/1950-0151$01.50/0

forward synthesis of **3a** with the hypervalent oxidative method of Moriarty et al.,[9] namely, $C_6H_5I(OAc)_2$–KOH/CH_3OH. This procedure yields as the primary product the dimethyl acetal derivative **4** of **3a**,[10] which may be converted either to *cis*-3-hydroxyflavanone (**3a**) or *trans*-3-hydroxyflavanone (**2a**) depending upon the choice of hydrolytic conditions (Scheme I).

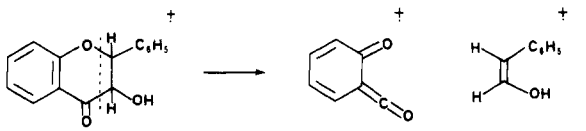
Reaction of **1** with 1.1 equiv of $C_6H_5I(OAc)_2$ in KOH/CH_3OH gave **4** in 68% yield. The structure of **4** is based upon an X-ray crystal structure determination.[10] The mass spectrum (discussed below) and ^1H NMR were also instructive particularly the C(2)–C(3) proton–proton coupling constant of 3.0 Hz which agrees with the assigned cis stereochemistry.

The stereochemistry of **4** may also be arrived at from its mechanism of formation which is considered to involve (a) enolate anion formation **1** → **5**, (b) addition of **5** to $C_6H_5I{=}O$ (formed in situ) at the face of the molecule anti to the C(2) phenyl ring (**5** → **6**) (c) addition of CH_3O^- to the carbonyl group **6** → **7** with intramolecular reductive elimination of C_6H_5I by the thus formed alkoxide anion (with inversion at C(3)), and finally, (d) by CH_3O^- ring opening of the epoxide with a second inversion of configuration **7** → **4**. Interestingly one may start with *o*-hydroxychalcone (**8**) and under the same reaction conditions, namely *i*, **4** is obtained in 65% yield. We interpret this as resulting from cyclization of the phenolate ion to give **5** which yields **4** in a 6-endo-Trig allowed process.[11]



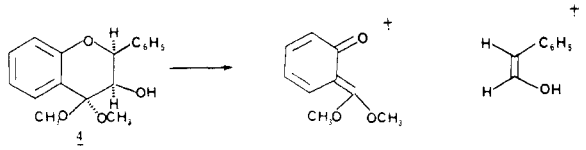
The principal objective of this study was to obtain *cis*-3-hydroxyflavone (**3a**). This could, in principle, be done by hydrolysis of the dimethyl acetal, **4** → **3a**, however, caution was called for based upon the reported inversion of configuration in the oximation of *cis*-3-methylflavanone to *trans*-3-methylflavanone oxime.[7] We established three sets of conditions (ii in Scheme I) for hydrolysis with retention of configuration in **4** → **3a**. Stronger conditions (iii in Scheme I) yielded the known *trans*-3-hydroxyflavanone (**2a**).[6] These two isomers, **3a**, mp 75–77 °C, obtained in 75% yield and **4b**, mp 185–187 °C, reported 185–187 °C,[12] had similar mass spectra (see below). The ^1H NMR spectra of **2a** and **3a** enabled a firm differentiation between the two. The coupling constant between the C(2) proton centered at 5.72 ppm and the C(3) proton centered at 4.82 ppm was 6.0 Hz the analogous coupling constant for the trans compound **2a** is 12 Hz.[12] The derived acetate **2b** also showed a 12-Hz coupling constant for the C(2) and C(3) protons. Although the cis coupling constant in **4** is 3.0 Hz, and 6.0 Hz in **3a**, it should be noted that cis coupling constants for the C(2)–C(3) protons in 3-substituted chromanones ranged from 2.6 to 5.4 Hz.[13]

The mass spectral fragmentation pattern for **2a** relative to **3a** did not show significant mutual differences. An important fragmentation was the retro-Diels-Alder cleavage (which occurred for both C(3) stereoisomers).

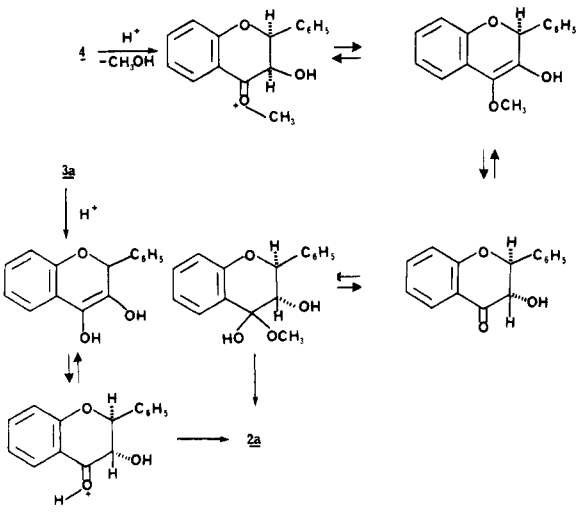


m/z = 120 (33) *m/z* = 240 (16)
m/z + 1 = 121 (100)

The retro-Diels-Alder pathway was also observed by Buset et al.[8b] Comparison of **4** with **2a** and **3a** with regard to the retro-Diels-Alder process is instructive. In this case the geminal dimethoxy groups stablize the positive resulting fragment.



The formation of **2** in the hydrolysis of **4** may result from the following type of process.



Finally the isomerization of **3a** to **2** may be effected by simple addition of concentrated HCl to an acetone solution of **3a** at room temperature. The trans product **2a** crystallized out of solution after 15 min. Thus we have a straightforward procedure for obtaining both C(3) isomers **2a** and **3a**, respectively.

(8) There are two reports on *cis*-3-hydroxyflavanone (**3a**): (a) A Japanese patent [Umino, N.; Ito, N.; Ishida, R. Japan Kokai, 7 562 977, May, 1975; *Chem. Abstr.* **1975**, *83*, 1788252] describe the preparation of **3a** as an antiinflammatory agent. The method is very lengthy and involves the preparation of 3-(methylsulfenyl)flavanone [Amino, N.; Ito, N.; Ishida, R. Japan Kodai, 7 562 975, May, 1975; *Chem. Abstr.* **1975**, *83*, 178826a] which is then treated with acetic anhydride in the presence of sulfuric acid and the product thus obtained is converted into *cis*-3-acetoxyflavanone (**3b**). On deacetylation **3b** gives **3a**. (b) In this report [Buset, H.; Scheline, R. R. *Biomed. Mass Spectrom.* **1979** *6*, 213] **3a** is identified by its mass spectrum as a urinary metabolite of flavanone (**1**) in the rat. No confirmation comparison with an authentic sample was made.

(9) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283. Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Commun.* **1981**, 641. Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686. Moriarty, R. M.; Hu, H. *Tetrahedron Lett.* **1981**, *22*, 2747. Moriarty, R. M.; Hou, K. C. *Tetrahedron Lett.* **1984**, *25*, 691.

(10) Moriarty, R. M.; Prakash, O.; Freeman, W. A. *J. Chem. Soc., Chem. Commun.* **1984**, 927.

(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(12) (a) An authentic sample of **2a** was synthesized for establishment of this trans coupling constant [Gripenberg, J. *Acta Chem. Scand.* **1953**, *7*, 1323]. (b) The coupling constant values of various *trans*-3-(hydroxymethoxy)flavanones, reported by Clark et al. [Clark, J. W.; Lewis, L.; Jackman, M.; Spotswood, T. M. *Aust. J. Chem.* **1964**, *17*, 632] are in agreement.

(13) Katrizky, A. R.; Ternai, B. *J. Heterocycl. Chem.* **1968**, *5*, 745.

Experimental Section

Melting points are uncorrected. The IR spectra were obtained with a Unicam SP1000 spectrophotometer. The ^1H NMR spectra were recorded on a Varian A-60 spectrometer with Me_4Si as an internal standard. Mass spectra were measured with a Hewlett Packard GC/MS 5985 apparatus at 70 eV.

Flavanone (1) and iodobenzene diacetate are commercial products (Aldrich). *o*-Hydroxychalcone[14] was prepared by the reported procedure.

***cis*-3-Hydroxyflavanone Dimethyl Acetal (4). Method A (From Flavanone (1)).** Flavanone (1) (0.02 mol. 4.48 g) was dissolved in 100 mL of absolute methanol and added dropwise to a stirred solution of potassium hydroxide (0.06 mol, 3.36 g) in 50 mL of methanol over a period of 15 min at 5–10 °C. After the solution had stirred for an additional 10 min, iodobenzene diacetate (0.022 mol, 7.0 g) was added in 4 portions during 10 min and the resulting mixture was allowed to stir overnight. Then most of the methanol was removed in vacuo and to the residue was added 100 mL of water. A yellow solid separated from solution upon addition of 25 mL of cold hexane with stirring. The solid was filtered, washed with cold water (20 mL) and cold hexane (20 mL), and dried. The aqueous layer was extracted with chloroform (3 × 25 mL) and the chloroform extracts were dried ($MgSO_4$) and evaporated in vacuo to give additional product. The combined crude material upon recrystallation from hexane yielded 3.88 g (68% yield) of 4 as a white crystalline compound, mp 126–127 °C.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.02; H, 6.29. Found: C, 70.91; H, 6.40. IR (Nujol): 3500 cm^{-1} (OH, str); NMR ($CDCl_3$) δ 3.2 (3 H, s, C_4 α-OCH_3), 3.38 (3 H, s, C_4 β-OCH_3), 4.05 (1 H, dd, C_3-H), 6.8–7.65 (9-H, aromatic protons); NMR ($CDCl_3$–D_2O) δ 4.05 (d, 1 H, d, C_3-H), doublet at 1.8 disappears; MS, *m/z* 286 (M^+, 3), 255 (3), 167 (90), 166 (60), 134 (55), 121 (100), 120 (18), 106 (16), 91 (90), 78 (23), 77 (86).

Method B (From *o*-Hydroxychalcone (8)). A solution of *o*-hydroxychalcone (8) (0.01 mol, 2.24 g) in methanol (50 mL) was added dropwise to a stirred solution of potassium hydroxide (0.03 mol, 1.68 g) in 30 mL of methanol over a period of 15 min at 5–10 °C. The resulting yellow-brown solution was stirred for 10 min and then was added iodobenzene diacetate (0.011 mol, 3.45 g) in four portions during 10 min. The reaction mixture was stirred over night at room temperature and worked up according to method A to yield 4, mp 126–127 °C, in 65% yield (1.85 g).

***cis*-3-Hydroxyflavanone (3a). Method A.** To a solution of 0.005 mol (1.43 g) of 4 in 30 mL of ethanol was added 10 mL of 3 N hydrochloric acid. After the reaction mixture was stirred for 30 min at room temperature, 80 mL of water was added and the solution was stirred for a further 10–15 min, during which time a white solid separated. This crystalline solid was filtered and dried to afford 1.0 g, mp 74–76 °C. Recrystallization from hexane gave 0.9 g (75% yield), mp 75–77 °C.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.00; H, 5.00. Found: C, 75.05; H, 5.04. IR (Nujol) cm^{-1} 3430–3480 (OH, str), 1695 (C=O, str); ^1H NMR ($CDCl_3$) δ 4.82 (1 H, d, C_3-H), 5.72 (1 H d, C_2-H), 3.52 (1 H, OH, disappears with D_2O) (J_{2-3} = 6 H), 6.85–7.85 (9 H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ[15] 72.69 (C_3), 80.94 (C_2), 106.01 (=C—C=O), 160.72 (=CO), 192.52 (O=C_4), and aromatic carbons between 118.01 or 136.81; MS, M^+ *m/z* 240 (16), 211 (55), 133 (39), 121 (100), 120 (33), 91 (49), 78, 77.

Method B. A mixture of 4 (0.005 mol, 1.43 g) and 40 mL of 50% acetic acid was stirred at 60–70 °C for 6 h. The resulting solution after cooling was mixed with 40 mL of water and extracted with ether (3 × 25 mL). The ether extracts were combined and washed with water, aqueous sodium bicarbonate, and water, dried ($MgSO_4$), and concentrated in vacuo to yield 1 g of an oil which on crystallization from hexane yielded 0.85 g (71%) of 3, mp 75–77 °C. Spectral properties of this product were identical with compound **3a** obtained in the previous experiment.

Method C. A mixture of 4 (0.005 mol, 1.43 g) and 50 mg of *p*-toluenesulfonic acid was dissolved in acetone (100 mL) and then 2 mL of water was added. After the solution was kept stirring for 3 days, the solvent was removed in vacuo. Aqueous sodium bicarbonate (5%) solution was added to the residue until basic and the solution was extracted with ether (3 × 25 mL). The ether extract was dried and the solvent removed to yield viscous oil which upon crystallization from hexane gave 0.96 g of **3a**, mp 75–77 °C.

***cis*-3-Acetoxyflavanone (3b).** To a solution of *cis*-3-hydroxyflavanone (**3a**) (1 mmol, 0.24 g) in chloroform (10 mL) was added 0.5 mL of acetic anhydride and one drop of pyridine and the solution was refluxed for 3 h. The chloroform was evaporated in vacuo and then crushed ice was added. The mixture was stirred for 10 min and then 20 mL of 5% aqueous sodium bicarbonate solution was added. An oil separated and extraction with chloroform (3 × 15 mL) followed by drying and concentration in vacuo gave a gummy mass which was crystallized from hexane or methanol to yield 0.174 (62%) of **3b**, mp 96–98 °C.[16]

Anal. Calcd for $C_{17}H_{14}O_3$: C, 72.34; H, 4.96. Found: C, 72.53; H, 5.01. IR (KBr) cm^{-1} 1680 (C_4=O, str) 1750 (carbonyl str in (O=)CCH_3); NMR ($CDCl_3$) δ 1.96 (3 H, s, $C_3OC(=O)CH_3$), 5.55 (1 H, d, C_3-H), 5.76 (1 H, d, C_2-H), (J_{2-3} = 6 H) 6.8–8.3 (9 aromatic protons); MS, *m/z* 282 (M^+, 14) 240 (M – CH_2=C=O, 38), 223 (6), 211 (37), 176 (23) 134 (12), 121 (100), 120 (79).

***trans*-3-Hydroxyflavanone (2a).** A solution (0.002 mol, 0.57 g) of 4 in 10 mL of acetone was treated with 2 mL of concentrated hydrochloric acid. The resulting solution was kept for 2 h at room temperature. During this time a white crystalline product separated. Filtration, washing with cold acetone (5 mL), and drying gave 0.43 g (90% yield) of **2a**: mp 185–187 °C;[12] IR (Nujol) cm^{-1} 3675 (OH, str), 1690 (C=O, str); NMR ($CDCl_3$) 4.58 (1 H, d, C_3H), 5.12 (1 H, d, C_2-H), 6.9–8.0 (9 H, aromatic protons); MS, M^+ 240 (23), 211 (67), 133 (71), 121 (100), 120 (40), 91 (43), 78 (7), 77 (7).

***trans*-3-Acetoxyflavanone (2b).** This compound was prepared as described above for **3b** and had mp 96–97 °C, reported 97 °C,[16] and mmp 78–82 °C with **2a**.

Isomerization of *cis*-3-Hydroxyflavanone (3a → 2a). To a solution of **3a** (1.0 mmol, 0.24 g) in acetone (5 mL) was added 1 mL of concentrated hydrochloric acid and the mixture was allowed to stand at room temperature. After 15 min colorless crystalline product separated out from the solution. Crystals were filtered, washed with cold acetone (1 mL), and dried to yield 0.21 g of pure **2a**, mp 185–187 °C (mmp with authentic sample was undepressed).[12]

Acknowledgment. We thank the USAMRDC for support of this work under contract DAMD 17-83-C-3107 and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(14) Feuerstein, W.; Kostanecki, St. V. *Chem. Ber.* **1898**, *31*, 710.

(15) These assignments are based on the reported C^{13} NMR data on related compounds [Kingsbury, C. A.; Looker, J. H. *J. Org. Chem.* **1975**, *40*, 1120].

(16) Cavill et al.[6b] reported the melting point of 3-acetoxyflavanone as 97 °C without assigning the stereochemistry.