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Synthesis and Antioxidant Activity of 5′-Methoxycurcumin: A Yellow Pigment from *Curcuma xanthorrhiza*†

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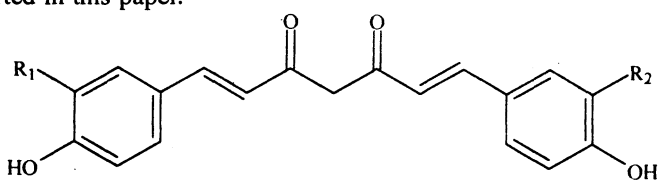
5′-Methoxycurcumin (**6**) an unsymmetrically substituted curcuminoid from *C. xanthorrhiza*, was synthesized starting from syringaldehyde (**4**) and vanillin (**5**), in a single step. The spectral data of synthetic **6** are in good agreement with those of natural **6** and it showed potent antioxidant activity.

Key words: 5′-Methoxycurcumin, *Curcuma xanthorrhiza*, Synthesis, antioxidant activity.

INTRODUCTION

Curcuminoids, phenolic diarylheptanoids (**1–3**) are characteristic yellow coloured constituents of turmeric (*Curcuma longa*) and are widely used in foods and cosmetics. These compounds were reported to possess antioxidant[1, 2], anti-inflammatory[3], anticancer[4, 5] and antiviral[6] properties. Discovery of antiviral properties in curcuminoids, particularly against HIV-1[6] is interesting and needs further study of their analogues. Because of the broad spectrum of biological activities exhibited by curcuminoids, a large number of these compounds have been synthesized and evaluated their phamacological potential. 5′-Methoxycurcumin [1-(4-hydroxy-3,5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-(1E,6E) -1,6-heptadiene-3,4-dione] was isolated as one of the constituents from *C. xanthorrhiza*[7]. Due to our interest in diarylheptanoids[8–10], we have synthesized **6**, an unsymmetrically substituted curcuminoid, for the first time and the results are reported in this paper.



1 = R_1=R_2=OCH_3; **2** = R_1=OCH_3, R_2=H; **3** = R_1=R_2=H

†Laila Impex Communication # 11.

EXPERIMENTAL

Melting points were recorded on a V. Scientific melting point apparatus, in open capillaries and are uncorrected. UV spectra were recorded on a Shimadzu UV-190 spectrophotometer, IR spectra were recorded on a Perkin-Elmer BX1 FTIR Spectrophotometer. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer and mass spectra on VG micromass 70-70H mass spectrometer. Acme silica gel-G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively.

Syringaldehyde (4): To a solution of 3,4,5-trimethoxybenzaldehyde (5.0 g) in glacial acetic acid (50 mL) was added hydrobromic acid (100 mL, 46–48%) and the mixture was heated at 80–90°C for 90 min on a water bath under nitrogen gas. After cooling, the reaction mixture was diluted with ice-cold water and extracted with chloroform. The organic layer was washed with water, brine and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane-ethyl acetate (80 : 20) as eluent to give **4** (3.0 g, 65%), m.p. 109–110°C; IR (neat) ν_{max}: 3366, 1694, 1586, 1497, 1455, 1421, 1386, 1327, 1230, 1140, 741, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.95 (6H, s, 2 × OMe), 6.39 (1H, br s, ArOH), 7.15 (2H, s, Ar-H), 9.81 (1H, s, CHO).

Condensation of syringaldehyde and vanillin with acetyl acetone: To a solution of boric oxide (2.0 g, 20 mmol) in DMF (4 mL) was added acetylacetone (2.04 mL, 20 mmol) followed by tributyl borate (10.8 mL, 40 mmol) at 60–70°C and stirred for 15 min. A mixture of syringaldehyde (**4**, 3.64 g, 20 mmol) and vanillin (**5**, 3.04 g, 20 mmol) was added and stirred for 5 min. Then a mixture of 1,2,3,4-tetrahydroquinoline (0.4 mL) and glacial acetic acid (1.2 mL) in DMF (4 mL) was added and heating was continued for 4 h at 100°C. After cooling, aqueous acetic acid (20%; 200 mL) was added with stirring. The precipitated solid was stirred further for 1 h. The oily residue was extracted with chloroform and the organic layer was washed with water, brine and dried over sodium sulfate. The residue obtained (3.5 g) after evaporation of the solvent was chromatographed over silica gel column eluting with chloroform-methanol to give **1** (0.56 g, 15%), m.p. 178–180°C (lit.[6] M.P. 180–182°C), **6** (0.8 g, 10%), m.p. 146–148°C and **7** (0.7 g, 16%), m.p. 184–186°C (lit.[11] m.p. 188–190°C).

1-(4-Hydroxy-3,5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-(1E, 6E)-1,6-heptadiene-3,4-dione (6): M.P. 146–148°C (lit.[7] m.p. 145–146°C); IR (KBr) ν_{max}: 3405, 1627, 1588, 1512, 1280, 1143, 1118, 965 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (6H, s), 3.95 (3H, s), 5.78 (1H, br s), 5.81 (^{1}H, s), 5.89 (1H, br s), 6.47 (1H, d, J = 15.8 Hz), 6.48 (1H, d, J = 15.8 Hz), 6.80 (2H, s), 6.93 (1H, d, J = 8.2 Hz), 7.05 (1H, d, J = 1.7 Hz), 7.12 (1H, dd, J = 8.2, 1.7 Hz), 7.57 (1H, d, J = 15.8 Hz), 7.59 (1H, d, J = 15.8 Hz); EIMS m/z (%): 399 (M + 1, 26), 398 (M^+, 75), 380 (55), 303 (17), 274 (15), 221 (22), 220 (42), 207 (47), 191 (31), 180 (32), 178 (19), 177 (100), 167 (34), 145 (41), 137 (42) and 64 (90).

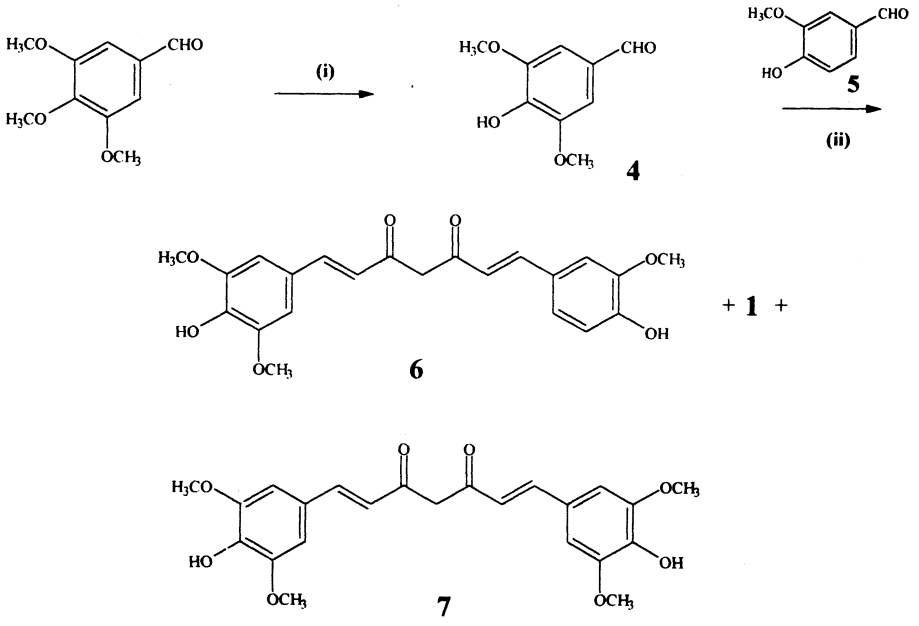
Antioxidant activity

Superoxide free radical-scavenging activity: The superoxide free radical-

scavenging activity was determined by the nitroblue tetrazolium (NBT) method[12, 13]. The reaction mixture contained EDTA (6.6 mM), NaCN (3 μg), riboflavin (2 μM), NBT (50 μM), various concentrations of the test drug in ethanol and a phosphate buffer (58 mM, pH 7.8) in a final volume of 3 mL. Optical density was measured at 560 nm. The test tubes were uniformly illuminated with an incandescent lamp for 15 min, after which the optical density was measured again at 560 nm. The percentage inhibition and superoxide radical generation was measured by comparing the absorbance values of the control and those of the test compounds. IC_{50} values were obtained from a plot of the concentration in μg against the percentage inhibition.

RESULTS AND DISCUSSION

5′-Methoxycurcumin (**6**) was synthesized by the reaction of equimolar ratio of syringaldehyde (**4**), vanillin (**5**) with acetylacetone in presence of boric oxide and tributyl borate[14]. Creating a boron complex of acetylacetone protects the higher acidic methylene protons from the usual Knoevenagel condensations and the reaction occurs at the terminal methyl groups of the diketone[15]. As expected, the reaction of **4** and **5** with acetylacetone under the above conditions gave **6**, but accompanied by the two other products **1** and **7** (**Scheme 1**). Chromatography of the product mixture over silica gel column gave **6** in 10% yield and its spectral data agree well with those reported for natural **6**.



Scheme 1: Reagents & conditions: (i) HBr, acetic acid, 80–90°C, 90 min, 65% (ii) B_2O_3, acetyl acetone, tributyl borate, DMF, 95–100°C, 4 h, 15% (**1**), 10% (**6**), 16% (**7**)

Antioxidant activity

In view of the structural similarity of **6** with curcumin **1**, we have screened **6** for antioxidant activity by the nitroblue tetrazolium (NBT) reduction method[12, 13]. **6** showed potent superoxide-scavenging activity (IC_{50}: 45 μM) compared to the other known antioxidants: curcumin **1** (IC_{50}: 54 μM), vitamin E (IC_{50}: 728 μM), vitamin C (IC_{50}: 852 μM), BHT (butylated hydroxytoluene, IC_{50}: 381 μM) and BHA (butylated hydroxyanisole, IC_{50}: 967 μM).

Antimicrobial activity

5′-Methoxycurcumin **(6)** was screened for its antibacterial activity by the agar cup-plate diffusion method[16]. It did not show any appreciable antibacterial activity against *Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis* and *Bacillus pumilis* and antifungal activity against *Aspergillus wentii* and *Aspergillus niger* even at 500 μg/mL concentration.

Conclusion

In conclusion, 5′-methoxycurcumin **(6)**, an unsymmetrically substituted curcuminoid from *Curcuma xanthorrhiza* was synthesized starting from syringaldehyde **(4)** and vanillin **(5)**. 5′-Methoxycurcumin **(6)** showed potent antioxidant activity and did not show any appreciable antibacterial, antifungal activity even at 500 μg/mL concentration.

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