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Synthesis of 5-carboxy-6-methyl-3,4-dihydro-2(1H)-pyridone derivatives and their electrochemical oxidation to 2-pyridones

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ABSTRACT

A series of variously substituted 5-carboxy-6-methyl-3,4-dihydro-2(1H)-pyridone derivatives were synthesized and their oxidation potentials determined by cyclic voltammetry. The resulting 2-pyridone structure and a tricyclic heterocycle which was formed during an attempted synthesis of 4-(2-hydroxyphenyl) substituted 3,4-dihydro-2(1H)-pyridone were confirmed by single crystal X-ray crystallography.

1. Introduction

The 2-pyridones form structural units of many natural products and also possess interesting pharmacological properties such as reverse transcriptase inhibition of human immunodeficiency virus-1 (HIV-1) [1,2], cardiotonic for the treatment of heart failure [3], antitumor [4,5], antibacterial [6], and other biological activities [7,8].

Since we are interested in using the 3,4-dihydropyridone scaffold as a linker for constructing amphiphilic compounds for use in drug delivery applications [9], the main goal of this work is to provide oxidation potentials of variously substituted 3,4-dihydropyridones. This is important in metabolic studies and also in chemical modifications. In our work we require bromination of the allylic methyl group at position 6 and in our experience 1,4-dihydropyridines are oxidized with liquid bromine thus the oxidation potentials would provide some indication how the 3,4-dihydropyridones would behave under similar bromination conditions. The 3,4-dihydropyridone oxidation potentials are compared to the extensively studied 1,4-dihydropyridine (DHP) oxidation potentials, some of which are good antioxidants.

2. Results and discussion

2.1. Synthesis of 5-carboxy-6-methyl-3,4-dihydro-2(1H)-pyridone derivatives

The variously substituted 5-carboxy-6-methyl-3,4-dihydro-2(1H)-pyridone derivatives **4–13** were synthesized using a Hantzsch-like reaction from Meldrum's acid, acetoacetate, aldehyde, and NH_4OAc in a 1:1:1:1 ratio in boiling glacial acetic acid according to a published procedure [10] in yields ranging from 10% to 80% (Scheme 1).

The N-benzyl 4-unsubstituted 3,4-dihydropyridone **3** was obtained by deprotonating the 4-unsubstituted 3,4-dihydropyridone [11] with sodium hydride and subsequently reacting with benzylbromide.

During the reaction with salicylaldehyde, and methyl acetoacetate a product mixture was isolated which according to LC/MS analysis indicated 2 compounds with different masses one in 40% and the other in 46% yield. The product mixture was fractionally crystallized from EtOAc and EtOH and a diastereomeric mixture of compounds separated. NMR analysis indicated that the mixture was made up of the known tricyclic compound **1** and a new tricyclic compound **2** [12]. Compound **1** has been synthesized using Meldrum's acid, salicylaldehyde, and urea in 67% yield, a possible mechanism was also proposed [13].

According to this mechanism, a substituted coumarine intermediate in our case would retain the ester group to form compound **2** and not undergo decarboxylation like in compound **1**. The structure of compound **2** was confirmed by single crystal X-ray crystallography (Figure 1), which indicated that the compound crystallizes as a dimer with its antipode (Figure 2).

In the crystal structure the chains along crystallographic parameter **a** are formed by means of intermolecular hydrogen bonds of NH···O type with length of 2.993(4) Å (H···O14 = 2.05 Å, N11–H···O14 = 160°). Formation of the chains is shown in (Figure 2). Also in the crystal structure there are weak CH···O type hydrogen bonds; the shortest of them is C19–H···O14 with length of 3.241(4) Å.

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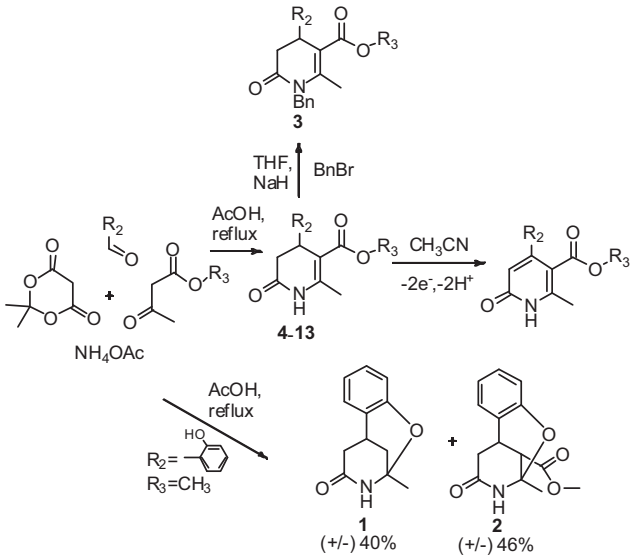


Scheme 1. Synthesis and electrochemical oxidation of 3,4-dihydropyridones and the formation of a tricyclic heterocycle when using salicylaldehyde in the *Hantzsch*-like reaction, the R groups are identified in Table 1.

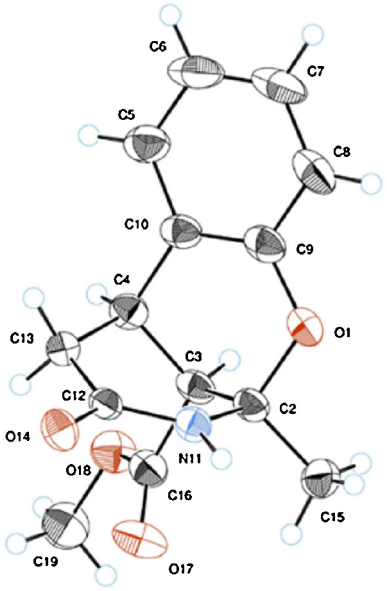


Figure 1. ORTEP molecular structure of compound **2**.

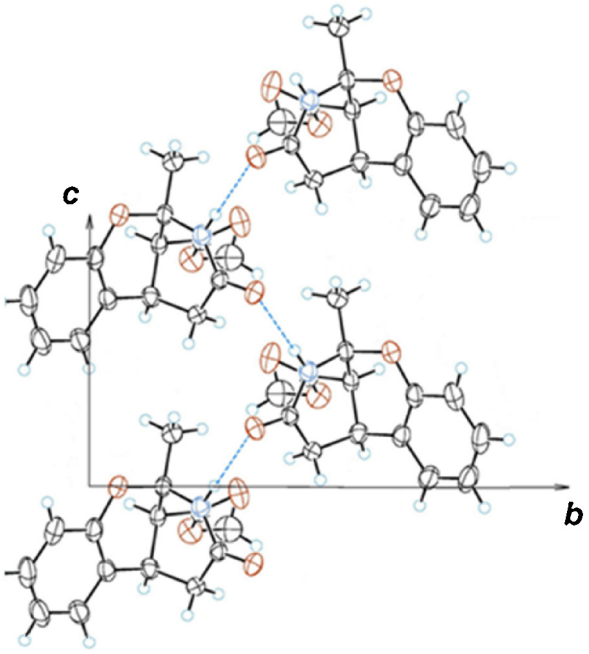


Figure 2. Formation of molecular chains in the crystal structure of **2** antipodes.

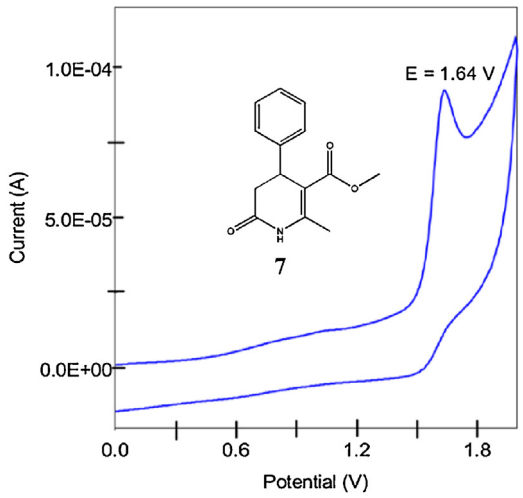


Figure 3. Cyclic voltammogram of 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester (**7**) $c = 2.5 \times 10^{-4}$ M in MeCN/0.1 M $NaClO_4$ on glassy carbon electrode.

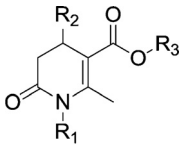
2.2. Electrochemical oxidation of 3,4-dihydropyridones

The electrochemical oxidation of 1,4-dihydropyridines has been extensively studied in different electrolytic media [14–19] which is of interest in biological redox processes and metabolic studies [20,21], but there is only one published report on the electrochemical oxidation of the related 3,4-dihydropyridones to obtain a quantitative account on the capacity of these compounds to undergo oxidation [22]. The 3,4-dihydropyridones can exist in two tautomeric forms – as derivatives of 6-oxo-1,2,3,4-tetrahydropyridine and 2-hydroxy-1,4-dihydropyridine. The NMR spectra in anhydrous CD_3CN show that these compounds at the selected experimental conditions for electrochemical study are in the undissociated oxo form. It has been demonstrated that the removal of electrons from 3,4-dihydropyridones proceeds with considerably greater difficulty than from the 3,5-diethoxycarbonyl-1,4-dihydropyridines [23,24].

Electrochemical oxidation of the 3,4-dihydropyridone derivatives synthesized in this work were studied by cyclic voltammetry (CV) on a stationary glassy carbon electrode in dry acetonitrile.

All the investigated 3,4-dihydropyridones undergo an irreversible oxidation (Figure 3) at potential $\geq$1.5 V *vs* NHE (Table 1). The oxidation potential of 3,4-dihydropyridones is not changed if the NH group is protected by a benzyl group, compound **3** (Table 1, entry 1). As one can see for compounds **4–6** (Table 1, entries 2–4) the length of the ester has no influence on the oxidation potentials of 4-unsubstituted 3,4-dihydropyridones, while a phenyl group at position 4 of the heterocycle **7** (Table 1, entry 5) shifts the oxidation potential 100 mV to more positive values compared to 4-unsubstituted analogue **4** (Table 1, entry 2). The presence of an electron withdrawing nitro group on the aromatic moiety causes the heterocycle to become more positive and thus more difficult to oxidize as indicated by an increase of about 80 mV in the oxidation potential for compounds **8** and **9** (Table 1, entries

Table 1
Oxidation potentials of 3,4-dihydropyridones **3**–**13** on glassy carbon electrode measured *vs* NHE in MeCN/0.1 M $NaClO_4$



3-13

Entry	Comp	R^1	R^2	R^3	*E*, V
1	**3**	$CH_2C_6H_5$	H	CH_3	1.52
2	**4**	H	H	CH_3	1.53
3	**5**	H	H	$C_{12}H_{25}$	1.53
4	**6**	H	H	$C_4H_8C_8F_{17}$	1.54
5	**7**	H	C_6H_5	CH_3	1.64
6	**8**	H	3-NO_2-C_6H_4	CH_3	1.72
7	**9**	H	4-NO_2-C_6H_4	CH_3	1.71
8	**10**	H	3-OH-C_6H_4	CH_3	1.58
9	**11**	H	4-OH-C_6H_4	CH_3	1.46
10	**12**	H	4-OCH_3-C_6H_4	CH_3	1.58
11	**13**	H	C_6H_5	$C_4H_8C_8F_{17}$	1.64

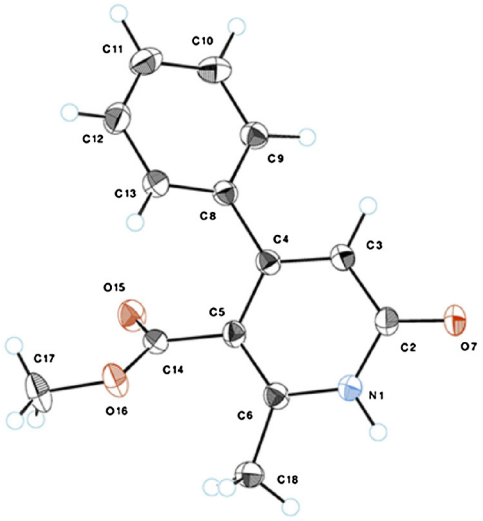


Figure 4. ORTEP molecular structure of compound **14**.

6 and 7), while an electron donating methoxy group of the compound **12** (Table 1, entry 10) or hydroxyl group of the compounds **10** and **11** (Table 1, entries 9 and 10) facilitates the anodic process and the oxidation potential is decreased by about 170 mV. Thus in aprotic media the 4-hydroxyphenyl group has quite a significant effect on the anodic process of the 3,4-dihydropyridone moiety for compound **11** as a decrease of 180 mV was observed compared to the unsubstituted 4-phenyl-3,4-dihydropyridone (**7**) this was not the case in oxidation of 4-hydroxy-phenylsubstituted 1,4-dihydropyridine where the decrease was only 24 mV compared to 4-phenyl-1,4-DHP [19]. Nevertheless, the 3,4-dihydropyridones **3**–**13** undergo electro-oxidation at about 600 mV higher potential than the corresponding 1,4-dihydropyridines [19,25,26]. 2-Methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester (**7**) was anodically oxidized on a preparative scale at a 1.8 V potential and after 24 h 2-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid methyl ester (**14**) was obtained quantitatively [27]. So, in the aprotic media the overall anodic oxidation of 3,4-dihydropyridones involves a loss of two electrons and two protons from the heterocycle (Scheme 1).

After isolation **14** was recrystallized from EtOH giving X-ray quality crystals which after X-ray diffraction confirmed the structure of the oxidized 4-phenyl-3,4-dihydropyridone. Figure 4 shows

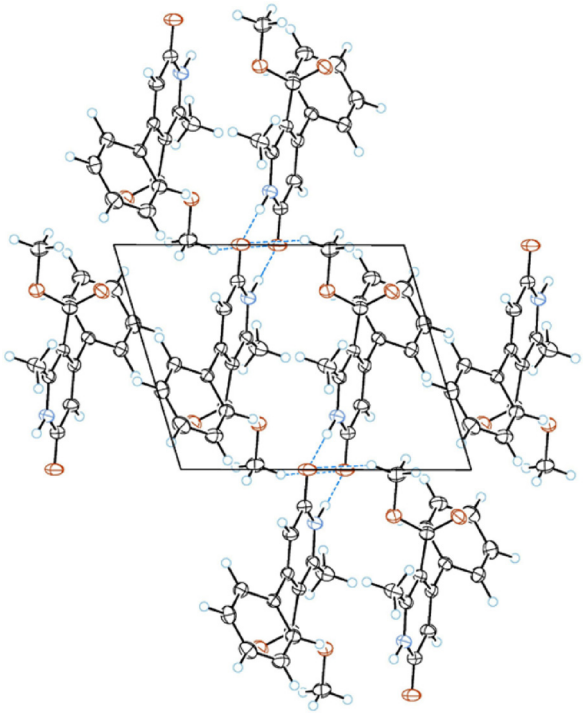


Figure 5. Projection of the crystal structure of **14** along crystallographic direction [1 0 0] showing intermolecular hydrogen bonds.

a perspective view of molecule **14** with thermal ellipsoids and the atom-numbering scheme followed in the text. The dihedral angle between the pyridone cycle and the phenyl ring are equal to 44.2(2)°; the pyridone and the ester group form a dihedral angle of 55.9(2)°. In the crystal structure the dimers of molecule **14** are formed by means of strong intermolecular hydrogen bonds of NH···O type (see Figure 5). The lengths of these bonds are 2.769(3) Å (H···O7 = 1.81 Å, N1–H···O7 = 177°). In the crystal structure the intramolecular contact C17···O7 (3.223(3) Å) can also be considered as a weak CH···O type hydrogen bond (H···O7 = 2.60 Å, C17–H···O7 = 123°).

3. Conclusions

In summary 3,4-dihydropyridone derivatives were prepared by a 4 component *Hantzsch*-like reaction and a tricyclic heterocycle was formed when salicylaldehyde was used as the aldehyde component. Comparing 3,4-dihydropyridones **3–13** and the corresponding 1,4-dihydropyridine derivatives it can be concluded that the difference between the electrochemical oxidation potentials of both heterocyclic systems is about 600 mV higher for the 3,4-dihydropyridones making allowing these heterocycles to be brominated using liquid bromine without undergoing oxidation. A phenyl group at position 4 of 3,4-dihydropyridone increases the oxidation potential and an electron withdrawing nitro group on the phenyl makes the heterocycle more positive and the oxidation potential is increased further, while an electron donating hydroxy or methoxy substituent on the phenyl group at position 4 of the heterocycle facilitates oxidation and the oxidation potential is reduced by about 170 mV. The tricyclic heterocycle formed during an attempted synthesis of 4-(2-hydroxyphenyl) substituted 3,4-dihydro-2(1H)-pyridone and the 2-pyridone structure **14** as the 3,4-dihydropyridone electro-oxidation product involving the removal of 2 electrons and 2 protons were confirmed by single crystal X-ray crystallography.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cplett.2016.02.045.

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[12] Data for (+/−)-methyl 9-methyl-11-oxo-8-oxa-10-azatricyclo[7.3.1.02,7] trideca-2,4,6-triene-13-carboxylate (**2**): MW 261.27 LC/MS (ESI+ 262), mp. 201–203 °C, Anal. Calcd for: $C_{14}H_{15}NO_4$: C(64.36) H(5.79) N(5.36) found: C(64.46) H(5.75) N(5.37), ^{1}H NMR 400 MHz ($CDCl_3$): δ = 7.20–7.14 (m, 1H), 7.08 (dd, J = 7.6, 1.7 Hz, 1H), 6.94 (td, J = 7.4, 1.2 Hz, 1H), 6.80 (dd, J = 8.2, 1.1 Hz, 1H), 6.37 (s, 1H), 3.79 (s, 3H), 3.48 (ddd, J = 5.3, 3.6, 1.9 Hz, 1H), 3.18 (dd, J = 2.4, 1.2 Hz, 1H), 2.86 (dd, J = 17.8, 5.2 Hz, 1H), 2.52 (dt, J = 17.8, 1.4 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR 100.3 MHz ($CDCl_3$): δ = 170.4, 170.3, 150.5, 129.2, 128.6, 124.9, 122.0, 117.7, 83.1, 52.5, 45.3, 36.7, 32.9, 25.8.
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[27] Data for methyl 2-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (**14**): MW 243.26 LC/MS (ESI+ 244) mp. 205–206 °C. Anal. Calcd for $C_{14}H_{13}NO_3$: C (69.12) H (5.39) N (5.76) found: C (69.08) H (5.24) N (5.72). ^{1}H NMR 400 MHz ($CDCl_3$): δ = 7.42–7.27 (m, 5H), 6.44 (s, 1H), 3.48 (s, 3H), 2.55 (s, 1H). ^{13}C NMR 100.3 MHz ($CDCl_3$): δ = 167.4, 164.6, 154.7, 147.5, 139.0, 128.6, 128.5, 126.9, 116.9, 112.7, 51.8, 18.1 ppm.