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Synthesis and electrochemical oxidation of hybrid compounds: dihydropyridine-fused coumarins

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ABSTRACT

In this paper, a series of six dihydropyridine-fused coumarins were synthesized and electrochemically characterized in dimethylformamide (DMF).

Dihydropyridine ring oxidation on glassy carbon electrode (GCE) for condensed heterocyclic compounds revealed a single anodic peak. Oxidation potential values correlated fairly well with substituent effects at 9-position. The overall oxidation mechanism involved 2-electrons and 2-protons as determined by chronoamperometry.

Controlled-potential electrolysis followed by UV-Visible spectroscopy proves that dihydropyridine-fused coumarins are electrochemically oxidized in DMF giving rise to the aromatic pyridine derivative. ESR experimental spectra show a triplet, due to the C-centered dihydropyridyl radical trapped with N-tert-butylamine-α-phenylnitrone (PBN). Hyperfine coupling constant values (*a*N) of dihydropyridine-fused coumarins were higher than corresponding values for non-fused ones. These results could be due to the effect of the coupling of the dihydropyridine moiety with the coumarin ring over the splitting constant.

1. Introduction

Within the wide field of pharmaceuticals compounds, 1,4-dihydropyridines (DHPs) are a class of drugs based on a pyridine core. They have an ample spectrum of biological and pharmacological actions. Their clinical success in the treatment of cardiovascular diseases, mainly arterial hypertension, are supported by its calcium-channel modulating actions [1]. Moreover, it has been demonstrated that DHPs could prove to be highly important as multidrug-resistance-reversing agents in cancer chemotherapy [2].

In recent publications [3–5] the use of the DHP motif as a scaffold in the synthesis of other more complex heterocyclic compounds with promissory pharmacological applications has been reported.

Described 1,4-DHPs exhibit a wide variety of structural modifications, but they must have some essential features for exhibiting pharmacological activity, i.e., they must have a secondary nitrogen atom on the dihydropyridine ring and substituents, including aromatic ones at 4-position [6].

Oxidation of 1,4-DHPs either by chemical reactions, photochemical decomposition, or electrochemical techniques has received much attention, because the biological and pharmacological activity of these compounds lies in the integrity of the dihydropyridine moiety [7–9]. Furthermore, the main metabolic pathway of dihydropyridine drugs in human beings involves the oxidation of the dihydropyridine ring to the pyridine derivative mediated by the P450 enzymes [10].

Electrochemical oxidation of 1,4-DHPs has been extensively studied in aprotic medium by our laboratory [11–21] and others [22–27]. These investigations were generally carried out by using mainly rotating ring disk electrode (RRDE), linear and cyclic voltammetry and ESR spectroscopy, and have revealed that in non-aqueous solutions, 1,4-dihydropyridine derivatives are oxidized in a two-electron and 2-protons reaction, involving an ECE mechanism.

Safak and Simsek [28] have reviewed the chemistry of fused-dihydropyridines, showing that the condensation modifies the pharmacological activity of these types of compounds. Thus, dual effects have been found, i.e. antagonistic-agonistic activities on the

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[1] Tel: 56 2 9782812
[2] The authors dedicated this paper to one of us, Luis J. Núñez-Vergara, who passed away on October 25th 2013 when this paper was in the revision process.

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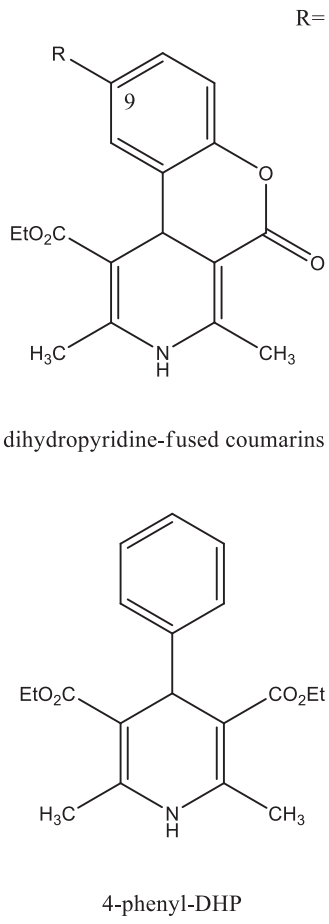

Fig. 1. - Chemical structures of studied compounds.

calcium channels, opening new avenues for its medical applications. To the best of our knowledge, this is the first study examining the effect of the condensation of dihydropyridines with coumarins on its electrochemical oxidation. Nevertheless, in a previous report [29], our laboratory established correlations between oxidation peak potential values and trypanosomicidal activity of some fused-dihydropyridines. Results demonstrated that these compounds had diminished inhibitory effects when compared with non-fused dihydropyridines.

In this paper we extended our interest on these types of molecules with the synthesis of a series of six dihydropyridine-fused coumarins with both electron withdrawing and electron-donor groups at 9-position which are electrochemically characterized on glassy carbon electrode in DMF.

Fig. 1

2. Experimental

2.1. Chemical structures of compounds are shown in Fig. 1.

All the new compounds were synthesized in accordance to previously reported procedures [30,31].

3. 4-phenyl-2,4-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine (4-ph-DHP)

^{1}HNMR (300 MHz, DMSO-d6): (δ) 1.16 (t, 6H, 2x -CH2CH3); 2.26 (s, 6H, 2x–CH3); 3.98 (q, 4H, 2x–OCH2CH3); 4.88 (s, 1H, ArCH); 7.18 (m, 3H, J= 6.975 Hz, 3x ArH) 7.22 (d, 2H, J= 8. 14 Hz, 2x ArH); 8.80 (s, 1H, NH). ^{13}CNMR (75 MHz, DMSO-d6): 10.51; 9.26; 9.07; 7.88; 7.78; 6.18; 2.09; 2.05; 2.04; 1.97; 0.63. Elem. Anal. $C_{19}H_{23}NO_4$: Calc. C: 62.28; H: 7.04; N: 4.25. Found: C: 62.08; H: 6.98, N: 4.30. Yield: 58%.

2,4-dimethyl-coumarin[3,4-c]dihydropyridine-1-carboxylic acid ethyl ester (H-CDHP): ^{1}HNMR (300 MHz, DMSO-d6): (δ) 1.10 (t, 3H, -CH3, J= 7.2); 2.00 (s, 3H, -CH3); 2.25 (s, 3H, -CH3); 4.09 (m, 2H, -CH2); 4.75 (s, 1H, -CH); 6.74-7.24 (m, 4H, -ArH); 8.97 (s, 1H, -NH). ^{13}CNMR (75 MHz, DMSO-d6): (δ) 13.4; 15.7; 17.7; 32.6; 58.6; 95.; 96.6; 115.7; 123.1; 123.4; 126.5; 131.7; 145.0; 147.1; 149.4; 163.9; 166.7. Elem. Anal. $C_{17}H_{17}NO_4$: Calc. C: 68.22; H: 5.73; N: 4.68. Found: C: 68.49; H: 5.70; N: 4.70. Yield: 34%.

9-methoxy-2,4-dimethyl-coumarin[3,4-c]dihydropyridine-1-carboxylic acid ethyl ester (MeO-CDHP):

^{1}HNMR (300 MHz, DMSO-d6): (δ) 1.05 (t, 3H, -CH3, J= 7.2); 2.62 (s, 3H, -CH3); 2.68 (s, 3H, -CH3); 3.76 (s, 3H, -OCH3); 4.17 (q, 2H, -CH2, J= 7.2); 6.89-7.36 (m, 3H, -ArH); 8.27 (s, 1H, -NH). ^{13}CNMR (75 MHz, DMSO-d6): (δ) 14.2; 19.4; 19.5; 47.5; 55.2; 60.1; 96.2; 101.4; 110.8; 11.9; 116.2; 117.7; 145.6; 146.7; 147.5; 155.3; 157.9; 165.3. Elem. Anal. $C_{18}H_{19}NO_5$: Calc. C: 65.64; H: 5.82; N: 4.25. Found: C: 65.90; H: 5.79; N: 4.24. Yield: 26%.

9-nitro-2,4-dimethyl-coumarin[3,4-c]dihydropyridine-1-carboxylic acid ethyl ester (NO_2-CDHP):

^{1}HNMR (300 MHz, DMSO-d6): (δ) 1.10 (t, 3H, -CH_3, J= 7.2); 2.04 (s, 3H, -CH_3); 2.30 (s, 3H, -CH_3); 4.12 (m, 2H, -CH_2); 4.87 (s, 1H, -CH); 7.32-8.17 (m, 3H, -ArH); 9.14 (s, 1H, -NH). ^{13}CNMR (75 MHz, DMSO-d6): (δ) 14.5; 17.0; 19.0; 33.9; 60.0; 94.0; 96.8; 118.2; 120.2; 127.9; 133.3; 143.8; 147.9; 149.1; 155.2; 163.4; 167.3. Elem. Anal. $C_{17}H_{16}N_2O_6$: Calc. C: 59.30; H: 4.68; N: 8.14. Found: C: 59.54; H: 4.70; N: 8.10. Yield: 14%.

2,4,9-trimethyl-coumarin[3,4-c]dihydropyridine-1-carboxylic acid ethyl ester (Me-CDHP)

^{1}HNMR (DMSO-d_6): (δ) 1.10 (*t*, 3H, CH_3-CH_2CO_2, J= 6.8 Hz), 2.25 (*s*, 3H, CH_3-Arom), 2.0 (*s*, 3H, 2.24, CH_3-DHP), 2.23 (*s*, 3H, 2.24, CH_3-DHP), 4.15 (*m*, 2H, CH_3-CH_2CO_2), 4.70 (*s*, 1H, 4H-DHP), 8.85 (*s*, 1H, NH-DHP), 6.97 (*m*, 3H, H-Arom). ^{13}CNMR (DMSO-d_6): 14.9, 17.16, 19.19, 21.46, 34.14, 60.00, 97.03, 97.90, 116.89, 125.19, 128.18, 132.77, 133.44, 146.10, 148.48, 148.78, 165.61, 168.07.Elem. Anal. $C_{18}H_{18}NO_3$: Calc. C: 72.95, H: 6.12, N: 4.73. Found: C: 72.85, H: 6.13, N: 4.75. Yield: 10%.

9-chloro-coumarin[3,4-c]dihydropyridine-1-carboxylic acid ethyl ester(Cl-CDHP)

^{1}HNMR (DMSO-d_6): (δ) 1.11 (*t*, 3H, CH_3-CH_2CO_2, J= 6.86 Hz), (δ) 2.0 (*s*, 3H, CH_3-DHP), 2.27 (*s*, 3H, CH_3-DHP), 4.10 (*m*, 2H, CH_3-CH_2CO_2), 4.75 (*s*, 1H, 4H-DHP), 9.04 (*s*, 1H, NH-DHP), 6.96 (*m*, 3H, H-Arom). ^{13}CNMR (DMSO-d_6): (δ) 13.53, 15.93, 18.02, 32.93, 58.82, 94.44, 95.96, 117.86, 123.40, 126.52, 127.24, 133.70, 145.84, 148.01, 148.25, 163.49, 166.48. Elem. Anal. $C_{17}H_{15}NO_3Cl$: Calc. C: 64.46, H: 4.77, N: 4.42. Found: C: 64.60, H: 4.76, N: 4.44. Yield: 14%.

9-bromo-coumarin[3,4-c]-dihydropyridine -1-carboxylic acid ethyl ester (Br-CDHP)

^{1}HNMR (300 MHz, CDCl3-d1) 1.37 (t, 3H, -CH3, J = 7.13), 2.62 (s, 3H, -CH3), 2.73 (s, 3H, -CH3),4.42 (q, 2H, -CH2-, J = 7.15), 7.15 (m, 3H, Ar-H). ^{13}CNMR (CDCl3-d1) d 13.2, 18.3, 22.7, 61.1, 112.8, 116.5, 117.3, 119.5, 127, 131.2, 134, 148.9, 149.9, 150.4, 158.2, 159.8, 168.5. Elem. Anal. $C_{17}H_{14}BrNO_4$: Calc. C: 54.27; H: 3.75; N: 3.72. Found: C: 54.20; H: 3.76; N: 3.71. Yield: 14%.

3.1. Electrochemical Characterization

3.1.1. Electrolytic medium

Dimethylformamide (DMF) containing 0.1 M tetrabutylammonium hexafluorophosphate (TBAHFP).