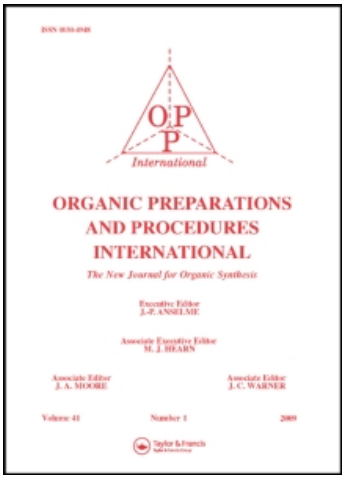

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HYDROXYMETHYLATION OF FLAVONES

György Litkei[a]; Tamás Patonay[a]; László Szilágyi[a]; Zoltán Dinya[a]
[a] Department of Organic Chemistry, Kossuth Laps University, Debrecen, HUNGARY

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HYDROXYMETHYLATION OF FLAVANONES

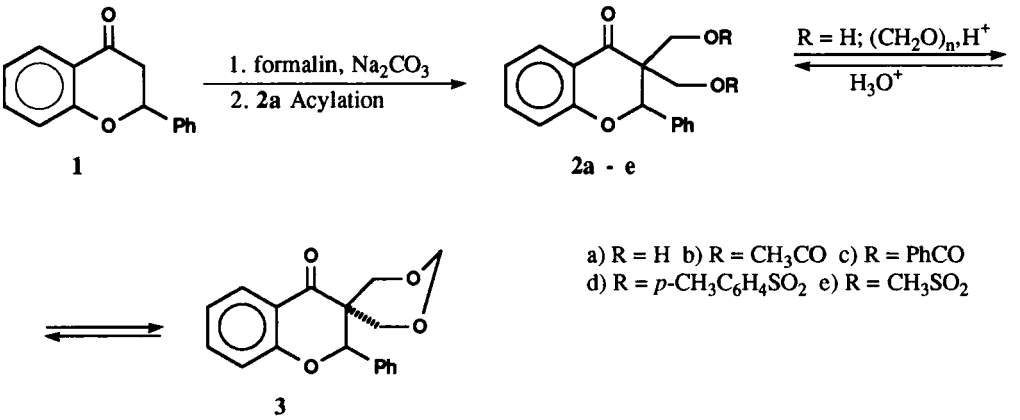
György Litkei*, Tamás Patonay, László Szilágyi and Zoltán Dinya

Department of Organic Chemistry
Kossuth Lajos University, H-4010 Debrecen, HUNGARY

In the context of a search for new derivatives in the 3-substituted flavanone and flavone series, a previous paper described the synthesis of Mannich compounds derived from flavanone.[1] Some of the C-3 substituted flavanones possessed remarkable pharmacological activity, which will be discussed in a forthcoming paper.[2]

It is well-known that the active methylene group of organic carbonyl compounds reacts with formaldehyde[6,7] or with paraformaldehyde in non-aqueous medium[3,4,8] under basic conditions to give α,α-bis(hydroxymethyl) derivatives as the major product.[3-7] Thus, acetophenone,[3] chromanone,[4,8] 1-thiochromanone,[4] indanone,[3] tetralone,[3,4,8] as well as acetone,[5] cyclohexanone,[6] cyclopentanone[6] and the 17-oxosteroids[7] can be readily converted into the corresponding a, α,α-bis(hydroxymethyl) analogues. The direct hydroxymethylation of flavanone has not been studied. Introduction of the hydroxymethyl group changes the hydrophilic character of flavanone, and furthermore, it provides possibility for the preparation of novel types of 3-substituted flavanones. This paper describes our work on the direct hydroxymethylation of flavanones.

The reaction of flavanone (**1**) with formaldehyde in dioxane in the presence of sodium carbonate gave 3,3-bis(hydroxymethyl)flavanone (**2a**); it was separated from the by-products by means of column chromatography. When 1,3-dioxane **3** was boiled in ethanol with dilute



1 **2a - e**

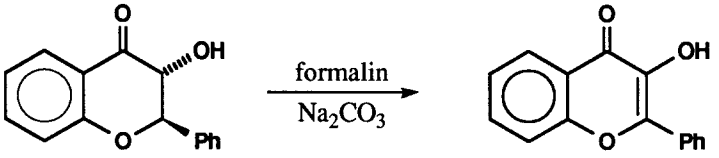
a) R = H b) R = CH_3CO c) R = PhCO
d) R = *p*-$CH_3C_6H_4SO_2$ e) R = CH_3SO_2

3

hydrochloric acid, the **2a** was also formed. Compound **2a** could also be obtained from **1** upon treatment with paraformaldehyde in dimethyl sulfoxide in the presence of potassium hydroxide. Acylation of the syrupy crude **2a** then gave crystalline acyl derivatives **2b-e**.

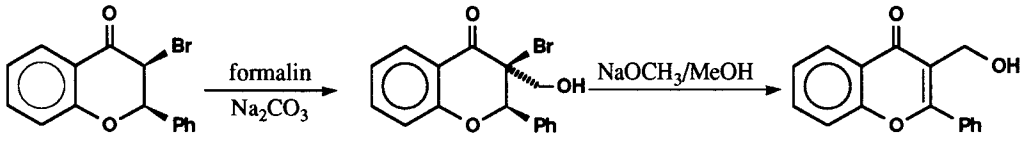
A recent paper[9] has reported that the acid-catalyzed hydroxymethylation of aliphatic ketones gives exclusively β-hydroxyketones. However, to our surprise, the transformation of flavanone with paraformaldehyde in trifluoroacetic acid afforded the 1,3-dioxane **3**. This compound was also produced from **2a** with paraformaldehyde in the presence of *p*-toluenesulfonic acid, or from the crude **2a** under the conditions of the Ritter reaction performed in absolute ether-acetonitrile in the presence of conc. sulfuric acid. This latter reaction also indicates that **2a** does not give the expected Ritter product. Lumma and Ma[10] have shown the formation of similar 1,3-dioxanes upon treatment of unsymmetrical aliphatic ketones with formaldehyde in trifluoroacetic acid.

The reaction of 2,3-*trans*-3-hydroxyflavanone **4** with formaldehyde in methanol in the presence of sodium hydrogen carbonate led to dehydrogenation into 3-hydroxyflavone **5**.



4 **5**

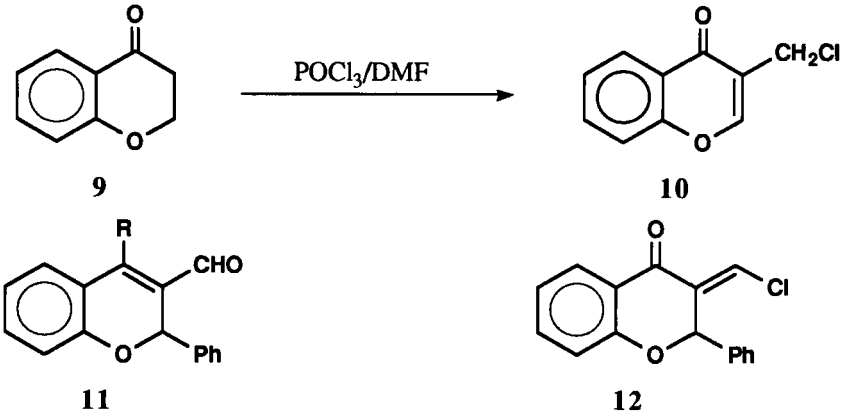
2,3-*trans*-3-Bromoflavanone did not react with formaldehyde, and the starting material was recovered. However, under similar conditions 2,3-*cis*-3-bromoflavanone **6** gave two products which were separated by means of column chromatography. The major product was shown to be 2,3-*cis*-3-bromo-3-hydroxymethylflavanone **7** whereas the structure of the minor product was identified as 3-hydroxymethylflavone **8**. The structure of **7** was also supported by the fact that upon treatment



6 **7** **8**

with sodium methoxide, flavone **8** was formed *via trans*-elimination of hydrogen bromide. Presumably the by-product flavone **8** was produced from the flavanone **7** during the reaction by the action of sodium hydrogen carbonate.

Recently Giles *et al.*[11] reported the preparation of 3-chloromethyl chromone **10** by means of treatment of chroman-4-one **9** with phosphorus oxychloride in N,N-dimethylformamide. In contrast, we found that upon heating of flavanone **1** in N,N-dimethylformamide with 5 equivalents of phosphorus oxychloride for 8 hrs, only (3-formyl-4-chloro)flav-3-ene **11a** was produced.



a) R = Cl b) R = OH

Under analogous conditions after 80 hrs, the reaction mixture did not contain the flav-3-ene **11a** but two new products were observed by TLC. Separation of this mixture by means of column chromatography then resulted in the isolation of (3-formyl-4-hydroxy)flav-3-ene **11b** and 3-chloromethyleneflavanone **12** in pure form. Further transformations of **2a-e** are in progress.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Bruker WP 200 SY spectrometer at 200 MHz, by using TMS as the internal standard (δ = 0.00 ppm). IR spectra were recorded with a Perkin-Elmer 283 instrument. Mass spectra were obtained with a VG-7035 (VG Analytical, Manchester) mass spectrometer, electron impact at 70 eV. Kieselgel 40 or 60 (Merck, 0.063-0.2 mm) was used for column chromatography. TLC was performed on Kieselgel 60 F_{254} (DC-Alurolle, Merck).

3,3-*bis*(Hydroxymethyl)flavanone 2a.- a) A mixture of flavanone **1** (23.5 mmol), 37% aqueous formaldehyde (50 mL) and sodium carbonate (5 g) in dioxane (200 mL) was stirred at room temperature for 24 hrs. The reaction was monitored by thin layer chromatography (4:1 toluene-ethyl acetate). After removal of the solid materials by filtration, the mixture was poured into dilute aqueous hydrochloric acid (250 mL) and extracted with dichloromethane. The dried ($MgSO_4$) organic phase was concentrated and the colorless syrupy residue (yield 90%) was purified by column chromatography (10:1 benzene-methanol) to afford pure **2a**, mp. 127-129° (MeOH). IR (KBr): (br) 3360 (OH), 1665 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.0-8.0 (m, 9H, ArH), 5.60 (s, 1H, C-2-H), 4. 10 (d, 1H, J = 10 Hz), 3.95 (d, 1H, J = 10 Hz, CH_2), 3.60 (m, 2H, CH_2), 2.80 (1H, OH, exchanges with D_2O), 2.40 (lH, OH, exchanges with D_2O).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.15; H, 5.55

b) To a stirred mixture of paraformaldehyde (35 mmol), potassium hydroxide (75 mg), ethanol (0.5

mL) and dimethyl sulfoxide (5 mL) a solution of flavanone **1** (15 mmol) in dimethyl sulfoxide (5 mL) was added dropwise. After stirring for 1 hr at room temperature the red solution was diluted with aqueous hydrochloric acid. The precipitate was purified by means of column chromatography as previously (70%), mp. 127° (MeOH). ^{1}H NMR ($CDCl_3$): δ 7.0-8.0 (m, 9H, ArH), 5.65 (s, 1H, C-2-H), 4.15 (d, 1H, J = 10 Hz), 4.05 (d, 1H, J = 10 Hz, CH_2), 3.70 (d, 1H, J = 2 Hz), 3.55 (d, IH, J = 2 Hz), 2.85 (lH, OH, exchanges with D_2O), 2.20 (lH, OH, exchanges with D_2O).
MS: 284, 253, 235, 223, 207, 159, 121 (100 %).

3,3-*bis*(Acetoxymethyl)flavanone 2b.- A mixture of crude 3,3-bis(hydroxymethyl)flavanone **2a** (10 mmol) acetic anhydride (20 mL) and abs. pyridine (2 mL) was kept on the hot water bath for 2 hrs. After pouring into water the precipitated amorphous product was isolated by filtration and then purified by column chromatography (15:1 benzene-ethyl acetate) to afford 5 mmol (50%) of **2b** as homogeneous syrup. IR (nujol): 1710, 1690 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.0-8.0 (m, 9H, ArH), 5.70 (s, 1H, C-2-H), 4.95 (d, 1H, J = 10 Hz), 4.55 (d, 1H, J = 10 Hz, CH_2), 4.10 (d, 1H, J = 10 Hz), 3.80 (d, 1H, J = 10 Hz, CH_2), 2.10 (s, 3H, CH_3), 1.90 (s, 3H, CH_3). MS: 368.

3,3-*bis*(Benzoyloxymethyl)flavanone 2c.- To an ice-cold solution of crude 3,3-bis(hydroxymethyl)flavanone **2a** (10 mmol) in abs. pyridine (20 mL) benzoyl chloride (25 mmol) was added dropwise. After standing for overnight the reaction mixture was poured onto ice, the solid material was filtered off and crystallized from methanol to give 7.5 mmol (70%) of **2c**, mp. 65-67°. IR (KBr): 1725, 1685 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.05-8.0 (m, 19H, ArH), 5.90 (s, 1H, C-2-H), 5.25 (d, 1H, J =10 Hz), 4.75 (d, 1H, J = 10 Hz, CH_2), 4. 40 (d, 1H, J = 10 Hz), 4. 20 (d, 1H, J = 10 Hz, CH_2).

Anal. Calcd. for $C_{31}H_{24}O_6$: C, 75.59; H, 4.91. Found: C, 75.62; H, 5.10

3,3-*bis*(Tosyloxymethyl)flavanone 2d.- A mixture of crude 3,3-bis(hydroxymethyl)flavanone **2a** (10 mmol), chloroform (20 mL), pyridine (3.7 mL) and tosyl chloride (25 mmol) was stirred at room temperature for 24 hrs. After addition of a further amount of tosyl chloride (5 mmol), the reaction mixture was stirred for one day and then poured into water and extracted with chloroform. The organic layer was washed with aqueous sodium hydrogen carbonate and water. After drying and evaporation the residue was crystallized from ethanol to yield 8.3 mmol (83%) of **2d**, mp. 154-156°. IR (KBr): 1692 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.80-7.70 (m, 17H, ArH), 5.70 (s, 1H, C-2-H), 4.60 (d, 1H, J = 9 Hz), 4.30 (d, 1H, J = 9 Hz, CH_2), 3.80 (d, 1H, J = 9 Hz), 3.70 (d, 1H, J = 9 Hz, CH_2).

Anal. Calcd. for $C_{31}H_{28}O_8S_2$: C, 62.83; H, 4.76; S, 10.81. Found: C, 63.05; H, 4.59; S, 10.44

3,3-*bis*(Mesyloxymethyl)flavanone 2e.- By applying the previous procedure but using methanesulfonyl chloride, the reaction mixture was kept at 0° for 2 hrs and then allowed to stay at room temperature for 5 hrs. After working up as described above for **2d** the residue was crystallized from a mixture of ethyl acetate and hexane to afford 7.5 mmol (75%) of **2e**, mp. 97-100°. IR (KBr): 1690

(CO) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 7.0-8.0 (m, 9H, ArH), 5.70 (s, 1H, C-2-H), 4.95 (d, 1H, J = 10 Hz), 4.65 (d, 1H, J = 10 Hz, CH_2), 4.20 (d, 1H, J = 10 Hz), 3.95 (d, 1H, J = 10 Hz, CH_2), 3.15 (s, 3H, CH_3), 2.80 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{20}O_8S_2$: C, 51.80; H, 4.57; S, 14.55. Found: C, 52.05; H, 4.65; S, 14.35

Spiro[flavanone-3,5'-(1',3'-dioxacyclohexane)] 3.- a) To a stirred solution of crude 3,3-bis(hydroxymethyl)flavanone **2a** (15 mmol) in abs. ether (75 mL) and acetonitrile (5 mL) a solution of conc. sulfuric acid (5 mL) in abs. ether (25 mL) was added dropwise with ice-cooling. Stirring was continued at room temperature for 24 hrs, and after pouring the reaction mixture onto ice, it was extracted with dichloromethane, the organic phase was washed with water and aqueous sodium hydrogen carbonate and dried. Following evaporation, the residue was purified by means of column chromatography (10:1 benzene-methanol) to yield 6 mmol (40%) of **3**, mp. 134-136° (MeOH).

b) A mixture of flavanone **1** (10 mmol), paraformaldehyde (30 mmol) in trifluoroacetic acid (2.5 mL) was reacted on the water bath for 24 hrs. The reaction mixture was then poured into an aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. After washing and drying, the solvent was evaporated and the residue was purified by means of column chromatography to give 5 mmol (50%) of **3**, mp. 134-136° (MeOH).

c) Crude 3,3-bis(hydroxymethyl)flavanone **2a** (5 mmol) was treated with paraformaldehyde (5.5 mmol) in benzene (50 mL) in the presence of *p*-toluenesulfonic acid (1 g) in a reaction vessel equipped with a Dean-Stark apparatus at 110° for 3 hrs. After washing with water, aqueous sodium hydrogen carbonate and drying, the organic solvent was distilled off and the residue was crystallized from methanol to yield 3.75 mmol (75%) of **3**, mp. 134-136°. IR (KBr): 1675 (CO) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 6.95-7.85 (m, 9H, ArH), 6.12 (s, 1H, C-2-H), 5.10 (d, IH, J = 5.0 Hz), 4.70 (d, 1H, J = 5.0 Hz), O-CH_2-O), 4.30 (d, 2H, J = 10 Hz, CH_2), 3.80 (d, 2H, J = 10 Hz, CH_2). MS: 296, 265, 250, 235, 223, 207, 159, 121 (100%).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.88; H, 5.39

Reaction of 2,3-*trans*-3-Hydroxyflavanone 4 with Formaldehyde. Isolation of 3-Hydroxyflavone 5.- 2,3-*trans*-3-Hydroxyflavanone[13] **4** (15 mmol) was reacted with 35% aqueous formaldehyde (40 mL) in methanol (125 mL) at room temperature for 24 hrs in the presence of sodium hydrogen carbonate (4 g). The reaction mixture was poured onto ice, the solid material was filtered off and crystallized from ethanol to afford 10 mmol (75%) of **5**, mp. 169-171°, lit.[14] mp. 169-170°. The mixed mp. of the product with a sample of lit. 3-hydroxyflavone showed no depression.

Reaction of 2,3-*cis*-3-Bromoflavanone 6 with Formaldehyde. Isolation of 2,3-*cis*-3-Bromo-3-hydroxymethylflavanone 7.- 2,3-*cis*-3-Bromoflavanone[12] **6** (30 mmol) was reacted with 35% aqueous formaldehyde (80 mL) in methanol (250 mL) at room temperature for 24 hrs in the presence

of sodium hydrogen carbonate (8 g). After addition of water, the mixture was extracted dichloromethane and the organic layer was dried and concentrated. The residue was submitted to column chromatography (4:1 toluene-ethyl acetate) to give 2,3-*cis*-3-bromo-3-hydroxymethyl-flavanone **7** and 3-hydroxymethylflavone **8**.

Compound **7**: yield 52%, mp. 131-133° (hexane), lit.[4] mp. 132-134°. IR (KBr): 3420 (OH), 1673 (CO) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 7.10-8.90 (m, 9H, ArH), 5. 70 (s, 1H, C-2-H), 4. 50 (d, 1H, CH_2), 3. 45 (d, 1H, CH_2, J_{AB} = 10 Hz). MS: 333 (10%).

Anal. Calcd. for $C_{16}H_{13}BrO_3$: C, 57.68; H, 3.93; Br, 23.97. Found: C, 57.75; H, 3.84; Br, 24.09

Compound **8**: yield 22%, mp. 163-164° (hexane), lit .[4] mp. 160-163°. IR (KBr): 3386 (OH), 1620 (CO) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 7.45-8.30 (m, 9H, ArH), 4.70 (d, 2H, CH_2), 3.60 (bs, 1H, exchanges with D_2O).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.17; H, 4.79. Found: C, 76.25; H, 4.82

3-Hydroxymethylflavone 8.- A solution of flavanone **7** (1 mmol) in abs. methanol (15 mL) was treated with sodium methoxide (2 mmol) at room temperature for 48 hrs. The mixture was then acidified with dilute acetic acid, dilute with water and extracted with dichloromethane. After drying the organic layer was concentrated and the residue was crystallized from hexane to yield 0.6 mmol (60%) of **8**, mp. 162-164°. The mixed mp. of the product with a sample of flavanone **8**, obtained as described above, showed no depression. IR (KBr): 3385 (OH), 1620 (CO) cm^{-1}.

(3-Formyl-4-chloro)flav-3-ene 11a.- A mixture of flavanone **1** (20 mmol) and abs. N,N-dimethylformamide (25 mL) was reacted with phosphorous oxychloride (100 mmol) on the water bath for 8 hrs. The excess of the reagent was distilled off on a rotary evaporator, the residue was diluted with water (100 mL) and the resulting solution was kept on the water bath for 2 hrs. After cooling the mixture was extracted with ether and after washing and drying the organic solvent was removed by evaporation. The residue was purified by means of column chromatography (4:1 hexane-ethyl acetate) to give 7.2 mmol (36%) of **11a**, mp. 106-108° (hexane). IR (KBr): 1660 (CHO) cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 10.3 (s, 1H, CHO), 6.85-7.75 (m, 9H, ArH), 6.40 (s, IH, C-2-H). MS: 270, 241 (100%), 235, 205, 193.

Anal. Calcd. for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.09; Cl, 13.09. Found: C, 71.25; H, 4.19; Cl, 12.92

(3-Formyl-4-hydroxy)flav-3-ene 11b and 3-Chloromethyleneflavanone 12.- The product of the above reaction, conducted for 80 hrs was submitted to column chromatography (4:1 hexane-ethyl acetate) to afford **11b** (30%), mp. 122-123° (ethyl acetate-hexane) and **12** (25%), mp. 132-134° (hexane).

Compound **11b**: IR (KBr): 3432 (OH), 1638 (CHO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20-8.20 (m, 10H, ArH and CHO), 5.95 (s, 1H, C-2-H), 4.0 (bs, 1H exchanges with D_2O). MS: 252 (100%), 234, 205.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18, H, 4.79. Found C, 76.28; H, 4.58

Compound **12**: IR (KBr): 1650 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30-8.25 (m, 9H, ArH), 8.10 (s, 1H, CHCl), 6.40 (s, 1H, C-2-H). MS: 270, 235 (100%).

Anal. Calcd. for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.09, Cl; 13.09. Found: C, 70.82; H, 4.11; Cl, 12.60

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