Autooxidation and rearrangement reactions of isoquinolinone derivatives

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Abstract

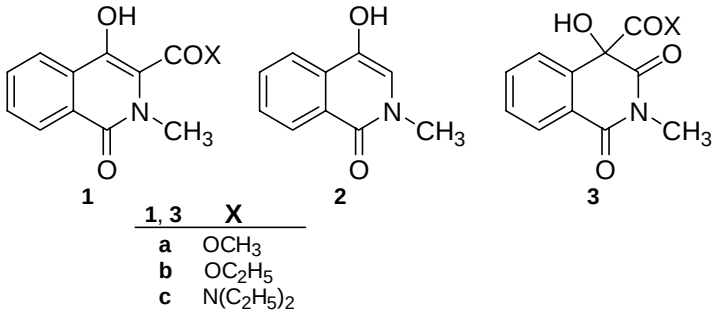
4-Hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid derivatives **1** in solution afford a mixture of the dealkoxycarbonylated product **2** and 4-hydroxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid derivatives **3**. Reactions **1→3** involve compounds **1** tautomerization, C-3 hydroxylation and final α-ketol type rearrangement. The synthetic utility of this transformation was explored.

Keywords: Isoquinolinones, autooxidation, rearrangement, tautomerization, hydroperoxide, hydroxylation

Introduction

Alkyl 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylates (**1**, X=OR) are useful polyfunctional synthetic intermediates for the preparation of biologically active compounds.[1] In the course of our previous research related to the synthesis and properties of isoquinolinones,[2] we observed that samples of such compounds decomposed in solution. This fact had previously been observed by Lombardino, who reported that methyl ester **1a** was unstable, but decomposition products were not isolated.[1a]

In this work we present the isolation and characterization of final decomposition products of methyl ester **1a**, as well as intermediaries leading to them. Structural requirements for such a transformation are evaluated and its synthetic utility is explored.



Results and Discussion

A sample of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester **1a** maintained in solution for several weeks, finally transformed into two products which were chromatographically isolated. The most mobile band developed colour with ferric chloride solution. The ^{1}H-NMR spectrum of the isolated compound showed a broad signal (exchangeable) at 9.2 ppm, coherent with an enol hydroxyl, five differentiated signals in the aromatic zone and only one signal corresponding to a lactam *N*-methyl in the aliphatic zone. Such results, together with MS data ($M^{+\cdot}$: *m/z* 175, 100%) lead us to propose the 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline **2** structure which was unequivocally confirmed by comparison with an authentic sample prepared by acid hydrolysis of **1**.[1a]

Elemental analysis and HRMS of compound obtained from the second eluted band fitted with molecular formula: $C_{12}H_{11}NO_5$ thus making evident an oxygen atom incorporation in starting compound **1a**. By bidimensional heteronuclear correlation spectra (HMQC, HMBC) structure of the product was established as a homophthlimide derivative, namely 4-hydroxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid methyl ester **3a**. The main correlations observed in the HMBC spectra which account for our proposed structure are shown in Figure 1.

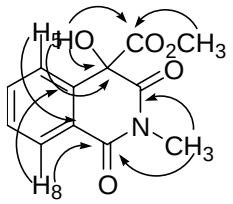
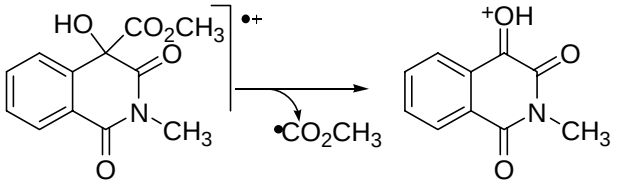


Figure 1. Main correlations in the HMBC spectrum of compound **3a**.

This structure is coherent with the observed fragmentation pattern in the mass spectra, showing *m/z* 190 as the base ion, resulting from $M^{+\cdot}$ alkoxydecarbonylation (Scheme 1).[3]



3a *m/z* 249 ($M^{+\bullet}$, 11%) *m/z* 190 (100%)

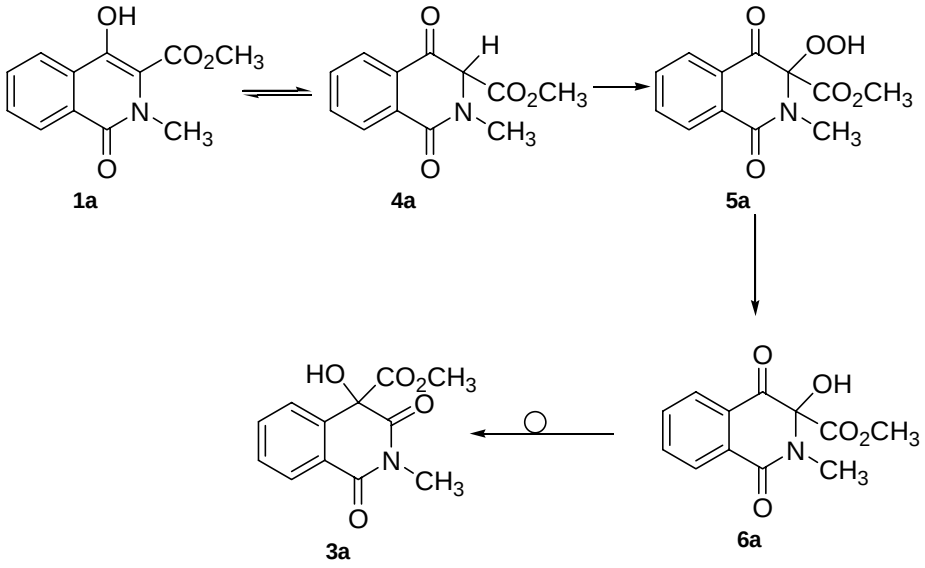
Scheme 1

Isolation of intermediaries in 1a → 3a transformation

Transformation **1a→3a** occurs in different solvents, especially in methanol, and yet slowly in the solid state. Several lines of evidences implicate an autooxidation process mediated by free radicals since transformation: i) is accelerated in air bubbled solvent indicating the role of oxygen in the process, ii) does not occur in the absence of light and under strictly deoxigenated conditions, iii) is inhibited by radical scavengers (BTH) and iv) results accelerated by benzoyl peroxide and light.

To ascertain the mechanism of such a profound transformation of isoquinolinone nucleous under mild conditions we made attempts to isolate intermediaries. Thus, a homogeneous sample of methyl ester **1a** having a neat enol structure[1a] was dissolved in chloroform, and after brief storage it was periodically analyzed by TLC. Besides products **2** and **3a**, appearance of three intermediate compounds of low R_f (chloroform-methanol 9:1), which were consumed by transforming into final products was observed. One of them, eluted under argon atmosphere and isolated as an oil, has the spectroscopic features of dicarbonyl tautomer **4a** of starting material (Scheme 2). NMR spectra present resonances which strongly diagnostic its structure. In ^{1}H-NMR spectrum a singlet at 7.9 ppm (one proton, not exchangeable) is attributed to H-3. In ^{13}C-NMR spectrum the keto carbonyl (C-4) resonance appears at 188.7 and C-3 (CH, Dept-90) at 90.8 ppm. In agreement with the proposed structure the IR spectra shows a band at 1724 cm^{-1} related to keto carbonyl stretching. This compound is highly reactive, being very quickly transformed in the presence of oxygen.

Another eluted band afforded a compound of mp 150-152 ºC which showed a positive potassium iodide starch test. The HRMS corresponds to a compound of molecular formula $C_{12}H_{11}NO_6$ and shows characteristic lost of OOH and O. The ^{1}H-NMR spectrum displays an exchangeable signal at 9.90 ppm and a characteristic set of signals for the aromatic protons similar to that of compound **4a**, so that hydroperoxide **5a** structure was assigned (Scheme 2). According to this ^{13}C-RMN spectrum shows typical signals of saturated carbon at 94.6 (C-3) and keto carbonyl (C-4) at 185.3 ppm.



Scheme 2

The third compound (mp 118-120 ºC) shows a set of signals for the aromatic protons similar to that of compounds **4a** and **5a** and a exchangeable signal at 4.89 ppm in the ^{1}H-NMR spectrum. ^{13}C-NMR shows characteristic signals of saturated carbon at 86.9 ppm (which do not present coupling C-H bond) and keto carbonyl at 188.3 (CO-4). HRMS indicates a molecular formula $C_{12}H_{11}NO_5$ so that **6a** structure was assigned to this derivative. Structure of compounds **5a** and **6a** were confirmed by comparison with authentic samples obtained from **1a** (see below, Scheme 4).

To rationalize our experimental results, we presumed that **1a** transformation begins with the tautomerization of compound **1a** to **4a** followed by C-3 hydroxylation to the hydroxy derivative **6a**, probably *via* the corresponding hydroperoxide **5a** as intermediate. Finally, **6a** rearrangement leads to the final product **3a** (a stable imide) (Scheme 2).

In the following section we analyze features of each step as well as previous literature reports.

The tautomerization 1a → 4a is the key step of the process, from which transformation of compound **1a** is unchained. The literature describes some antecedents of 4-hydroxyisoquinolinone tautomerization in solution where a shift towards dioxo form is observed.[4] Afterwards, isolation of two tautomeric forms of 2-(*o*-acetylaminophenyl)- 4-hydroxy-1-oxo-3-phenyl-1,2-dihydroisoquinoline was reported, although structures were only confirmed by IR spectroscopy.[5]

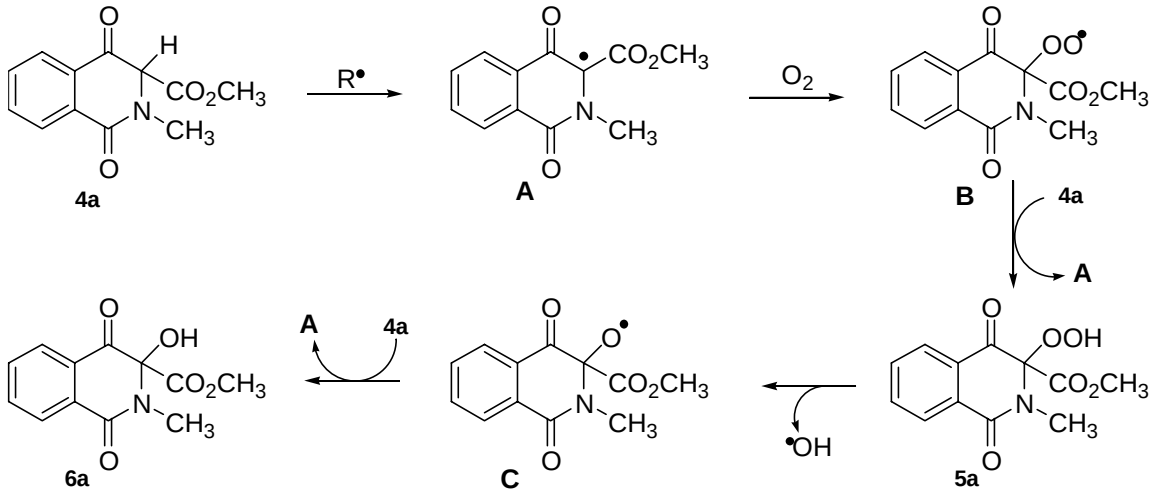
To the best of our knowledge, compound **4a** isolated in **1a** decomposition represents the first example of isolation of a highly reactive 4-hydroxyisoquinolinone keto tautomer which could be characterized by NMR spectroscopy. The highest speed of **1a → 3a** transformation in methanol may be related to this step, as it is well known that in keto-enol tautomerism, polar solvents favour the shift to the keto form (the most polar).[6]

Tautomer **4a** can also be the origin of compound **2**. Easy hydrolysis of β-ketoester (α-substituted with a strongly withdrawing group), together with spontaneous decarboxylation of the obtained β-ketoacid[7] probably accounts for attainment of decarbetoxylated product.

4-Hydroxyisoquinolinone C-3 hydroxylation has precedents in literature.[8-11]. It involves 3-acetoxylation of the keto form (generally employing Hg(II) or Pb(IV) acetates) with further hydrolysis.[12]

In our case, isolation of hydroperoxide **5a** from the reaction mixture as well as reaction conditions mentioned above made us presume that hydroxylation leading to compound **6a** is consequence of an autooxidation process mediated by free radicals, in which hydroperoxide **5a** is probably the intermediary. Among literature reports related to this fact, autooxidation of a 2,3-dialkyl-4-hydroxy-1,2-dihydroisoquinoline leading to a hydroperoxide and the corresponding alcohol as a result of C-3 oxidation can be mentioned.[14]

Although it is not the objective of our work to continue with the study of the precise mechanism of this reaction, we propose a possible pathway leading to intermediaries **5a** and **6a** (Scheme 3). Taking into account mechanistic antecedents of related reactions,[15] such process would be initiated by typical free radical sources leading to carbon radical **A**. This radical reacts with molecular oxygen to form peroxy radical species **B** which abstracts hydrogen from the substrate leading to hydroperoxide **5a** formation. Finally, formation of hydroxy derivative **6a** can be attributed to homolytic cleavage of the corresponding hydroperoxide to the active alkoxy radical **C**. Other possible mechanisms cannot be ruled out.



Scheme 3

The rearrangement 6a→3a may be interpreted as a consequence of 1,2-ethoxycarbonyl shift in an α-ketol type rearrangement,[16] favoured by OH acidity. This type of reactions has been widely studied in aliphatic and carbocyclic compounds, although examples in heterocyclic compounds having α-hydroxycarbonyl moiety such as 3-hydroxy-2,4-quinolinediones also exists.[17] It

generally occurs by acid or base catalysis although examples of thermally induced reactions have also been reported. In isoquinolone derivatives, literature describes thermal transformation of the 3-hydroxy-1,4-dioxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline into 4-hydroxy-1,3-dioxo-4-phenyl-1,2,3,4-tetrahydroisoquinoline[8] where phenyl is the migratory group. From a mechanistic point of view, it is generally accepted that the fundamental pathway in such rearrangements is an intramolecular migration of a group (which should acquire partial carbanionic character) from the carbinol carbon (C-3) to the potentially electrophylic carbonyl carbon (C-4) together with an intramolecular proton transfer (Figure 2).

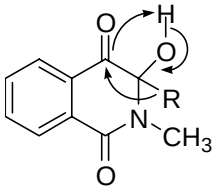


Figure 2. α-Ketol type rearrangement of compounds **6**.

However, a mechanism involving a transition state with pronounced dirradicaloid character such as that suggested by Sprecher[18] cannot be discarded. The facile 1,2-shift of the ethoxycarbonyl group in compound **6a** would be comprehensible in terms of the expected stability of the $^{\cdot}CO_2R$ radical.[19]

Scope of the transformation 1 → 3 and synthetic applications

Although our primary goal was aimed at a better understanding of the possible pathway leading to compound **3a**, we were also interested in investigating the scope of the transformation as well as its possible synthetic utility. Thus, a series of isoquinolinones having different structural features was subsequently evaluated.

Ethyl ester **1b** as well as the corresponding *N*,*N*-diethylamide **1c** show a similar behaviour to that of methyl ester **1a** affording **3b** and **3c** respectively, in approximately 20 days. As it can be expected, compound **3c** shows diastereotopic methylene hydrogens due to the presence of chiral C-4. In contrast to compounds **1a-c**, the corresponding *N*-lactam unsubstituted isoquinolinones are stable to the air. Stability of these compounds may be justified taking into account the presence of a resonance assisted hydrogen bonding effect (RAHB)[20] which involves the enol hydroxyl and the extranuclear carbonyl[21] (Figure 3).

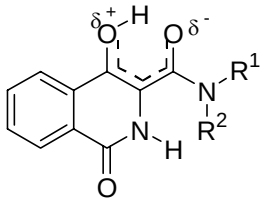


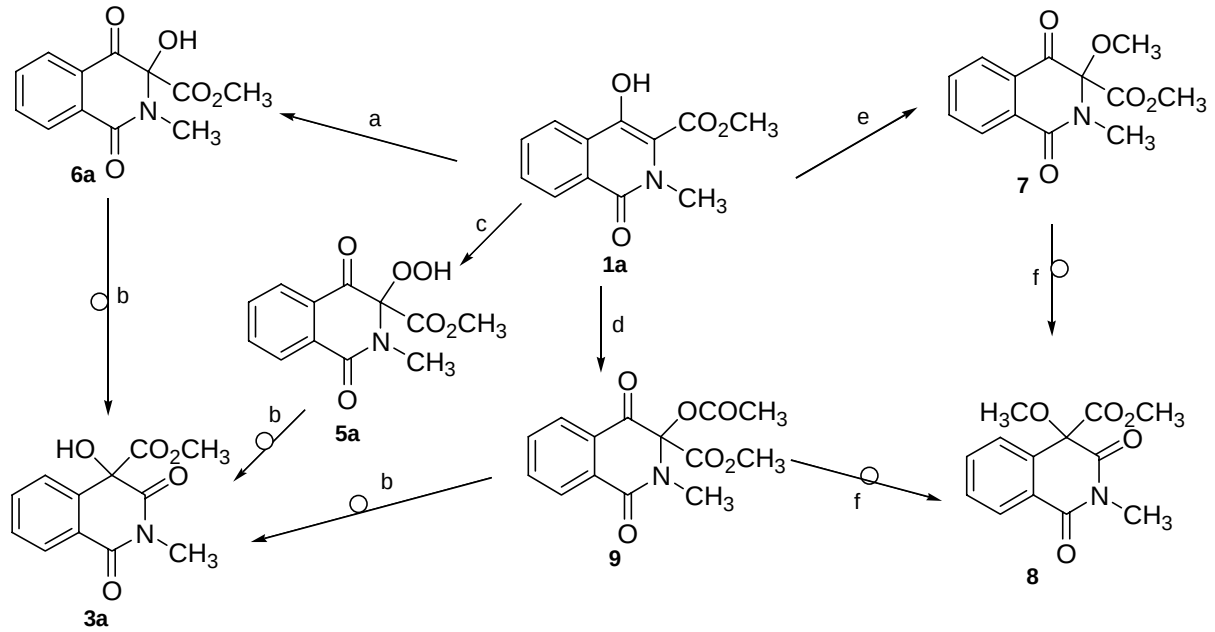
Figure 3. RAHB effect in *N*-lactam unsubstituted isoquinolinones.

Instead, in isoquinolinones **1a-c,** the lactam *N*-methyl steric effect inhibits keto-enol system planarity and hence the RAHB effect,[22] thus favouring the shift to keto tautomer and further hydroxylation and rearrangement.

In order to evaluate the importance of C-3 hydroxyl in the rearrangement, 3-methoxy derivative **7** was synthesized and tested (Scheme 4). It was obtained by reaction of **1a** with NBS in methanol at -10ºC. This compound is stable at room temperature but it rearranges to **8** by prolonged heating in methanol. The resistance of compound **7** to such rearrangement is probably related to the absence of hydroxyl hydrogen and would evidence a different mechanism from that of hydroxy derivatives **6**.

Finally, we turned our attention to explore synthetic utility of **1** → **3** transformation. As it is difficult to fix the best conditions for spontaneous autooxidation and rearrangement of compounds **1** in order to obtain acceptable yields of final products **3 ,** we explored other variants which allow us the application of this process as a synthetic tool.[23] Thus, preparation of hydroxy derivative **6a** by reaction of **1a** with NBS at room temperature and its further rearrangement by reflux in water for 2 hs leads to **3a** (72 %) (Scheme 4). Alternatively, transformation **1a** → **3a** may be attained via hydroperoxide **5a** obtained by catalytic hydroperoxydation of **1a** employing manganese(III) acetate (65% yield).

Acetoxy derivative **9** (easily obtained by treatment of **1a** with lead(IV) acetate) is also a proper synthetic precursor of 4,4-disubstituted isoquinolinodiones. Compound **9** is stable at room temperature but it is transformed to **3a** and **8** respectively by heating with water or methanol.



a: NBS/H_2O. b: H_2O, reflux. c: $Mn(Ac)_3$/AcOH. d: $Pb(Ac)_4$/AcOH. e: NBS/ CH_3OH. f: CH_3OH, reflux.

Scheme 4. Chemical transformations of compound **1a** with synthetic utility.

Experimental Section

General Procedures. Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer employing TMS as internal reference. Deuteriochloroform or DMSO-d6 were used as the solvent, and the standard concentration of the samples for ^{1}H-NMR was 10 mg/mL and 25 mg/mL for ^{13}C-NMR. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Deuterium oxide was employed to confirm exchangeable protons (ex). Splitting multiplicities are reported as singlet (s), broad signal (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Two-dimensional spectra (HMQC, HMBC and ROESY) were recorded with a Bruker AVANCE DRX 300 spectrometer. Electron impact MS were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 70 eV. Elemental analyses were carried out on a Carlo Erba EA 1108 instrument (Unidad de Microanálisis y Métodos Físicos Aplicados a la Química Orgánica, CONICET, FCEN, UBA). The IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. TLC analyses were carried out on Silica gel 60 F_{254} using chloroform-methanol (9:1) as solvent. Preparative thin layer separations (PLC) were carried out by centrifugally accelerated, radial chromatography using Chromatotron model 7924T. The rotors were coated with Silica Gel 60 PF_{254} and the layer thickness was 2 mm. Chloroform and increasing percentages of methanol were used as eluent. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

Compounds **1a-c** were prepared following literature procedure.[2]

Spontaneous transformation of compounds 1a-c

A typical procedure is described. A solution of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester **1a** (0.5 g) freshly prepared in chloroform (15 mL) was maintained at room temperature for 3-4 weeks until disappearance of the starting product. The crude product showed two main spots by TLC. Separation of the two compounds was achieved by centrifugal PLC. The first band eluted gave 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline **2** (21-32%). The structure was confirmed by comparison with an authentic sample prepared by acid hydrolysis of **1a**,[1a] mp and mixed mp 225-227 ºC. The slower moving band afforded the 4-hydroxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid methyl ester (**3a**) (40-55%).

In a manner analogous, spontaneous transformation of **1b** and **1c** afforded compounds **3b** and **3c** respectively.

4-Hydroxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid methyl ester (3a). Yield 38-44%, mp 88-90 ºC (2-propanol). Analyses (%C, %H, %N) calcd for $C_{12}H_{11}NO_5$: 57.83, 4.45, 5.62; found: 57.88, 4.50, 5.57; ν_{max}/cm^{-1} (KBr): 3300, 3060, 1740, 1732, 1596, 1250; δ_H (DMSO-d6) 8.15 (1H, dd, $^{3}J_{8,7}$= 7.6, $^{4}J_{8,6}$= 1.6, H-8), 7.78 (1H, dt, $^{3}J_{6,5/6,7}$= 7.6, $^{4}J_{6,8}$= 1.6, H-6), 7.64 (1H, t, $^{3}J_{7,6/7,8}$= 7.6, H-7), 7.62 (1H, d, $^{3}J_{5,6}$= 7.6, H-5), 7.60 (1H, ex, br

s, OH), 3.61 (3H, s, OCH_3) and 3.27 (3H, s, NCH_3); δ_C (DMSO-d6) 170.4 (C-3), 169.1 (CO_2), 163.4 (C-1), 137.1 (C-4a), 134.5 (C-6), 129.7 (C-7), 128.1 (C-8), 126.1 (C-5), 124.2 (C-8a), 75.5 (C-4), 53.6 (OCH_3) and 27.1 (NCH_3); *m/z* (EI) 250 ($M^{+\cdot}$ + 1, 2%), 190 ($M^{+\cdot} - CO_2CH_3$, 100%), 189 ($M^{+\cdot} - CO_2CH_3 - H$, 8%), 162 ($M^{+\cdot} - CO_2CH_3 - CO$, 9%), 161 ($M^{+\cdot} - CO_2CH_3 - H$ - CO, 7%), 149 (25%), 132 ($M^{+\cdot} - CO_2CH_3 - OCNCH_3$, 5%), 104 (18%).

4-Hydroxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid ethyl ester (3b). Yield 44-52%; mp 77-79 ºC (2-propanol). Analyses (%C, %H, %N) calcd for $C_{13}H_{13}NO_5$: 59.31, 4.98, 5.32; found: 59.39, 4.94, 5.36; ν_{max}/cm^{-1} (KBr): 3306, 3068, 1743, 1730, 1599; δ_H (DMSO-d6) 8.18 (1H, dd, $^3J_{8,7}$= 7.7, $^4J_{8,6}$= 1.5, H-8), 7.79 (1H, dt, $^3J_{6,5/6,7}$= 7.7, $^4J_{6,8}$= 1.5, H-6), 7.66 (1H, t, $^3J_{7,6/7,8}$= 7.7, H-7), 7.60 (1H, d, $^3J_{5,6}$= 7.7, H-5), 7.49 (1H, ex, br s, OH), 4.24 (2H, q, $^3J_{CH2,CH3}$= 7.2, OCH_2), 3.29 (3H, s, NCH_3) and 1.29 (3H, t $^3J_{CH3,CH2}$= 7.2, CH_3); δ_C (DMSO-d6) 170.0 (C-3), 167.1 (CO_2), 161.2 (C-1), 136.3 (C-4a), 134.8 (C-6), 129.4 (C-7), 127.9 (C-8), 125.6 (C-5), 124.0 (C-8a), 75.8 (C-4), 62.1 (OCH_2), 26.2 (NCH_3) and 14.0 (CH_3); *m/z* (EI) 263 ($M^{+\cdot}$ + 1, 1%), 190 ($M^{+\cdot} - CO_2C_2H_5$, 100%), 189 ($M^{+\cdot} - CO_2C_2H_5 - H$, 9%), 162 ($M^{+\cdot} - CO_2C_2H_5 - CO$, 7%), 161 ($M^{+\cdot} - CO_2C_2H_5 - H$ - CO, 10%), 149 (23%), 132 ($M^{+\cdot} - CO_2C_2H_5 - OCNCH_3$, 5%), 104 (19%).

***N,N*-Diethyl-4-hydroxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (3c).** Yield 45-56%; mp 96-98 ºC (2-propanol). Analyses (%C, %H, %N) calcd for $C_{15}H_{18}N_2O_4$: 62.06, 6.25, 9.65; found: 62.15, 6.28, 9.62; ν_{max}/cm^{-1} (KBr): 3310, 3050, 1746, 1731, 1600, 1590; δ_H (DMSO-d6) 8.36 (1H, dd, $^3J_{8,7}$= 7.4, $^4J_{8,6}$= 1.3, H-8), 7.81 (1H, dt, $^3J_{6,5/6,7}$= 7.4, $^4J_{6,8}$= 1.3, H-6), 7.70 (1H, t, $^3J_{7,6/7,8}$= 7.4, H-7), 7.66 (1H, d, $^3J_{5,6}$= 7.4, H-5), 6.51 (1H, ex, br s, OH), 3.75-3.49 (4H, m, NCH_2), 3.45 (3H, s, NCH_3), 1.31 (3H, t $^3J_{CH3,CH2}$= 7.2, CH_3) and 1.13 (3H, t $^3J_{CH3,CH2}$= 7.1, CH_3); δ_C (DMSO-d6) 172.1 (C-3), 165.0 (CON), 160.3 (C-1), 137.3 (C-4a), 134.4 (C-6), 129.1 (C-7), 127.5 (C-8), 126.1 (C-5), 124.2 (C-8a), 77.3 (C-4), 41.3 (NCH_2), 40.9 (NCH_2), 27.0 (NCH_3), 14.1 (CH_3) and 12.8 (CH_3); *m/z* (EI) 290 ($M^{+\cdot}$, 12%), 190 ($M^{+\cdot} - CON(C_2H_5)_2$, 40%), 162 ($M^{+\cdot} - CON(C_2H_5)_2 - CO$, 5%), 149 (20%), 104 (17%), 100 ($CON(C_2H_5)_2^+$, 60%), 72 ($N(C_2H_5)_2^+$, 100%).

Isolation of intermediaries in the transformation 1a into 3a. A solution of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester **1a** (0.5 g) freshly prepared in chloroform (15 mL) was maintained at room temperature for approximately 2 weeks until the sample showed by TLC three low R_f spots besides compounds **1a**, **2** and **3a**. Separation of the compounds was achieved by centrifugal PLC. After the elution of **2** and **3a** ($HCCl_3$-CH_3OH 9:1), the rotor was dried and the low R_f bands were eluted with DCM under argon atmosphere affording compounds **4a**, **5a** and **6a**

2-Methyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (4a). This compound can not be isolated as a pure oil due to it is easily autooxidable. ν_{max}/cm^{-1} (NaCl film): 2957, 1724, 1641, 1585, 1445, 1323, 1247, 1006, 765; δ_H (DMSO-d6) 8.21 (1H, d, $^3J_{5,6}$= 7.8, H-5), 8.01-7.95 (2H, m, H-7 and H-8), 7.90 (1H, s, H-3), 7.86 (1H, t, $^3J_{6,5/6,7}$= 7.8, H-6), 3.71 (3H, s, OCH_3) and 2.95 (3H, s, NCH_3); δ_C (DMSO-d6) 188.7 (C-4), 168.5 (CO_2), 161.4 (C-1), 136.1

(C-7), 132.9 (C-6), 131.9 (C-8a), 129.0 (C-5), 128.2 (C-4a), 126.8 (C-8), 90.8 (C-3), 54.5 (OCH_3) and 29.2 (NCH_3).

3-Hydroperoxy-2-methyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (5a). Yield 9-12%, mp 150-152 ºC (diethyl ether-hexane). This compound presents positive potassium iodide starch test and decomposes slowly on standing affording **3a**. Analyses (%C, %H, %N) calcd for $C_{12}H_{11}NO_6$: 54.34, 4.18, 5.28; found: 54.24, 4.15, 5.31; ν_{max}/cm^{-1} (NaCl film): 3215, 2958, 1768, 1707, 1648, 1598, 1582, 1435, 1388, 1300, 1073; δ_H (DCl_3C) 9.90 (1H, ex, br s, OOH), 8.30 (1H, dd, $^3J_{5,6}$= 7.6, $^4J_{5,7}$= 1.2, H-5), 8.08 (1H, dd, $^3J_{8,7}$= 7.6, $^4J_{8,6}$= 1.2, H-8), 7.84 (1H, dt, $^3J_{7,6/7,8}$= 7.6, $^4J_{7,5}$= 1.2, H-7), 7.72 (1H, dt, $^3J_{6,5/6,7}$= 7.6, $^4J_{6,8}$= 1.2, H-6), 3.83 (3H, s, OCH_3) and 3.13 (3H, s, NCH_3); δ_C (DMSO-d6) 185.3 (C-4), 163.7 and 162.4 (CO_2 and C-1), 136.0 (C-7), 133.1 (C-6), 131.2 and 130.0 (C-4a and C-8a), 129.1 (C-5), 126.4 (C-8), 94.6 (C-3), 54.0 (OCH_3) and 29.8 (NCH_3); *m/z* (EI) 266 ($M^{+\cdot}$ + 1, 3%), 250 ($M^{+\cdot}$ + 1 - O, 2%), 232 ($M^{+\cdot}$ - OOH, 32%), 206 ($M^{+\cdot}$ - CO_2CH_3, 20%), 190 ($M^{+\cdot}$ - CO_2CH_3 - O, 19%), 176 (32%), 163 (36%), 162 (23%), 161 (83%), 149 (36%), 133 (23%), 132 (34%), 117 (63%), 105 (36%), 104 (100%), 77 (50%), 76 (83%).

3-Hydroxy-2-methyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (6a). Yield 10-15%, mp 118-120 ºC (2-propanol). Analyses (%C, %H, %N) calcd for $C_{12}H_{11}NO_5$: 57.83, 4.45, 5.62; found: 57.90, 4.48, 5.57; ν_{max}/cm^{-1} (KBr): 3395, 2957, 1762, 1703, 1670, 1598, 1433, 1301, 1239, 1081; δ_H (DCl_3C), 8.35 (1H, d, $^3J_{5,6}$= 7.6, H-5), 8.04 (1H, dd, $^3J_{8,7}$= 7.6, $^4J_{8,6}$= 1.5, H-8), 7.85 (1H, t, $^3J_{7,6/7,8}$= 7.6, H-7), 7.73 (1H, dt, $^3J_{6,5/6,7}$= 7.6, $^4J_{6,8}$= 1.5, H-6), 4.89 (1H, ex, br s, OH), 3.81 (3H, s, OCH_3) and 3.29 (3H, s, NCH_3); δ_C (DMSO-d6) 188.3 (C-4), 168.5 (CO_2), 161.4 (C-1), 136.1 (C-7), 132.9 (C-6), 131.9 and 129.0 (C-4a and C-8a), 129.0 (C-5), 126.5 (C-8), 86.9 (C-3), 54.4 (OCH_3) and 29.1 (NCH_3); *m/z* (EI) 250 ($M^{+\cdot}$ + 1, 14%), 232 ($M^{+\cdot}$ + 1 – H_2O, 6%), 190 ($M^{+\cdot}$ - CO_2CH_3, 100%), 162 ($M^{+\cdot}$ - CO_2CH_3 - CO, 29%), 149 (66%), 133 (14%), 121 (14%), 105 (20%), 104 (45%), 93 (19%), 76 (40%), 65 (23%).

Synthesis of 5a from 1a and conversion to 3a. A mixture of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester (**1a**) (100 mg, 0.43 mmol) and manganese(III) acetate dihydrate (11.5 mg, 0.043 mmol) in glacial acetic acid (10 mL) was stirred at 25 ºC for 2 h in air, and then the reaction was quenched by adding water (8 mL). The aqueous reaction mixture was extracted with DCM (3x9 mL) and the combined extracts were washed with water and with saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by centrifugal PLC. The obtained hydroperoxide **5a** was further recrystallized, yield 76 %. Mp and mixed mp with **5a** isolated from the spontaneous transformation **1a** into **3a**: 150-152 ºC.

A suspension of **5a** (100 mg, 0.38 mmol) in water (5 mL) was heated at reflux for 2 h affording **3a** (85 %).

Synthesis of 6a from 1a and conversion to 3a. To a cold suspension (0-5ºC) of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester (**1a**) (100 mg, 0.43 mmol)

in water (13 mL), freshly recrystallized NBS (77 mg, 0.43 mmol) was added. After stirring for 15 minutes, the precipitate was filtered off and washed with cold water. Recrystallization from 2-propanol afforded **6a** (yield 91 %). Mp and mixed mp with **6a** isolated from the spontaneous transformation **1a** into **3a**: 118-120 ºC. A suspension of **6a** (100 mg, 0.40 mmol) in water (5 mL) was heated at reflux for 2 h affording **3a** (79%).

3-Methoxy-2-methyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (7). To a cold suspension (0-5ºC) of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester (**1a**) (100 mg, 0.43 mmol) in methanol (13 mL), freshly recrystallized NBS (77 mg, 0.43 mmol) was added. After stirring for 15 minutes, the precipitate was filtered off and washed with cold methanol. Recrystallization from 2-propanol afforded **7**. Yield 84%; mp 136-138 ºC (2-propanol). Analyses (%C, %H, %N) calcd for $C_{13}H_{13}NO_5$: 59.31, 4.98, 5.32; found: 59.40, 4.95, 5.29; ν_{max}/cm^{-1} (KBr): 2956, 1773, 1698, 1661, 1598, 1429, 1377, 1299, 1246, 1090; δ_H (DCl_3C), 8.37 (1H, dd, $^3J_{5,6}$= 7.6, $^4J_{5,7}$= 1.2, H-5), 8.09 (1H, dd, $^3J_{8,7}$= 7.6, $^4J_{8,6}$= 1.0, H-8), 7.87 (1H, dt, $^3J_{7,6/7,8}$= 7.6, $^4J_{7,5}$= 1.2, H-7), 7.73 (1H, dt, $^3J_{6,5/6,7}$= 7.6, $^4J_{6,8}$= 1.0, H-6), 3.76 (3H, s, CO_2CH_3), 3.27 (3H, s, OCH_3) and 3.08 (3H, s, NCH_3); δ_C (DMSO-d6) 189.0 (C-4), 165.4 and 162.2 (CO_2 and C-1), 136.1 (C-7), 133.0 (C-6), 131.6 and 130.2 (C-4a and C-8a), 129.1 (C-5), 126.3 (C-8), 89.9 (C-3), 53.8 (OCH_3), 51.8 (OCH_3) and 28.9 (NCH_3); *m/z* (EI) 264 ($M^{+\cdot}$ + 1, 2%), 232 ($M^{+\cdot}$ + 1 – OCH_3, 12%), 204 ($M^{+\cdot}$ - CO_2CH_3, 100%), 176 ($M^{+\cdot}$ - CO_2CH_3 - CO, 55%), 163 (99%), 133 (13%), 105 (19%), 104 (66%), 77 (26%), 76 (41%).

4-Methoxy-2-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid methyl ester (8). A suspension of **7** (100 mg, 0.38 mmol) in methanol (7 mL) was heated at reflux for 6 h affording **8**. Yield 56%; mp 98-100 ºC (2-propanol). Analyses (%C, %H, %N) calcd for $C_{13}H_{13}NO_5$: 59.31, 4.98, 5.32; found: 59.22, 4.94, 5.28; ν_{max}/cm^{-1} (KBr): 1771, 1701, 1665, 1597, 1426, 1376, 1298, 1087; δ_H (DMSO-d6) 7.71 (1H, dd, $^3J_{8,7}$= 7.5, $^4J_{8,6}$= 1.5, H-8), 7.67 (1H, dt, $^3J_{6,5/6,7}$= 7.5, $^4J_{6,8}$= 1.5, H-6), 7.62 (1H, dd, $^3J_{5,6}$= 7.5, $^4J_{5,7}$= 1.5, H-5), 7.59 (1H, dt, $^3J_{7,6/7,8}$= 7.5, $^4J_{7,5}$= 1.5, H-.7), 3.68 (3H, s, CO_2CH_3), 3.13 (3H, s, OCH_3) and 2.93 (3H, s, NCH_3); δ_C (DMSO-d6) 169.2 (CO_2), 168.0 (C-3), 166.1 (C-1), 144.5 (C-4a), 132.9 (C-6), 130.8 (C-7), 123.4 (C-8a), 123.2 (C-5), 123.1 (C-8), 89.1 (C-4), 53.6 (CO_2CH_3), 49.2 (OCH_3) and 24.2 (NCH_3); *m/z* (EI) 264 ($M^{+\cdot}$ + 1, 6%), 232 ($M^{+\cdot}$ + 1 – OCH_3, 17%), 204 ($M^{+\cdot}$ - CO_2CH_3, 84%), 176 ($M^{+\cdot}$ - CO_2CH_3 - CO, 66%), 163 (100%), 133 (36%), 105 (51%), 104 (29%), 77 (58%), 76 (71%), 75 (37%).

3-Acetoxy-2-methyl-1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (9). To a suspension of 4-hydroxy-2-methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester (**1a**) (100 mg, 0.43 mmol) and magnesium oxide (35 mg, 0.86 mmol) in dry DCM (2 mL) lead(IV) acetate (189 mg, 0.43 mmol) was added. The reaction mixture was stirred for 3 h at room temperature and filtered. The filtrate was washed with water, dried and evaporated to dryness. Recrystallization of the residue afforded **9**. Yield 78%; mp 161-163 ºC (benzene). Analyses (%C, %H, %N) calcd for $C_{14}H_{13}NO_6$: 57.73, 4.50, 4.81; found: 57.64, 4.53, 4.79; ν_{max}/cm^{-1} (KBr): 3030, 2298, 1757, 1702, 1669, 1525, 1370, 1235, 1044; δ_H (DCl_3C), 8.33 (1H, dd, $^3J_{5,6}$= 7.7, $^4J_{5,7}$= 1.4, H-5), 8.07 (1H, dd, $^3J_{8,7}$= 7.7, $^4J_{8,6}$= 1.4, H-8), 7.85 (1H, dt, $^3J_{7,6/7,8}$= 7.7,

$^4J_{7,5}$= 1.4, H-7), 7.81 (1H, dt, $^3J_{6,5/6,7}$= 7.7, $^4J_{6,8}$= 1.4, H-6), 3.77 (3H, s, OCH_3), 3.06 (3H, s, NCH_3) and 2.21 (3H, s, $COCH_3$); δ_C (DMSO-d6) 184.5 (C-4), 168.7, 164.9 and 161.3 (CO_2, *C*OCH_3 and C-1), 136.0 (C-7), 133.2 (C-6), 132.0 and 131.2 (C-4a and C-8a), 129.0 (C-5), 125.1 (C-8), 87.4 (C-3), 54.0 (OCH_3), 29.9 (NCH_3) and 20.8 ($COCH_3$); *m/z* (EI) 292 ($M^{+\cdot}$ + 1, 8%), 232 ($M^{+\cdot} - C_2H_3O_2$, 47%), 190 ($M^{+\cdot}$ - CO_2CH_3, 100%), 162 ($M^{+\cdot}$ - CO_2CH_3 - CO, 11%), 149 (9%), 43 (22%).

A suspension of **9** (100 mg, 0.34 mmol) in water was heated at reflux for 5 h affording **3a** (74%). Similarly, a suspension of **9** (100 mg, 0.34 mmol) in methanol was heated at reflux for 9 h affording **8** (64%).

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