DEMETHYLATION-SULFONATION OF 2',3',4'-TRIMETHOXY-FLAVONES

Amar Habsaoui,* José Luis Franquet Cami, Emile M. Gaydou, and Jean-Claude Wallet

Laboratoire de Phytochimie, Case 412,
Faculté des Sciences et Techniques de Saint-Jérôme
Avenue Escadrille Normandie-Niemen
13397 Marseille Cedex 20, France

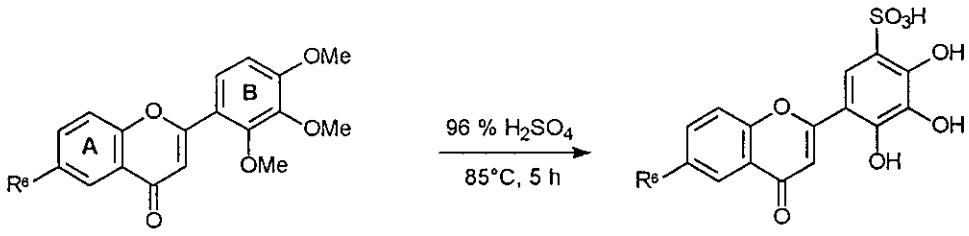
Abstract - Total demethylation of 2',3',4'-trimethoxyflavones with sulfuric acid was realised at mild temperature giving respective 2',3',4'-trihydroxyflavone-5'-sulfonic acids. A multi steps mechanism is proposed in the light of earlier results and the complete assignment of the ^{1}H and ^{13}C NMR spectra of a suggested 3'-hydroxy-2',4'-dimethoxy intermediate.

INTRODUCTION

Flavonoids have numerous interactions with different enzymes and hydroxyflavones are known having antioxidant properties.[1,2] Their chelating action with metal ions and their potential reactivity with oxygen species have been demonstrated in several biochemical processes. These activities seem to require an *ortho*-dihydroxy group, particularly at the 3'- and 4'-positions. Moreover, a pyrogallol moiety on the B-ring of flavones gives rise to radical scavenger activity.[3] Little is known about 2',3',4'-hydroxyflavones which are not widespread in plants.[4] In order to synthesize 2',3',4'-trihydroxy-substituted flavones we have applied the reaction of demethylation-sulfonation[5] to a series of 2',3',4'-trimethoxyflavones. It resulted from this reaction a new series of 2',3',4'-trihydroxyflavone-5'-sulfonic acids. The presence of a sulfonic group should improve their solubility in water and modify their biological activities. Sulfonated molecules are potential pharmaceutical agents.[6,7] Interactions of sulfonated azo dyes with amino acids have recently been published giving useful details in understanding the biomolecular process.[8] Former sulfonated azo dyes have been reinvestigated. Evans Blue and Congo Red dyes were able to bind to the HIV protein and reverse transcriptase, inhibiting viral replication.[9,10] In this paper, using ^{13}C NMR, heteronuclear ^{1}H-^{13}C correlation experiments and, earlier results about sulfonation of 2',3'-dimethoxyflavones[5] we propose a mechanism for the demethylation-sulfonation.

RESULTS AND DISCUSSION

When 2',3',4'-trimethoxyflavones are submitted to sulfonation they give the corresponding new 2',3',4'-trihydroxyflavone-5'-sulfonic acids (Scheme 1).

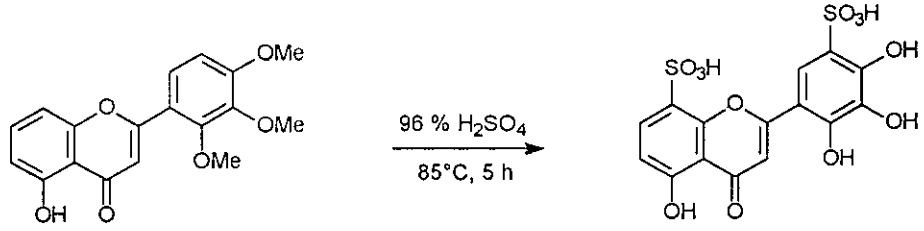


R6 = H(1a), F(2a), Cl(3a), Br(4a)
OH(5a), Me(6a)

1d - 6d

Scheme 1

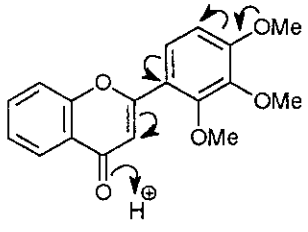
However with 5-hydroxy-2',3',4'-trimethoxyflavone a disulfonic flavone was obtained (Scheme 2).



7a **7b**

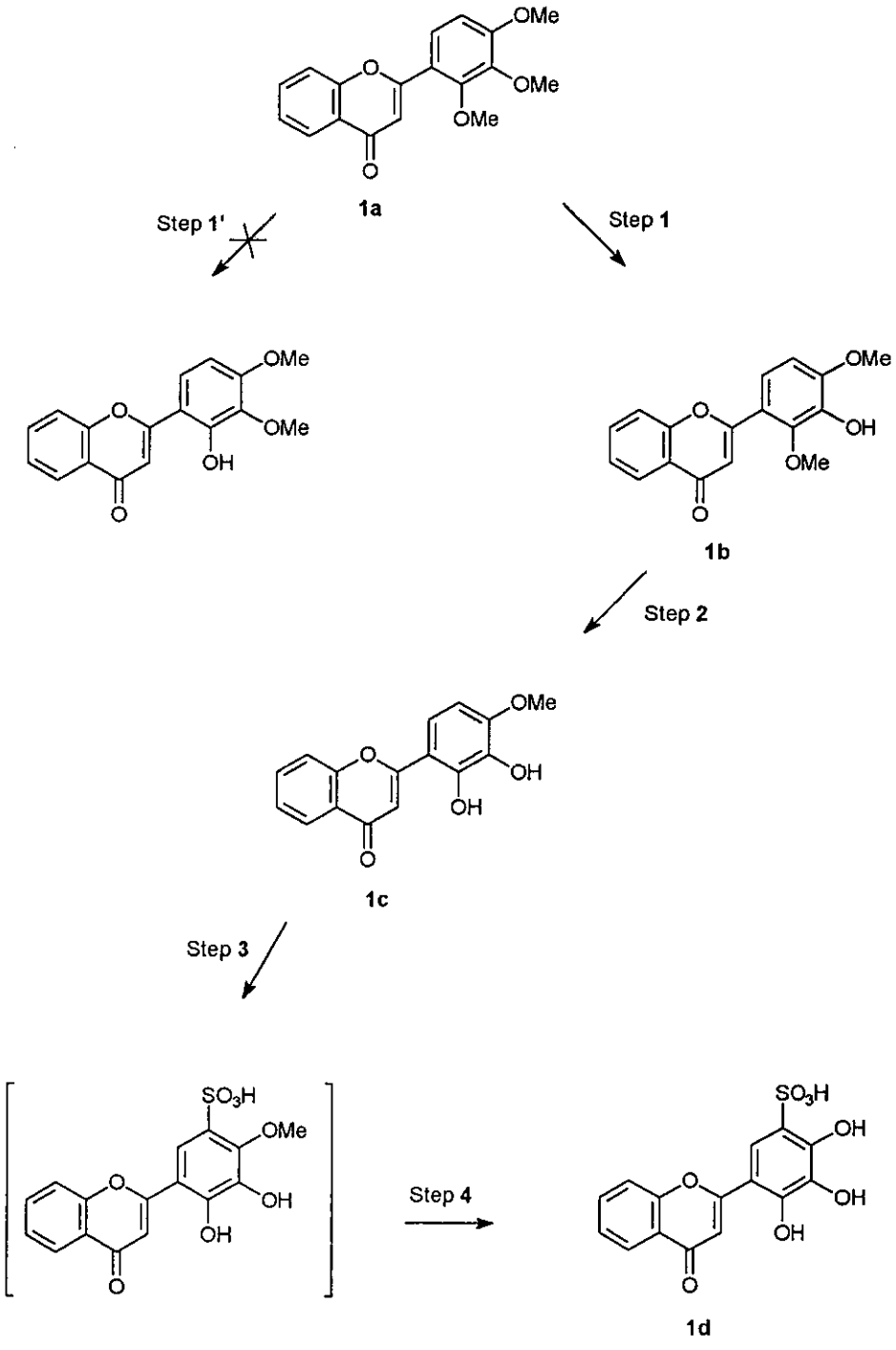
Scheme 2

Sulfonation on B-ring occurs at 5'-position. A methoxyl group (or a hydroxyl group when the demethylation has taken place) is an *ortho* and *para* directing substituent, so the 5'-position is favored (*para* to the 2'-position and *ortho* to the 4'-position).



Scheme 3

Moreover the stabilisation of the negative charge on the carbonyl oxygen by protons from acidic medium induces a modification of the electronic density along the C4-C3-C2-C1'-C6'-C5' chain (Scheme 3). The position of the sulfonic group was confirmed by ^{1}H and ^{13}C NMR. The H-3 proton in these 2',3',4'-


OMe
OMe
OMe
O
1a
Step 1'
Step 1
OMe
OMe
OH
O
OMe
OH
OMe
O
1b
Step 2
OMe
OH
OH
O
1c
Step 3
SO3H
OMe
OH
OH
O
Step 4
SO3H
OH
OH
OH
O
1d

Scheme 4

trihydroxyflavone-5'-sulfonic acids appears between 6.96-7.15 ppm. This is characteristic of flavones which possess a 2'-substituent without a 6'-substituent.[11] The chemical shift of the carbon at C-3 reflects also the substitution pattern at C2' and C-6'. Values of chemical shifts are in the range expected for flavones with a 2'-methoxy group but without substituent at the 6'-position.[12] A plausible reaction sequence is proposed on the basis of products formed and spectral data (Scheme 4). Monodemethylation affords the 3'-hydroxy-2',4'-dimethoxyflavone (**1b**) which was characterized by ^{1}H and ^{13}C NMR spectral correlations.[13] The second step affords the 2',3'-dihydroxy-4'-methoxyflavone (**1c**) since di-*ortho*-methoxy group is easier to cleave. Step 3 corresponds to the fixation of the sulfonic group *para* to the 2'-hydroxy group. This can be achieved if the 4'-methoxy group is in an out-of-plane conformation. Such a conformation is promoted by protons which stabilize the negative charge on the methoxyl oxygen. Then, the 4'-methoxy group also hindered by the sulfonic group (Step 3) is easily cleaved to give the 2',3',4'-trihydroxyflavone-5'-sulfonic acid (**1d**). 2',3',4'-Trihydroxyflavone-5'-sulfonic acids have a zwitterionic structure. This has been confirmed by a ^{13}C NMR study of the 6-fluoro-2',3',4'-trihydroxyflavone-5'-sulfonic acid.[14]

EXPERIMENTAL

Materials.

2-Hydroxyacetophenones and benzoic acids were purchased from Aldrich or Merck.

2',3',4'-Trimethoxyflavones and their corresponding sulfonic acids were obtained following the same experimental procedure as previously reported.[5] They were both recrystallized from ethanol. All the flavone sulfonic acids are yellow solids. Single isomers were obtained for all compounds. The ^{13}C NMR spectra were obtained at 25°C on a Bruker AC-200 spectrometer operating at 50.32 MHz using 0.5M solutions in DMSO-d_6 and taking the solvent signal as reference. The ^{1}H and ^{13}C chemical shifts of the solvent were used as a secondary reference and referred to the TMS signal from the usual relationships.[15] Resonance multiplicities of carbon were obtained using DEPT pulse sequence. For the DEPT spectra the width of a ^{13}C 90° pulse was 6μs, the width of a ^{1}H 90° pulse was 5.5 μs and the $(2J)^{-1}$ delay was set equal to 3.1 ms. Typical experimental conditions for ^{13}C spectra recording were as follows : spectral width, 12KHz; pulse width, 4μs; acquisition time, 0.68s; number of transients, 200-500; number of data points, 16K; ^{1}H CPD decoupling; no zero filling.

All melting points (uncorrected) were taken in open capillary tubes using an Electrotermal apparatus. Sulfonic derivatives were hygroscopic, they decomposed with melting points higher than 300°C. They were characterized as their *para*-toluidinium salts.[16] The 2',3',4'-Trihydroxyflavone-5'-sulfonic acid (**1a**) was dissolved in a minimum of solvent (methanol : water, 30 : 70). A saturated aqueous solution of *para*-toluidinium chloride was added. Fine crystals of the *para*-toluidinium salt of the flavone sulfonic acid precipitated. They were filtered and dried.

2',3',4'-Trimethoxyflavone (1a)

mp 96°C (39%)[17]

6-Fluoro-2',3',4'-trimethoxyflavone (2a)

mp 148°C (34%) **^{1}H-NMR** (DMSO-d_6) δ 3.78, 3.86, 3.87(3s, 9H, 3xOCH_3), 6.77(s, 1H, H-3), 6.98(d, J=8.9 Hz, 1H, H-5'), 7.58(d, J=8.9 Hz, 1H, H-6'), 7.70(m, 1H, H-7), 7.70(m, 1H, H-8), 7.79(m, 1H, H-5); **^{13}C-NMR** (DMSO-d_6) δ 60.4, 61.0(2xOCH_3-2',3'), 56.0(OCH_3-4'), 108.2(C-5'), 109.0(d, J=24 Hz, C-5), 108.8(C-3), 121.7(d, J=8 Hz, C-8), 118.4(C-1'), 123.0(d, J=25 Hz, C-7), 124. 1(C-6'), 124.1(C-l0), 142.3(C-3'), 152.2(C-9), 152.2(C-2'), 158.8(d, J=-241.5 Hz, C-6), 156.0(C-4'), 160.8(C-2), 177.0(C-4). *Anal.* Calcd for $C_{18}H_{15}O_5F$: C, 65.45 ; H, 4.54. Found : C, 65.44; H, 4.52.

6-Chloro-2',3',4'-trimethoxyflavone (3a)

mp 118°C (34%) **^{1}H-NMR** (DMSO-d_6) δ 3.78, 3.85, 3.87(3s, 9H, 3xOCH_3), 6.78(s, 1H, H-3), 6.96(d, J=9.0 Hz, 1H, H-5'), 7.57(d, J=8.9 Hz, 1H, H-6'), 7.72(d, J=8.9 Hz, 1H, H-8), 7.80(dd, J=8.9 and 2.5 Hz, 1H, H-7), 7.89(d, J=2.5 Hz, 1H, H-5); **^{13}C-NMR** (DMSO-d_6) δ 56.1(OCH_3-4'), 60.5, 61.0(2xOCH_3-2',3'), 108.2(C-5'), 109.8(C-3), 117.6(C-1'), 120.8(C-8), 123.6(C-5), 124.1(C-10), 124. 3 (C-6'), 129.7(C-6), 133.9(C-7), 142.2(C-3'), 152.3(C-2'), 154.3(C-9), 156.3(C-4'), 161.4(C-2), 175.8(C-4). *Anal.* Calcd for $C_{18}H_{15}O_5Cl$: C, 62.33 ; H, 4.32. Found : C, 62.30 ; H, 4.29.

6-Bromo-2',3',4'-trimethoxyflavone (4a)

mp 113°C (33%) **^{1}H-NMR** (DMSO-d_6) δ 3.78, 3.86, 3.87(3s, 9H, 3xOCH_3), 6.79(s, 1H, H-3), 6.96(d, J=9.0 Hz, 1H, H-5'), 7.57(d, J=9.0 Hz, 1H, H-6'), 7.66(d, J=9.0 Hz, 1H, H-8), 7.91(dd, J=9.0 and 1.2 Hz, 1H, H-7), 8.04(d, J=2.3 Hz, 1H, H-5); **^{13}C-NMR** (DMSO-d_6) δ 56.0(OCH_3-4'), 60.4, 61.0(2xOCH_3-2',3'), 108.2(C-5'), 109.9(C-3), 117.5(C-1'), 117.6(C-6), 121.0(C-8), 124.3(C-6'), 124.5 (C-10), 126.7(C-5), 136.6(C-7), 142.1(C-3'), 152.3(C-2'), 154.6(C-9), 156.2(C-4'), 161.3(C-2), 175.6(C-4). *Anal.* Calcd for $C_{18}H_{15}O_5Br$: C, 55.24 ; H, 3.83. Found : C, 55.22; H, 3.82.

6-Hydroxy-2',3',4'-trimethoxyflavone (5a)

mp 204-206°C (30%)[17]

6-Methyl-2',3',4'-trimethoxyflavone (6a)

mp 105-106°C (35%) **^{1}H-NMR** (DMSO-d_6) δ 2.40(s, 3H, CH_3-6), 3.78, 3.85, 3.86(3s, 9H, 3xOCH_3), 6.73(s, 1H, H-3), 6.97(d, J=8.9 Hz, 1H, H-5'), 7.56(d, J=8.9 Hz, 1H, H-6'), 7.58(s, 2H, H-7,8), 7.79(d, J=0.6 Hz, 1H, H-5); **^{13}C-NMR** (DMSO-d_6) δ 20.3 (CH_3-6), 56.0(OCH_3-4'), 60.4, 61.0(2xOCH_3-2',3'), 108.2(C-5'), 109.9(C-3), 118.0(C-8), 118.1(C-1'), 122.7(C-10), 123.9(C-5), 124.1 (C-6'), 134.7(C-6), 135.0(C-7), 142.2(C-3'), 152.1(C-2'), 154.0(C-9), 156.0(C-4'), 160.9(C-2), 176.9(C-4). *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.93 ; H, 5.52. Found : C, 69.95; H, 5.51.

5-Hydroxy-2',3',4'-trimethoxyflavone (7a)

mp 144°C (29%)[17]

3'-Hydroxy-2',4'-dimethoxyflavone (1b)

mp 176°C (35%) **^{1}H-NMR** (DMSO-d_6) δ 3.79(s, 3H, OCH_3-4'), 3.86(s, 3H, OCH_3-2'), 6.78(s, 1H, H-3), 6.92(d, J=8.9 Hz, 1H, H-5'), 7.33(d, J=8.8 Hz, 1H, H-6'), 7.48(ddd, J=9.1, 7.0 and 1.3 Hz, 1H, H-6), 7.69(dd, J=8.4 and 0.8 Hz, 1H, H-8), 7.81(ddd, J=7.8, 6.9 and 1.7 Hz, 1H, H-7), 8.03(dd, J=7.9 and 1.5 Hz, 1H, H-5), 9.12(s, 1H, OH-3'); **^{13}C-NMR** (DMSO-d_6) δ 56.0(OCH_3-4'), 60.1(OCH_3-2'), 107.5(C-5'), 109.8(C-3), 118.0(C-1'), 118.3(C-8), 119.1(C-6'), 123.1(C-10), 124.7(C-5), 125. 3(C-6), 134.1(C-7), 139.9(C-3'), 146.7(C-2'), 151.6(C-4'), 155.8(C-9), 161.7(C-2), 177.0(C-4). *Anal.* Calcd for $C_{17}H_{14}O_5$: C, 68.45 ; H, 4.69. Found : C, 68.42; H, 4.65.

2',3'-Dihydroxy-4'-methoxyflavone (1c)

mp 256°C (32%) **^{1}H-NMR** (DMSO-d_6) δ 3.86(s, 3H, OCH_3), 6.70(d, J=9.1 Hz, 1H, H-5'), 7.11(s, 1H, H-3), 7.43(d, H=9.1 Hz, 1H, H-6'), 7.44(ddd, J=8.0, 6.8 and 1.4 Hz, 1H, H-6), 7.68(dd, J=8.4 and 1.2 Hz, 1H, H-8), 7.74(ddd, J=8.5, 6.8 and 1.6 Hz, 1H, H-7), 8.01(dd, J=7.8 and 1.5 Hz, 1H, H-5), 9.62, 9.10(2s, 2H, OH-2', OH-3'); **^{13}C-NMR** (DMSO-d_6) δ 55.9(OCH_3-4'), 103.5(C-5'), 109.7(C-3), 111.6(C-1'), 118.2(C-8), 118.7(C-6'), 123.1(C-10), 124.6(C-5), 125.0(C-6), 133.8(C3'), 134.0(C-7), 146.2(C-2'), 150.7(C-4'), 155.7(C-9), 161.1(C-2), 177.1(C-4). *Anal.* Calcd for $C_{16}H_{12}O_5$: C, 67.60 ; H, 4.22. Found : C, 67.49 ; H, 4.18.

2',3',4'-Trihydroxyflavone-5'-sulfonic acid (1d)

(90%) **^{1}H-NMR** (DMSO-d_6) δ 7.13(s, 1H, H-3), 7.50(ddd, J=8.0, 7.7 and 1.4 Hz, 1H, H-6), 7.62(s, 1H, H-6'), 7.71(dd, J=8.2 and 1.2 Hz, 1H, H-8), 7.79(ddd, J=8.4, 7.0 and 1.6 Hz, 1H, H-7), 8.01(dd, J=7.9 and 1.4 Hz, 1H, H-5); **^{13}C-NMR** (DMSO-d_6) δ 109.6(C-1'), 110.0(C-3), 117.2(C-6'), 118.4(C-8), 123.4(C-5'), 123.8(C-10), 125 0(C-6), 125.5(C-5), 133.1(C-3'), 134.4(C-7), 146.1(C-2'), 147.7(C-4'), 156.0(C-9), 161.2(C-2), 177.5(C-4).

p-Toluidinium salt : mp 222°C, $C_{15}H_9O_8S^-$. $C_7H_{10}N^+$: *Anal.* Calcd for $C_{22}H_{19}NO_8S$: C, 55.57 ; H, 4.00 ; N, 2.94. Found : C, 55.42 ; H, 4.17; N, 2.77.

6-Fluoro-2',3',4'-trihydroxyflavone-5'-sulfonic acid (2d)

(85%) **^{1}H-NMR** (DMSO-d_6) δ 7.13(s, 1H, H-3), 7.61(s, 1H, H-6'), 7.67(m, 2H, H-7,8), 7.83(m, 1H, H-5). **^{13}C-NMR** (DMSO-d_6) δ 109.1(C-3), 109.4(d, J=25 Hz, C-5), 109.7(C-1'), 116.9(C-6'), 121.1(d, J=8.7 Hz, C-8), 122.6(d, J=25 Hz, C-7), 123.7(C-5'), 124.4(d, J=7.2 Hz, C-10), 132.9(C-3'), 146.0(C-2'), 147.6(C-4'), 152.5(C-9), 159.0(d, J=-242.7 Hz, C-6), 161.3(C-2), 176.6(d, J=2.8 Hz, C-4).

p-Toluidinium salt : mp 244°C, $C_{15}H_8O_8FS^-$. $C_7H_{10}N^+$. H_2O : *Anal.* Calcd for $C_{24}H_{20}NO_9FS$: C, 53.54 ; H, 4.05; N, 2.83. Found : C, 53.37; H, 4.17; N, 2.33.

6-Chloro-2',3',4'-trihydroxyflavone-5'-sulfonic acid (3d)

(89%) **^{1}H-NMR** (DMSO-d_6) δ 7.15(s, 1H, H-3), 7.62(s, 1H, H6'), 7.78(m, 2H, H-7,8), 7.92(d, J=1.5 Hz, 1H, H-5). **^{13}C-NMR** (DMSO-d_6) δ 108.9(C-1'), 109.6(C-3), 116.8(C-6'), 120.8(C-8), 123.7(C-5'), 123.7(C-5), 124.3(C-10), 129.6(C-6), 132.8(C-3'), 133.9(C-7), 145.9(C-2'), 147.6(C-4'), 154.3(C-9), 161.2(C-2), 176.0(C-4).

p-Toluidinium salt : mp 275°C, $C_{15}H_8O_8ClS^-$. $C_7H_{10}N^+$. H_2O : *Anal.* Calcd for $C_{24}H_{20}NO_9ClS$: C, 51.81 ; H, 3.92 ; N, 2.74. Found : C, 52.06 ; H, 3.77 ; N, 2.45.

6-Bromo-2',3',4'-trihydroxyflavone-5'-sulfonic acid (4d)

(89%) **^{1}H-NMR** (DMSO-d_6) δ 7.15(s, 1H, H-3), 7.61(s, 1H, H-6'), 7.71(d, J=8.9 Hz, 1H, H-8), 7.91(dd, J=8.9 and 2.5 Hz, 1H, H-7), 8.05(d, J=2.4 Hz, 1H, H-5). **^{13}C-NMR** (DMSO-d_6) δ 108.9(C-1'), 109.7(C-3), 116.8(C-6'), 117.5(C-6), 121.1(C-8), 123.7(C-5'), 124.8(C-10), 126.9(C-5), 132.8(C-3'), 136.6(C-7), 146.0(C-2'), 147.6(C-4'), 154.7(C-9), 161.2(C-2), 175.9(C-4).

p-Toluidinium salt : mp 282°C, $C_{15}H_8O_8BrS^-$. $C_7H_{10}N^+$. H_2O : *Anal.* Calcd for $C_{22}H_{20}NO_9BrS$: C, 47.65 ; H, 3.61 ; N, 2.52. Found : C, 48.43; H, 3.83; N, 2.35.

6,2',3',4'-Tetrahydroxyflavone-5'-sulfonic acid (5d)

(86%) **^{1}H-NMR** (DMSO-d_6) δ 7.02(s, 1H, H-3), 7.19(dd, J=8.9 and 3.0 Hz, 1H, H-7), 7.28(d, J=2.9 Hz, 1H, H-5), 7.55(s, 1H, H-6'), 7.56(d, J=8.9 Hz, 1H, H-8), 9.74(s, 2xOH), 11.03(s, 1H, OH-6). **^{13}C-NMR** (DMSO-d_6) δ 107.5(C-5), 108.8(C-3), 109.4(C-1'), 116.6(C-8), 119.5(C-6'), 122.8(C-7), 123.6(C-5'), 124.0(C-l0), 132.7(C-3'), 145.5(C-2'), 147.2(C-4'), 149.5(C-9), 154.6(C-6), 160.5(C-2), 177.0(C-4).

p-Toluidinium salt : mp 256°C, $C_{15}H_9O_9S^-$. $C_7H_{10}N^+$. $2H_2O$: *Anal.* Calcd for $C_{22}H_{23}NO_{11}S$: C, 51.86 ; H, 4.51 ; N, 2.75. Found : C, 51.19 ; H, 4.24 ; N, 2.52.

6-Methyl-2',3',4'-trihydroxyflavone-5'-sulfonic acid (6d)

(91%) **^{1}H-NMR** (DMSO-d_6) δ 2.40(s, 3H, CH_3-6), 7.09(s, 1H, H-3), 7.59(m, 2H, H-6,8), 7.60(s, 1H, H-6'), 7.79(s, 1H, H-5). **^{13}C-NMR** (DMSO-d_6) δ 20.5(CH_3), 109.3(C-1'), 109.7(C-3), 116.7(C-6'), 118.1(C-8), 122.9(C-10), 123.6(C-5'), 124.1(C-5), 132.8(C-3'), 134.7(C-6), 135.1(C-7), 145.7(C-2'), 147.4(C-4'), 154.0(C-9), 160.7(C-2), 177.2(C-4).

p-Toluidinium salt : mp 258°C, $C_{16}H_{11}O_8S^-$. $C_7H_{10}N^+$. H_2O : *Anal.* Calcd for $C_{23}H_{23}NO_9S$: C, 56.44 ; H, 4.70 ; N, 2.86. Found : C, 57.03 ; H, 4.89 ; N, 2.37.

2',3',4',5-Tetrahydroxyflavone-5',8-disulfonic acid (7d)

(20%) **^{1}H-NMR** (DMSO-d_6) δ 7.73(d, 1H, J=8.5 Hz, H-6), 7.02(s, 1H, H-3), 7.90(s, 1H, H-6'), 7.94(d, J=8.5 Hz, 1H, H-7), 10.02(s, 1H, OH), 10.92(s, 1H, OH), 13.13(s, 1H, OH-5). **^{13}C-NMR** (DMSO-d_6) δ 107.1(C-10), 108.2(C-1'), 108.8(C-6), 109.0(C-3), 118.4(C-6'), 123.1(C-5'), 125.1(C-8), 132.6(C-3'), 133.9(C-7), 145.8(C-2'), 147.2(C-4'), 151.2(C-5), 160.2(C-9), 162.7(C-2), 182.3(C-4).

p-Toluidinium salt : mp 290°C (decomp), $C_{15}H_9O_{12}S_2^-$. $C_7H_{10}N^+$. $4.5H_2O$: *Anal.* Calcd for $C_{44}H_{56}N_2O_{33}S_4$: C, 41.64 ; H, 4.41 ; N, 2.20. Found : C, 41.37 ; H, 4.21 ; N, 2.06.

REFERENCES

1. S. Natori and I. Ueno, *Bioact. Mol.*, 1987, **2**, 53.

2. D. Pathak, K. Pathak, and A. K. Singla, *Fitoterapia*, 1991, **LXII**, 371.

3. N. Cotelle, J.L. Bernier, J.P. Hénichart, J.P. Catteau, E.M. Gaydou, and J.-C. Wallet, *Free Radical Biol. Med.*, 1992, **13**, 211.
4. M. Iinuma and M. Mizuno, *Phytochemistry*, 1989, **28**, 681.
5. A. Habsaoui, J.L. Franquet Cami, J.-C. Wallet, and E.M.Gaydou, *Heterocycles*, 1998, **48**, 1759.
6. P. Mohan, R. Singh, and M. Baba, *Drug Des. Discovery*, 1991, **8**, 69.
7. P. Mohan, *Pharm. Res.*, 1992, **9**, 703.
8. W. H. Ojala, E.A. Sudbeck, L.K. Lu, T.I. Richardson, R.E. Lovrien, and W.B. Gleason, *J. Am. Chem. Soc.*, 1996, **118**, 2131.
9. R.I. Brinkworth and D.P. Fairlie, *Biochem. Biophys. Res. Commun.*, 1992, **188**, 624.
10. J. Bolzarini, H. Mitsuya, E. De Clercq, and S. Broder, *Int. J. Cancer*, 1986, **37**, 451.
11. T. Tanaka, M. Iinuma, and M. Mizuno, *Chem. Pharm. Bull.*, 1986, **34**, 1667.
12. M. Iimuna, S. Matsuura, and K. Kusuda, *Chem. Pharm. Bull.*, 1980, **28**, 708.
13. A. Habsaoui, J.-C. Wallet, and E.M. Gaydou, *Magn. Reson. Chem.* (to submit).
14. A. Habsaoui, J.-C. Wallet, and E.M. Gaydou, *Magn. Reson. Chem.*, 1998, **36**, 621.
15. H. Günther, La spectroscopie de RMN, Masson, Paris, 1994, p. 60.
16. A.I. Vogel, Practical Organic Chemistry 1967, 3rd ed., John Wiley, New York, pp. 552-555.
17. J.-C. Wallet and E. M. Gaydou, *Magn. Reson. Chem.*, 1993, **31**, 518.

Received, 5th March, 1999