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Mechanistic study of reversible solid-state melt isomerization of 2-oxindoles to 2-quinolinones and its occurrence in a mass spectrometer

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ABSTRACT

An eco-friendly equilibrated rearrangement of a series of 2-oxo-3-indolyl acetic acids (**1**) with 2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid derivatives (**2**) was investigated through a solid state melt reaction (SSMR). Mechanistic insight into the thermal rearrangement is provided by ^{13}C-isotopic labeling. The standard mass spectra of **1** and **2** were virtually identical preventing their reliable identification. Reversible interconversion of **1** and **2** was evidenced to occur in the inlet system of a mass spectrometer under electron impact conditions. Relative abundances of fragment ions were found to be a function of temperature.

1. Introduction

Isomerization reactions are relevant in organic synthesis and play a key role in the properties and function of diverse biological active molecules, including retinal, lipids, carbohydrates, peptides and proteins, and in the operation of molecular machines [1–3]. One of the most intriguing aspects of heterocyclic chemistry is the conversion of one heterocyclic system into other. These ring-rearrangements represent a class of reactions which is largely documented in the literature and could be useful synthetic routes to target biologically active heterocycles [4]. Among these rearrangements, thermally or photochemically induced heterocycle-to-heterocycle transformations have been widely performed and their mechanistic interpretation often represents a challenging research area.

Detailed studies of the thermal chemistry of five-membered nitrogenated heterocycles such as methylpyrrole, dimethylpyrrole, and methylindole have provided telling insights on the ring expansion process and other competitive reactions [5–8]. Modeling and quantum chemical calculations on the compounds mentioned have shown that at high temperature the ring expansion process takes place from radical intermediates [7,9].

Despite the many reported ring transformations of oxindoles, 2-oxindoles to 2-quinolinones interconversions have received little attention. In this regard, in solution, 2-oxindole derivatives undergo ring expansion to 2-quinolinones under acidic or basic conditions or by treatment with nucleophiles via ring opening of oxindole at amide linkage [10–12]. While for methyloxindoles in the gas-phase, these ring transformations occur under flash vacuum pyrolysis and the mechanism is likely to proceed via free radicals [13,14].

In the light of this background, in this paper we report an example showing that the reversible thermal rearrangement of a series of 2-oxo-3-indolylacetic acids (**1a**-**1e**) into the corresponding

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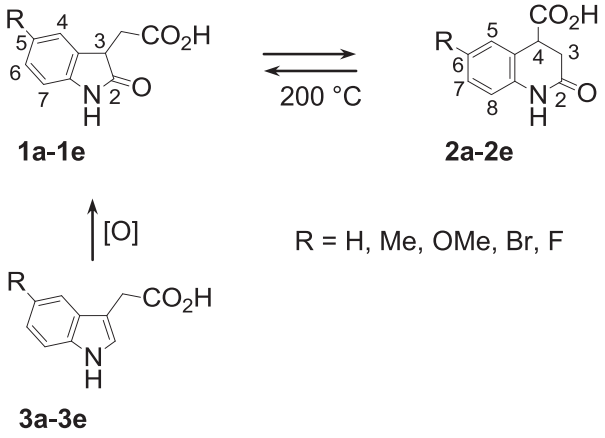
2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid derivatives (**2a**-**2e**), that occurs in conditions of electronic impact in a mass spectrometer, has analogy with the reversible thermal isomerization reaction performed in solid phase for these same compounds. The protocol was conducted through a solid state melt reaction (SSMR) that does not require a catalyst or solvent, very important criteria in green synthesis [15–17]. The interest in correlating the isomeric interconversion of series **1** and **2** under the conditions of the SSMR with what can take place in a mass spectrometer [18] lies in the fact that, this last technique, is widely applied in the detection of low abundance plant metabolites due to its unparalleled sensitivity and specificity [19,20]. In this regard, oxindole (**1a**) is a catabolic oxidation product of plant growth hormone, indole-3-acetic acid [21,22]. Therefore, it is interesting to see whether mass spectrometry could be used to differentiate and identify the isomeric compounds **1a**-**1e** and **2a**-**2e** under electron impact conditions. Starting **1a**-**1e** were prepared by oxidation with DMSO/HCl of the corresponding 3-indolyl acetic acids **3a**-**3e** following previously published procedure (Scheme 1) [12].

2. Experimental section

2.1. Materials and methods

All reagent-grade chemicals were purchased from Sigma-Aldrich Co. and were used as received. Melting points (mp) were determined using a Fisher-Johns apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated aluminum sheets (Merck TLC, silica gel 60 F254) with detection by UV light. Flash chromatography was performed on silica gel 60 (230–400 mesh). IR spectra were obtained using a Perkin-Elmer 16 FPC FT spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 HDMS spectrometer at the Central Analytical Laboratory, Department of Chemistry and Biochemistry, University of Colorado at Boulder. NMR spectra were recorded on Mercury spectrometers working at 300 and 75.4 MHz for ^{1}H and ^{13}C, using CD_3OD as a solvent, chemical shifts were measured in ppm (δ) relative to internal tetramethylsilane (TMS) and coupling constants (J) are in Hz. The spectral assignments were confirmed by standard procedures (gHSQC, gHMBC, DEPT). Signals, when declared, are expressed as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). 2-Oxo-3-indolylacetic acid (**1c**) [12] and 2-oxo-4-quinolinecarboxylic acids (**2a** and **2c**) [12,23] are known. Although oxindole (**1a**) [24] and quinolinone (**2b**) [23] are also known, to our knowledge they are spectroscopically not yet fully characterized. Thus, data for **1a** and **2b** are also included.



Scheme 1. Solid-state melt isomerization of 2-oxindoles (**1a**-**1e**) to 2-quinolinones (**2a**-**2e**).

2.2. EI-MS analysis

The DIP-MS analyses were performed using an ion trap Varian Saturn 2000 spectrometer (70 eV) coupled with a Varian 3800 gas chromatograph. The solid sample was introduced into a glass insert and placed on the tip of the probe with probe temperature ramps from 70 to 280 °C at 100 °C/min and from 200 to 280 °C at 100 °C/min using helium as carrier gas (1.0 mL/min). The MS conditions were as follows: transfer line heater, 280 °C; ion source temperature, 200 °C; electron impact ionization mode; ionization energy, 70 eV; electron multiplier voltage, 1800 V. The typical mass spectrum was recorded by averaging 1200 scans from m/z 20 to 650 at a scan rate of 1 s/scan.

2.3. General oxidation procedure

A suspension of 2-oxindole (5.14 mmol) in DMSO/37% aq HCl/AcOH (1:5:10, v/v) (6 mL) was stirred at room temperature until disappearance of starting material (TLC) (6 h). The reaction was then quenched by addition of ice-water (25 mL), and extracted with EtOAc (3 × 40 mL). The combined organic layer was successively washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo.

2.3.1. (±)-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid (*1a*)

Prepared from **3a** (900 mg, 5.14 mmol) according to the general oxidation procedure. The residue was crystallized from CH_2Cl_2 to give **1a** as pale pink solid (815 mg, 83%): mp 151–152 °C (Lit. 146 °C, Ref. [24]); R_f: 0.36 (CH_2Cl_2/MeOH, 5:1); ^{1}H NMR (300 MHz, CD_3OD): δ 7.21 (2H, m, H4, H6), 7.01 (1H, ddd, J = 7.6, 7.5, 1.0 Hz, H5), 6.92 (1H, br d, J = 7.8 Hz, H7), 3.75 (1H, ABX, J = 7.5, 4.5 Hz, H3, CD_3OD exchangeable), 3.06 and 2.80 (2H, ABX, J = 17.0, 7.5, 4.4 Hz, CH_2); ^{13}C NMR (75.4 MHz, CD_3OD): δ 182.4 (CO), 175.3 (CO_2H), 144.6 (C7a), 131.5 (C3a), 130.0 (C6), 125.7 (C4), 124.1 (C5), 111.7 (C7), 44.6 (C3–H), 44.3 (br t, $^{1}J_{C,D}$ = 20.4 Hz, C3-D), 36.1 (CH_2); DIP-MS (EI, 70 eV), see Tables 3 and 5. It must be mentioned that the product ion spectrum of **1a**, introduced as methanol solution, gave rise to molecular ion with m/z 191 accompanied by a significant peak shifted up by 14 Da (m/z 205) due to an esterification reaction of **1a** prior to mass spectrometric fragmentation [25].

2.3.2. (±)-(5-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid (*1b*)

Prepared from **3b** (973 mg, 5.14 mmol) according to the general oxidation procedure. The residue was crystallized from CH_2Cl_2 to give **1b** as pale purple solid (612 mg, 58%): mp 196–197 °C; R_f: 0.5 (CH_2Cl_2/MeOH, 5:1); IR (KBr) 3193, 1709, 1657 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 7.12 (1H, m, H4), 7.04 (1H, dm, J = 7.9 Hz, H6), 6.8 (1H, d, J = 7.9 Hz, H7), 3.72 (1H, ABX, J = 7.5, 4.4 Hz, H3, CD_3OD exchangeable), 3.04 and 2.79 (2H, ABX, J = 17.0, 7.5, 4.4 Hz, CH_2), 2.31 (3H, s, CH_3); ^{13}C NMR (75.4 MHz, CD_3OD): δ 182.4 (CO), 175.4 (CO_2H), 142.1 (C7a), 133.7 (C5), 131.6 (C3a), 130.3 (C6), 126.5 (C4), 111.4 (C7), 44.7 (C3), 36.1 (CH_2), 22.0 (CH_3); DIP-MS (EI, 70 eV), see Tables 3 and 5; HRMS (ESI) Calcd. for $C_{11}H_{11}NO_3$ ([M + Na]$^{+}$): 228.0631, Found: 228.0635.

2.3.3. (±)-(5-Methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl)acetic acid (*1c*)

Prepared from **3c** (1.05 g, 5.14 mmol) according to the general oxidation procedure. The residue was crystallized from CH_2Cl_2 to give **1c** as pale purple solid (648 mg, 57%): mp 193–194 °C (Lit. 181–182 °C, Ref. [12]); R_f: 0.42 (CH_2Cl_2/MeOH, 5:1); DIP-MS (EI, 70 eV): see Tables 3 and 5.