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# Synthesis of 5,7-Dihydroxy-6-methoxy-2-(2-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one and Reassignment of Structure of Tamaridone[1]

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# SYNTHESIS OF 5,7-DIHYDROXY-6-METHOXY-2-(2-HYDROXY-4-METHOXYPHENYL)-4H-1-BENZOPYRAN-4-ONE AND REASSIGNMENT OF STRUCTURE OF TAMARIDONE[1]

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**Abstract**: The proposed structure of a new flavone, tamaridone, isolated from *Tamarix dioica* Roxb is untenable on the basis of comparison with its synthetic sample. Its structure has been now revised to 5,7-dihydroxy-8-methoxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one by careful spectral studies.

## INTRODUCTION

A new flavone (tamaridone) has been recently isolated by Parmar et al.[2] from *Tamarix dioica* Roxb and its structure was proposed as unique 5,7-dihydroxy-6-methoxy-2-(2-hydroxy-4-methoxyphenyl) -4H-1-benzopyran-4-one (1) on the basis of the colour reactions and spectroscopic studies. To the best of our knowledge, flavones bearing such a novel 5,6,7,2',4'-pentaoxygenated pattern are not known as natural products and only very few have been synthesised earlier.[3] Nevertheless,

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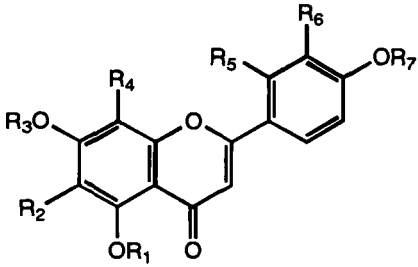
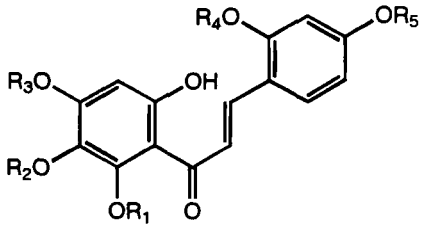
5,6,7-trioxygenated pattern in ring A and 2'or 4'-mono oxygenated pattern in ring B have been separately found to be present in quite a few naturally occurring flavones, some of which have been reported to possess varied biological activities, such as antiviral[4], antiasthmatic[5], hypolipidemic and antiatherosclerotic.[6] In view of this and the fact that the proposed structure for tamaridone contained a novel oxygenation pattern, we synthesised **1** and compared it directly with the natural sample of tamaridone[7] in order to establish its unique proposed structure. It was found that the two samples were different on TLC and in melting point, though they have close similar spectral properties, therefore suggesting that the proposed structure of tamaridone must be revised. This paper reports the synthesis of **1** and proposes a revised structure of tamaridone.

**Synthesis of 5,7-dihydroxy-6-methoxy-2-(2-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (1)**

We envisaged the synthesis of **1** starting from 2'-hydroxy-2,4',6'-triisopropyloxy-4,5'-dimethoxychalcone (**2**) which in turn could be obtained by condensing 2-hydroxy-4,6-diisopropyloxy-5-methoxyacetophenone[8] and 2-isopropyloxy-4-methoxybenzaldehyde in the presence of dilute aqueous or ethanolic potassium hydroxide solution. However 2-isopropyloxy-4-methoxybenzaldehyde required for this purpose could not be obtained by direct isopropylation of 2-hydroxy-4-methoxybenzaldehyde as each time C-alkylation occurred in place of desired O-alkylation. The hydroxyl group at C-2 position has probably resisted O-isopropylation due to its chelation with the neighbouring formyl group and also because of steric factors. We, therefore prepared an alternate synthone 2-benzyloxy-4-methoxybenzaldehyde[9] by direct benzylation using benzylchloride in N,N-dimethyl formamide. Condensation of 2-hydroxy-4,6-diisopropyloxy-5-methoxy-




**1** $R_1=R_3=R_4=R_6=H$; $R_2=OCH_3$; $R_5=OH$; $R_7=CH_3$

**2** $R_1=R_3=R_4=(CH_3)_2CH$; $R_2=R_5=CH_3$

**4** $R_1=R_3=(CH_3)_2CH$; $R_2=OCH_3$; $R_4=R_6=H$; $R_5=CH_2C_6H_5$; $R_7=CH_3$

**3** $R_1=R_3=(CH_3)_2CH$; $R_2=R_5=CH_3$; $R_4=CH_2C_6H_5$

**5** $R_1=R_2=R_3=R_5=H$; $R_4=OCH_3$; $R_6=OH$; $R_7=CH_3$

**6** $R_1=R_3=R_4=R_5=H$; $R_2=OCH_3$; $R_6=OH$; $R_7=CH_3$

acetophenone with 2-benzyloxy-4-methoxybenzaldehyde in ethanol under alkaline conditions gave 2-benzyloxy-2'-hydroxy-4',6'-diisopropyloxy-4,5'-dimethoxychalcone (**3**) which on oxidation with selenium dioxide in amyl alcohol cyclised to 5,7-diisopropyloxy-6-methoxy-2-(2-benzyloxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**4**). The flavone **4** contained three different groups, benzyloxy, isopropyloxy and methoxy, out of which benzyloxy and isopropyloxy had to be knocked off in order to achieve the synthesis of the desired flavone **1**. Many reagents have been used in the past to remove selectively either benzyloxy[10] or isopropyloxy groups[11], but we have used herein a more efficient and convenient method to knock off both these protecting groups simultaneously in preference to the methoxy groups in one step using boron trichloride under control conditions. This reagent has been earlier used[12] in carbohydrate chemistry for debenzylation and we have now extended its use to polyphenolics. Thus **4** on treatment with $BCl_3$ in $CH_2Cl_2$ at -5°C under nitrogen gave the desired flavone **1** in good yield. The $^1H$ NMR spectrum of synthetic

flavone **1** fully supported the fact that selective debenzylation and deisopropylation had occurred simultaneously without any demethylation. The structure of the synthetic flavone **1** was further confirmed by its mass fragmentation pattern and other spectral data such as UV and $^{13}C$ NMR.

## RESULTS AND DISCUSSION

On direct comparison the natural sample of tamaridone[7] did not match with the synthetic sample of 5,7-dihydroxy-6-methoxy-2-(2-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**1**), on TLC and also in physical and spectral properties, therefore suggesting that the proposed structure of tamaridone must be revised. For this purpose, we studied the published spectral data of tamaridone very carefully and found that one methoxy and one hydroxy group in ring A and B respectively are wrongly placed in the proposed structure **1**. We have now arrived at an alternate isomeric structure of tamaridone as 5,7-dihydroxy-8-methoxy-2-(3-hydroxy-4-methoxyphenyl) -4H-1-benzopyran-4-one (**5**).

*Revision of Original Assignment* Mass spectrum of the natural flavone exhibited two prominent fragments[13] at m/z 133$[B\text{-}CH_3]^+$ and 151$[B_2]^+$ thus showing the presence of one hydroxy and one methoxy group in ring B. Since its UV spectrum did not show any bathochromic shift in sodium methoxide therefore the hydroxy group in ring B can not be placed at either C-4' or C-2' position. In the latter case a large bathochromic shift of the order of 60 nm should have been observed as reported earlier[14] and was also observed by us with our synthetic compound **1**. So, the only possibility left is that tamaridone may contain 3',4'-dioxygenation system, commonly known to occur among flavonoids. This fact is supported by its $^1H$ NMR which showed the presence of ortho, meta and ortho-meta coupled protons in ring B. Thus, tamaridone could be 5,7-dihydroxy-6-methoxy-2-(3-hydroxy-4-

methoxyphenyl)-4H-1-benzopyran-4-one (**6**) which is earlier reported in literature.[15,16] However on comparison, the melting point and spectral properties of tamaridone[2] did not also agree with those reported for **6** (Table 1), so the structure further needs modification probably with respect to the position of methoxyl and hydroxyls present in ring A of tamaridone.

The position of hydroxyl at C-5 and C-7 positions, as placed earlier in natural flavone, is justified as it showed bathochromic shifts in $AlCl_3$-HCl and sodium acetate respectively in its UV spectrum. Therefore the only alternate left is to place a methoxy group in ring A at C-8 position instead of C-6, thus leaving latter free. This placement is strongly supported by a characteristic upfield signal at δ 100.3 for carbon at 6 position which is now flanked by two oxygenated functions at C-5 and C-7 in its $^{13}C$ NMR spectrum.[17] The UV spectrum also confirms the unsubstituted C-6 position in ring A as it showed a bathochromic shift of 55 nm in $AlCl_3$-HCl Vs MeOH.[18] Beside these, if position C-8 is unsubstituted in ring A then a characteristic signal at δ 94.0 in $^{13}C$ NMR of tamaridone should have been observed as reported earlier in literature[19,20] and also observed by us with our synthetic flavone **1**. However, the absence of such signal in the published spectral data of tamaridone further confirms that C-8 position is substituted in the natural product. Thus tamaridone contains 5,7-dihydroxy-8-methoxy system rather than 5,7-dihydroxy-6-methoxy in ring A and consequently its structure should be revised to 5,7-dihydroxy-8-methoxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**5**) which to the best of our knowledge is also a new natural flavone. Chemical shift values (δ) observed in $^1H$ NMR and $^{13}C$ NMR of tamaridone have been reassigned for **5** and are represented in Table 1.

**Table 1. Comparison of spectral data of tamaridone with 5,7-dihydroxy-6-methoxy-2-(2-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (1) and its isomers**

| Compound | m.pt.(°C) | UVdata (nm) | $^1$H NMR data (δ) | $^{13}$C NMR data(δ) | Mass (*m/z*) |
|---|---|---|---|---|---|
| **Tamaridone**[2] | 208-12 | $\lambda_{max}$($CH_3OH$) 339, 274<br>+$AlCl_3$ 394(sh),359,300,280<br>+HCl 394(sh),359,351,300, 280<br>+NaOAc 380, 320, 281<br>+$H_3BO_3$ 335, 274<br>+NaOMe 388(sh), 308, 274 | 7.46(dd, J=7.8, 2.0Hz, H-5'), 7.40(d, J=2.0Hz, H-3'), 7.05(d, J=7.8Hz, H-6') 6.55(s,H-8), 6.20(s,H-3), 3.90(s,2x$OCH_3$) | 165.7(C-2), 104.4(C-3), 184.0(C-4), 158.7(C-5), 125.1(C-6), 158.3(C-7), 113.9(C-8), 105.3(C-4a), 151.3(C-8a), 129.0(C-1'), 148.3(C-2'), 100.3(C-3'), 152.7(C-4'), 112.8(C-5'), 120.1(C-6'), 56.0 and 62.1 (2x-$OCH_3$) | 331($M^+$+1), 330($M^+$), 315, 167, 151, 148, 139 |
| **1** | 246-47 | Spectral data given in experimental section | | | |
| **5** | 208-12 | $\lambda_{max}$($CH_3OH$) 339, 274,<br>+$AlCl_3$ 394(sh),359,300,280<br>+HCl 394(sh),359,351,300, 280<br>+NaOAc 380, 320, 281<br>+$H_3BO_3$ 335, 274<br>+NaOMe 388(sh), 308, 274 | 7.46(dd, J=7.8, 2.0Hz, H-6'), 7.40(d,J=2.0Hz, H-2'), 7.05(d, J=7.8Hz, H-5'), 6.55(s,H-3), 6.20(s,H-6), 3.90(s, 2x$OCH_3$) | 165.7(C-2), 104.4(C-3), 184.0(C-4), 158.7(C-5), 100.3(C-6), 158.3(C-7), 129.0(C-8), 105.3(C-4a), 151.3(C-8a), 125.1(C-1'), 113.9(C-2'), 148.3(C-3'), 152.7(C-4'), 112.8(C-5'), 120.1(C-6'), 56.0 and 62.1 (2x-$OCH_3$) | 331($M^+$+1), 330($M^+$), 315, 167, 151, 148, 139 |
| **6**[15,16] | 268-70 | $\lambda_{max}$($CH_3OH$) 343, 274<br>+$AlCl_3$ 370, 280<br>+HCl 363, 286<br>+NaOMe 383, 273 | 7.60-7.33(m,H-2' and H-6'), 7.09(d,H-5'), 6.72(s,H-8), 6.56(s,H-3), 3.84(s, $OCH_3$), 3.74(s, $OCH_3$) | — | 330($M^+$), 315, 312, 300,287, 167,165,139, 86 |

## EXPERIMENTAL

**General information.** Melting points and boiling points are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectrums were recorded in $CDCl_3$ and DMSO $d_6$ at 250 MHz and 62.89 MHz respectively with a Bruker AC-250 instrument using TMS as an internal standard. Chemical shifts are reported ($\delta$ ) relative to TMS. UV spectra ($\lambda_{max}$ in nm) were recorded on a Beckman DU-64 spectrophotometer. Mass spectra were recorded on a Varian MAT 311A instrument. All the solvents employed in the present study were purified using literature procedure.

**2-Benzyloxy-2'-hydroxy-4',6'-diisopropyloxy-4,5'-dimethoxychalcone (3).** A mixture of 2-hydroxy-4,6-diisopropyloxy-5-methoxyacetophenone (1.7 g, 6 mmole) and 2-benzyloxy-4-methoxybenzaldehyde (1.6g, 6.5 mmole) in ethanol (20 ml) were treated with aqueous potassium hydroxide solution (30 ml; 10%). The reaction mixture was kept at room temperature for 48 h, acidified with dilute hydrochloric acid and then extracted with $Et_2O$(3x50ml). The organic phase was washed with brine (50 ml), dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue left was purified by column chromatography (petrol/ benzene) to obtain **3** as yellow oil, 1.2g. $R_f$=0.45 [benzene : petrol (3:1)]. It gave greenish colour with ethanolic ferric chloride; $^1H$ NMR($CDCl_3$, 250 MHz): $\delta$ 13.62 (s, 1H, OH), 8.22 (d, J=15.8 Hz, 1H, H-$\alpha$), 7.98 (d, J=15.8 Hz, 1H, H-$\beta$ ), 7.67 (d, J=9.0Hz, 1H, H-6), 7.43-7.25 (m, 5H, Ar-H), 6.53 (m, 2H, H-3 and H-5), 6.24 (s, 1H, H-3'), 5.17 (s, 2H, $OCH_2Ph$), 4.62 (hept, 2H, 2xCH<), 3.81 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 1.32 (d, J=6.0Hz, 12H, 2x$(CH_3)_2$); EIMS (70 eV): *m/z* (rel. int.%) 506 ($M^+$,24), 463(12), 373(12), 331(12), 267(8), 239(10), 224(17), 183(42), 167(15), 149(56), 111(14), 91(100), 83(26), 71(43), 59(45); CIMS: *m/z* 507($M^+$+1), 464, 391, 331, 283, 267, 240, 224, 205, 183, 137, 91, 81.

**5,7-Diisopropyloxy-6-methoxy-2-(2-benzyloxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (4).** A mixture of compound **3** (0.5 g, 1mmole), selenium dioxide (0.75 g, 6.75mmole) and freshly distilled amyl alcohol (25 ml) was heated under reflux in an oil bath for 24 h. The precipitated selenium metal was filtered and the solvent was evaporated in vacuo. The residue left was steam distilled and purified by preparative TLC using benzene : ethylacetate (9:1) as the developing solvent. **4** was obtained as a light yellow oil, 0.28 g. It did not give any colour with alcoholic ferric chloride; UV(MeOH): 324, 240nm; $^1$H NMR ($CDCl_3$, 250 MHz): δ 7.75 (d, J=9.0 Hz, 1H, H-6'), 7.44-7.28(m, 5H, Ar-H), 6.85 (s, 1H, H-3), 6.67 (s, 1H, H-8), 6.62 (dd, J=9.0, 2.2 Hz, 1H, H-5'), 6.58 (d, J=2.2 Hz, 1H, H-3'), 5.20 (s, 2H, $OCH_2Ph$), 4.60(hept, 2H, 2xCH<), 3.88(s,3H,$OCH_3$), 3.82(s, 3H, $OCH_3$), 1.43 (d, J=6.0Hz, 12H, 2x$(CH_3)_2$), ; EIMS (70 eV): *m/z* (rel. int.%) 504 ($M^+$, 15), 489(100), 461(58), 446(40), 429(20), 419(23), 403(71), 387(23), 312(19), 241(8), 238(10), 223(8).

**5,7-Dihydroxy-6-methoxy-2-(2-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (1).** The flavone **4** (0.2 g) was dissolved in dry $CH_2Cl_2$ (8.0 ml) and contents cooled to -5°C under nitrogen. Boron trichloride in dichloromethane (7.0 ml, 20%) was then slowly added to the above stirred solution under nitrogen atmosphere. The reaction was monitored by TLC using benzene:ethylacetate (3:1) as the developing solvent. After 30 minutes, TLC showed the absence of **4** and the presence of a new compound at a lower $R_f$ value. Water (30 ml) was immediately added and contents extracted with ether. The organic layer was dried over anhydrous sodium sulphate and filtered. The solvent was evaporated in vacuo and a yellow coloured residue was crystallized from methanol-chloroform to obtain **1** as light yellow needles, 0.03 g, mp. 246-47°C. It gave dark greenish colour with alcoholic ferric

chloride and yellow colour with sulphuric acid on heating. UV (MeOH) : 344, 269 nm; + $AlCl_3$ : 374, 274; + $AlCl_3$ /HCl : 415(sh), 362, 278; + NaOAc : 358, 266; + NaOAc/$H_3BO_3$ : 344, 266; +NaOMe : 403, 272; $^1$H NMR(DMSO-$d_6$,250 MHz): δ 13.09(s,1H, C-5-OH), 7.83(d, J=9.0Hz,1H, H-6'), 7.00(s,1H,H-3), 6.63(dd, J=9.0, 2.5Hz, 1H, H-5'), 6.58(d, J=2.5Hz, 1H, H-3'), 6.57(s,1H,H-8), 3.79(s,3H,$OCH_3$), 3.74(s,3H,$OCH_3$); $^{13}$C NMR (DMSO $d_6$, 62.89MHz) : δ 165.4 (C-2), 106.3 (C-3), 181.2 (C-4), 152.5 (C-5), 129.6 (C-6), 157.0 (C-7), 94.0 (C-8), 103.5(C-4a), 152.3(C-8a), 129.4 (C-1'), 158.4 (C-2'), 101.6 (C-3'), 160.4 (C-4'), 110.0 (C-5'), 127.3 (C-6'), 55.2 and 60.1 (2x$OCH_3$); EIMS (70 eV): *m/z* (rel. int.%) 331 ($M^+$+1, 23), 330 ($M^+$,100), 329(9), 315(70), 313(20), 301(8), 287(17), 167(15), 151(12), 148(14), 139(11), 133(7), 121(10), 91(5), 69(23), 57(7).

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