

Synthesis and Structural Characterization of 1,4-Diazepines Related to Curcumin

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Abstract: The reactivity of (*E*)-5-(4-hydroxy-3-methoxyphenyl)-1-phenylpent-4-ene-1,3-dione with ethylenediamine has been studied in different experimental conditions. Two dihydro-1,4-diazepines have been obtained and fully characterized by 1D and 2D multinuclear NMR spectroscopy and HRMS.

Keywords: 1,4-diazepines, curcumin, ¹H, ¹³C, ¹⁵N NMR

Introduction

The interest in curcumin (**1**)¹ has prompted many studies on the synthesis, characterization and biological properties of compounds resulting from structural modifications, i.e. the hemicurcuminoids, obtained by replacement of one styryl (2-methoxy-4-vinylphenol) branch of curcumin by a simpler group.² Curcumin or [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione], is a β-diketone that owing to its symmetry has only two tautomers, enol **1a** and keto **1b** (Fig. 1), the third one being identical to **1a**.

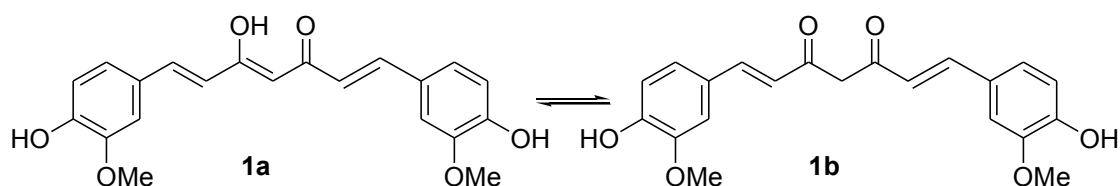


Figure 1. Curcumin tautomers.

Curcumin and hemicurcuminoids have different reactive functional groups,^{1d} β-diketo and α,β-unsaturated keto, that can participate in nucleophilic addition reactions to yield pyrazoles,³ isoxazoles,⁴ and other heterocyclic systems.⁵ The phenolic group can react with fatty acids, amino acids, etc. to enhance bioavailability.⁶

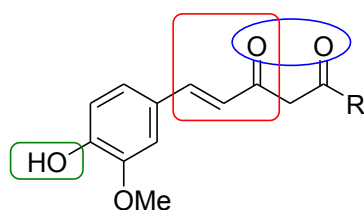
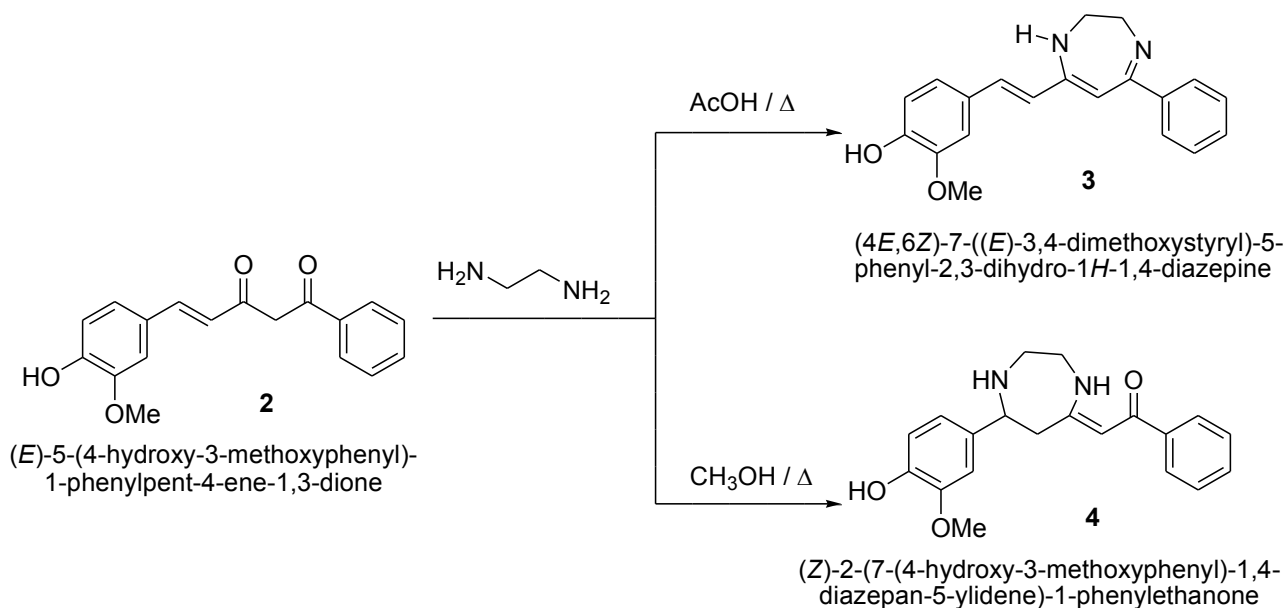


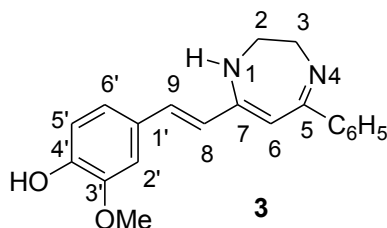
Figure 2. Reactive functional groups of hemicurcuminoids.

Results and discussion

The reactivity of curcumin with 1,2-ethylenediamine has already been studied by two research groups.^{7,8} In this work we present the reaction of the hemicurcuminoid (*E*)-5-(4-hydroxy-3-methoxyphenyl)-1-phenylpent-4-ene-1,3-dione (**2**),^{2a} with ethylenediamine in two different media. In acetic acid it reacts as a β -dicarbonyl compound leading to (4*E*,6*Z*)-7-((*E*)-3,4-dimethoxystyryl)-5-phenyl-2,3-dihydro-1*H*-1,4-diazepine (**3**). Differently, in methanol it reacts as a α,β -unsaturated ketone to give (*Z*)-2-(7-(4-hydroxy-3-methoxyphenyl)-1,4-diazepan-5-ylidene)-1-phenylethanone (**4**), as shown in Scheme 1. Yields were almost quantitative in both cases, but after purification **3** [recrystallized from H₂O/EtOH; HRMS (ESI) *m/z* calcd for C₂₀H₂₀N₂O₂: 320.15, found: 321.15 (M+H)⁺] was obtained in a 60 % and **4** [chromatographed over Silica gel and recrystallized from EtOH; HRMS (ESI) *m/z* calcd for C₂₀H₂₂N₂O₃: 338.16, found: 339.17 (M+H)⁺] in a 35 %.



In Tables 1 and 2 are gathered the most significant ¹H, ¹³C and ¹⁵N NMR experimental data chemical shifts (δ in ppm) and coupling constants (*J* in Hz). The attribution of the chemical shifts was based on the multiplicity of the signals as well as on the cross-peaks observed in the (¹H-¹³C) gs-HMQC and (¹H-¹³C) gs-HMBC bidimensional spectra.

Table 1. NMR data, chemical shifts (δ , ppm) and coupling constants (J , Hz), of compound **3**

| Nuclei | HMPA- d_{18} at 340 K | | | TFA at 300 K | | |
|--------------------------|-------------------------|---------------------|----------------------------------------|-----------------------------------------------------------------------|---------------------|----------------------------------------|
| | δ | gs-HMQC correlation | gs-HMBC correlation | δ | gs-HMQC correlation | gs-HMBC correlation |
| 1-NH | n.o. | -- | -- | -249.5* | 9.59(NH) | 5.70 (H6) |
| 2-CH₂ | 50.3 | 3.49 | -- | 48.0* | ^a | |
| 3-CH₂ | 55.6 | 3.88 | | 47.7* | ^a | |
| 4-N | n.o. | --- | -- | -251.8* | 9.86(NH) | 5.70 (H6) |
| 5-C | 165.3 (br) | | | 166.8 | | 7.50 (Ho) |
| 6-C | 93.1 | 5.33 (H6) | 6.63 (H8) | 88.8 ¹ J= 163.0 | 5.70 (H6) | 6.62 (H8) |
| 7-C | 151.7 (br) | | | 163.3 | | 7.29 (H9) |
| 8-C | 125.6 (br) | 6.56 (H8) | | 119.8 ¹ J= 158.8 | 6.62 (H8) | 5.70 (H6) |
| 9-C | 131.8 | 7.12 (H9) | 6.91 (H6') 7.00 (H2') | 140.5 ¹ J=152.3 | 7.29 (H9) | 7.02 (H6') |
| C_i | 143.4 (br) | | 7.33 (Hm/p) | 135.1 | | 5.70 (H6) 7.40 (Hm) |
| C1' | 128.1 | | 6.63 (H8) 6.86 (H5') | 127.5 ³ J= ³ J= 6.5 | | 6.62 (H8) 6.88 (H5') |
| C2' | 113.0 | 7.00 (H2') | | 109.9 ¹ J= 157.7 ³ J= ³ J= 5.9 | 7.04 (H2') | 7.02 (H6') 7.27 (C9) |
| C3' | 148.9 | | 3.80 (OCH ₃) 6.86 (H5') | 146.4 | | 3.80 (OCH ₃) 6.80 (H5') |
| 3-OCH₃ | 56.8 | 3.80 | | 54.8 ¹ J= 145.5 | 3.85 | |
| C4' | 150.0 | | 6.91 (H6') 7.00 (H2') | 145.7 | | 7.02 (H6') 7.04 (H2') |
| C5' | 116.4 | 6.86 (H5') | | 114.4 ¹ J= 162.4 | 6.88 (H5') | |
| C6' | 120.9 | 6.91 (H6') | 7.00 (H2') | 122.3 ¹ J= 160.7 | 7.02 (H6') | 7.04 (H2') 7.29 (H9) |

^aThe signal appears as a broad singlet at about 3.80 ppm; ^bSignals of the C₆H₅ group appear in the usual range.

In compound **3**, to assign the C5 and C7 chemical shifts we have used the correlation between them with H_o and H₈/H₉, respectively (Figure 3a); and the correlation of C3' with the protons of methoxy group, has permitted to distinguish it from C4' (Figure 3b)

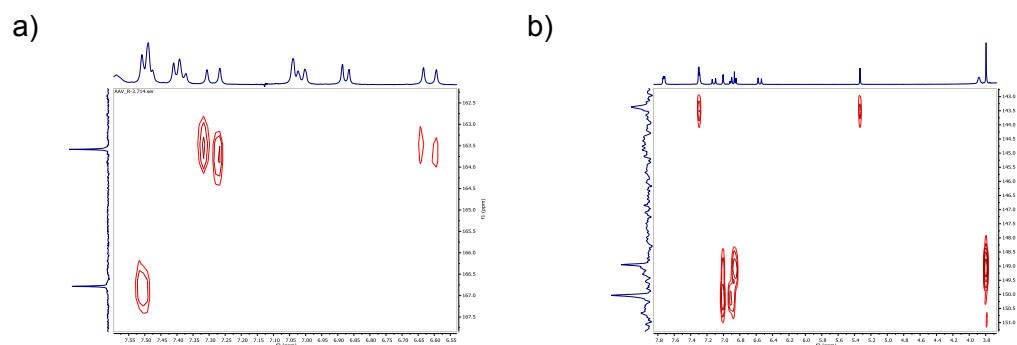
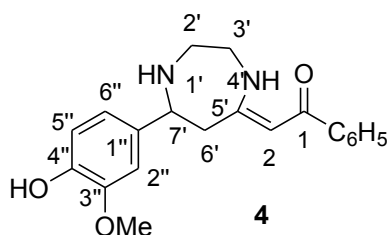


Figure 3. a) (¹H-¹³C) gs-HMBC of C5 and C7 in TFA, b) (¹H-¹³C) gs-HMBC of C_i, C3' and C4' in HMPA-*d*₁₈

Table 4. NMR data, chemical shifts (δ , ppm) and coupling constants (J , Hz), of compound **4**



| Nuclei | CDCl ₃ at 300 K | | DMSO- <i>d</i> ₆ at 300 K | |
|--------------------|----------------------------|-----------------------------------------------------------|--------------------------------------|--------------------------------------------------------------|
| | δ | J | δ | J |
| 1-CO | 188.5 | | 186.0 | ³ J= ³ J= ³ J=3.9 |
| 2-CH | 92.0 | ¹ J= 160.8 | 91.0 | ¹ J=161.3 |
| 1'-NH | -318.3 | | -319.9 | |
| 2'-CH ₂ | 50.2 | ¹ J= 133.1 | 49.5 | ¹ J= 133.4 |
| 3'-CH ₂ | 46.5* | ¹ J= 136.0 | 46.4* | ¹ J= 138.1 |
| 4'-NH | -264.6 | | -261.1 | |
| 5'-C | 168.4 | | 168.9 | |
| 6'-CH ₂ | 46.6* | ¹ J= 132.1 | 46.2* | ¹ J= 131.6 |
| 7'-CH | 61.9 | ¹ J= 137.1 | 60.7 | ¹ J= 134.5 |
| 1''-C | 137.0 | | 136.6 | |
| 2''-CH | 108.7 | ¹ J=156.5, ³ J= ³ J= 5.4 | 110.7 | ¹ J=156.3 |
| 3''-C | 146.7 | | 147.4 | |
| OCH ₃ | 56.0 | ¹ J= 144.8 | 55.6 | ¹ J=144.1 |
| 4''-C | 145.2 | ³ J= ³ J=6.5 | 145.2 | |
| 5''-CH | 114.4 | ¹ J=159.6 | 115.1 | ¹ J=157.8 |
| 6''-CH | 119.3 | ¹ J=158.6, ³ J= ³ J= 5.5 | 118.76 | ¹ J=158.7, ³ J=7.5, ³ J=4.7 |

In compound **4**, all the methylene protons (2-CH₂, 3-CH₂ and 6-CH₂) of the dihydrodiazepine ring are diastereotopic (Figure 4a) and the assignment is based on the values of the geminal coupling constants and confirmed by the (¹H-¹H) gs-COSY spectrum (Figure 4b).

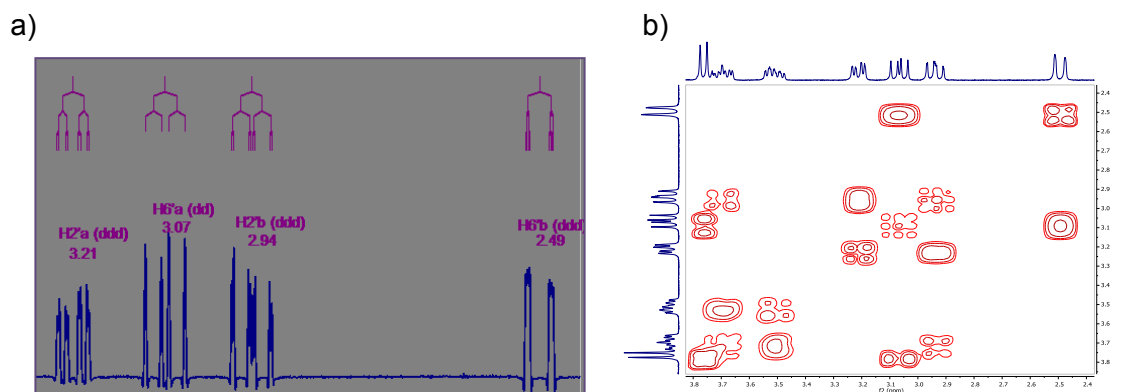


Figure 4. a) ¹H RMN spectrum, b) (¹H-¹H) gs-COSY of **4** in CDCl₃.

In what concerns ¹⁵N NMR, for diazepine **3** in neutral medium we have not been able to observe the nitrogen signals and in acid media the two signals are very similar -249.5 and -251.8 ppm (Figure 5a). In the case of diazepine **4** the two nitrogen signals appear clearly differentiated, enamino at -264.6 ppm and amino at -318.3 ppm (Figure 5b).

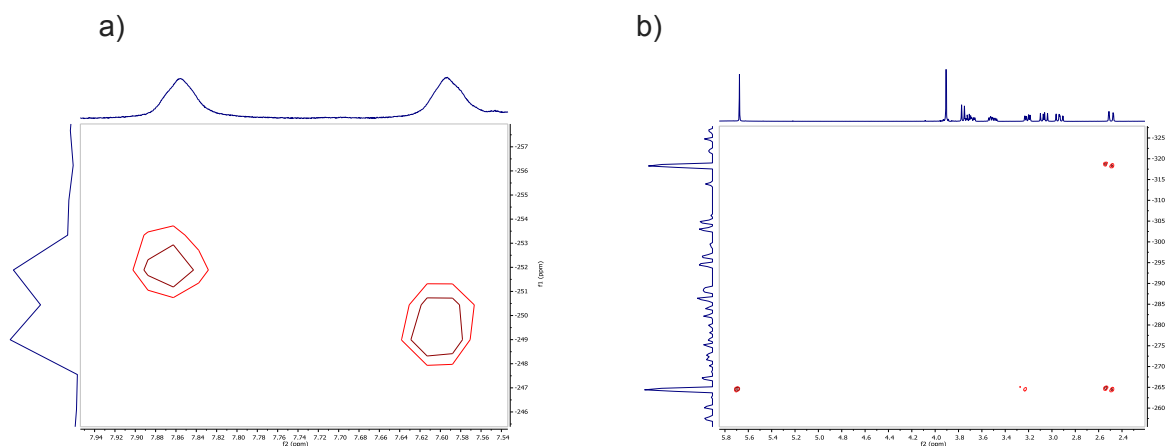


Figure 5. a) ¹H-¹⁵N HMBC NMR spectrum in TFA of compound **3**, b) ¹H-¹⁵N HMBC NMR spectrum of compound **4** in CDCl₃.

Experimental Procedure

Solution spectra were recorded at 300 K on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ¹H, 100.62 MHz for ¹³C and 40.56 MHz for ¹⁵N) spectrometer with a 5-mm inverse detection H-X probe equipped with a z-gradient coil for ¹H, ¹³C and ¹⁵N, save specified. Chemical shifts (δ in ppm)

are given from internal solvents, DMSO- d_6 (2.49 for ^1H and 39.5 for ^{13}C), CDCl_3 (7.26 for ^1H and 77.0 for ^{13}C) and HMPA- d_{18} (2.51 for ^1H and 35.8 for ^{13}C). And external reference $\text{CH}_3^{15}\text{NO}_2$ (0.00) for ^{15}N NMR was used. 2D (^1H - ^1H) gs-COSY and inverse proton detected heteronuclear shift correlation spectra, (^1H - ^{13}C) gs-HMQC, (^1H - ^{13}C) gs-HMBC, (^1H - ^{15}N) gs-HMQC, and (^1H - ^{15}N) gs-HMBC, were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode.⁹ Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms. Variable temperature experiments were recorded on the same spectrometer. A Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures.

Acknowledgments

Thanks are given to the Ministerio de Economía y Competitividad of Spain for financial support (Project number CTQ2014-56833-R).

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