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STRUCTURAL CHARACTERIZATION OF ISOMERIC METHYL 2-(2-OXO-3-INDOLYL)ACETATE AND METHYL 1-(2-OXO-4-QUINOLYL)FORMATE

Ernesto Rivera-Becerril,[a] Nury Pérez-Hernández,[b] Pedro Joseph-Nathan,[a] and Martha S. Morales-Ríos[a]*

[a]Departamento de Química and Sección Externa de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México D. F., 07000 México. smorales@cinvestav.mx
[b]Escuela de Medicina. Universidad Autónoma del Estado de Hidalgo, Apartado 1-622, Pachuca, Hidalgo 42001, México.

Abstract – Crystalline and amorphous forms of methyl 2-(2-oxo-3-indolyl)acetate (**1**) were obtained showing significant differences in their melting points. The X-ray structure for the trigonal polymorph is reported. In addition, oxindole (**1**) was easily acid-catalyzed ring enlarged to give the structural isomer quinolone (**2**) for which the crystal structure was also determined. These results resolve several chemical inquiries related to the structural characterization of **1** and **2**.

INTRODUCTION

During the course of our studies toward the total synthesis of flustramine type alkaloids we became interested in the use of methyl 2-(2-oxo-3-indolyl)acetate (**1**) as an approach to the synthesis of enantiopure debromoflustramine B.[1] Careful revision of literature revealed that oxindole (**1**) was first isolated from aqueous methanol extracts of rice bran by Kinashi and co-workers[2] in 1976, the reported melting point being 170-172 °C. This compound was mentioned again in the literature in 1985 when Canoira and Rodriguez,[3,4] prepared it and reported a defined melting point (185-186 °C),[3,4] in disagreement to the original value.[2] In subsequent years, syntheses of **1** were reported in the literature by three groups, for which the melting points show: 164-167 °C,[5] 171-172 °C[6] and unreported.[7] In 2000 Lorenz and Stermitz[8] characterized oxindole (**1**) (mp 169-172 °C) as the main component from the flowers of several *Oenothera* species, based on two reports[2,4] in which the melting point differs by 15 °C.

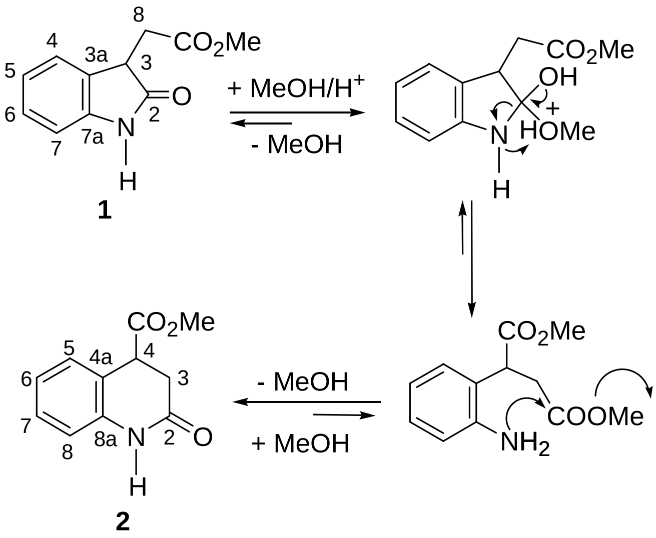
Adding more elements to this confusion, in 2001 a publication by Selvakumar and co-workers[9] described the preparation of oxindole (**1**) together with 2-quinolone (**2**), a structural isomer of **1**, by catalytic reduction of an *o*-nitrobenzene derivative. However, identity properties for these two compounds were absent.[9] In an independent report,[10] a very broad melting point range of 145-165 °C was ascribed to 2-quinolone (**2**). It should be pointed out that 2-(2-oxo-3-indolyl)acetic acid and its ethyl ester are prone to undergo acid-catalyzed ring enlargement to give 2-quinolones via an opening/reclosure mechanism.[11] In order to clarify the above mentioned disagreements, we report herein the preparation and physical and spectroscopic properties of compounds (**1**) and (**2**), as well as their X-Ray crystallographic analysis.

RESULTS AND DISCUSSION

A sample of **1** was obtained by esterification of 2-(2-oxo-3-indolyl)acetic acid with CH_2N_2 in Et_2O/MeOH at 0 °C.[12] Compound (**1**), identified by standard spectroscopic means, was crystallized from acetone or methanol to give in both cases two polymorphs. Thus, when oxindole (**1**) was dissolved in the hot solvent followed by rapid cooling in an ice/water bath, an amorphous material with mp 171-173 °C was formed, while slow crystallization of **1** at room temperature gives colorless prismatic crystals with mp 187-188 °C, in agreement to that obtained by Canoira and Rodriguez.[3,4]

In order to prepare quinolone (**2**), 2-(2-oxo-3-indolyl)acetic acid was treated with methanolic hydrogen chloride at room temperature, following the reaction course by TLC employing hexane-AcOEt (3:7) as developing solvent mixture and detecting the components under UV light. After 10 minutes, the consumption of starting material and the formation of two UV absorbing products, at R_f 0.54 (**1**) and 0.42 (**2**), in approximately a 3:1 ratio was observed. The higher R_f product, identified as oxindole (**1**) by comparison with an authentic sample, is time equilibrated to produce after 30 h a mixture of **1** and **2** in a 1:8 ratio. After chromatographic separation, crystallization of **2** from DMSO affords colorless crystals, mp 170-171 °C. The same 1:8 ratio was observed when pure quinolone (**2**) was equilibrated during 30 h. The proposed mechanism for the equilibrium between **1** and **2** (Scheme 1) includes acid-catalyzed alkoxylation of **1** followed by ring cleavage to give the corresponding common intermediate γ-diester, and subsequent lactamization of such γ-diester leading to quinolone (**2**) as the major component. The fact that the equilibrium favors quinolone (**2**) is in accord with theoretical calculations[13] which show a difference in energy between **1** and **2** of 4 kcal/mol in favor of **2**.

According to the ^1H NMR spectra, compounds (**1**) and (**2**) share structural features which seriously impeded their recognition. Both show the spin systems of an *o*-substituted benzene and an ABX type pattern. Excepting for the labile hydrogen atom, for each resonance signal the largest chemical shift difference between both compounds was found to be of only 0.13 ppm (see experimental). For the ^{13}C NMR spectra an analogous situation was observed, the largest chemical shift difference of 8.9 ppm occurs when comparing quaternary carbons (see experimental).



Scheme 1. Proposed reaction mechanism for the equilibrium between **1** and **2**.

The EIMS analysis revealed that the molecular weights of both products (*m*/*z* = 205) are consistent with those of structural isomers (**1**) or (**2**). The same fragmentation pattern is observed for both compounds, excepting the ion at *m*/*z* 173 which is missing in the spectrum of **2**. The IR spectrum (in KBr) was of great significance to distinguish between structural isomers (**1**) and (**2**), because it shows for oxindole (**1**) two intense bands at 1728 and 1703 cm^{-1} corresponding to characteristic vibrations for carbonyl ester and secondary γ-lactam absortions,[14] respectively, whereas for quinolone (**2**) two well defined bands at 1728 and 1689 cm^{-1} corresponding to ester and secondary δ-lactam carbonyl absorptions, respectively, were observed. On the other hand the IR spectra of the two polymorphs of **1** do not allowed distinction between crystalline and amorphous material, as is reported in the literature for some cases where IR absorptions are different between crystalline forms.[15] The IR spectra in solution ($CHCl_3$) were also obtained for **1** and **2** in order to clarify the values given in the literature, as one sharp and intense band at 1723 cm^{-1} observed for **1**, while two well defined bands at 1728 and 1689 cm^{-1} were observed for **2** (see experimental).

Since the observed melting point 170-171 °C of **2** has been reported repeatedly for **1**, in order to avoid any chance for error, the structures of oxindole (**1**) and quinolone (**2**) were unambiguously confirmed by single crystal X-Ray diffraction analysis (Figure 1, Tables 1 and 2).

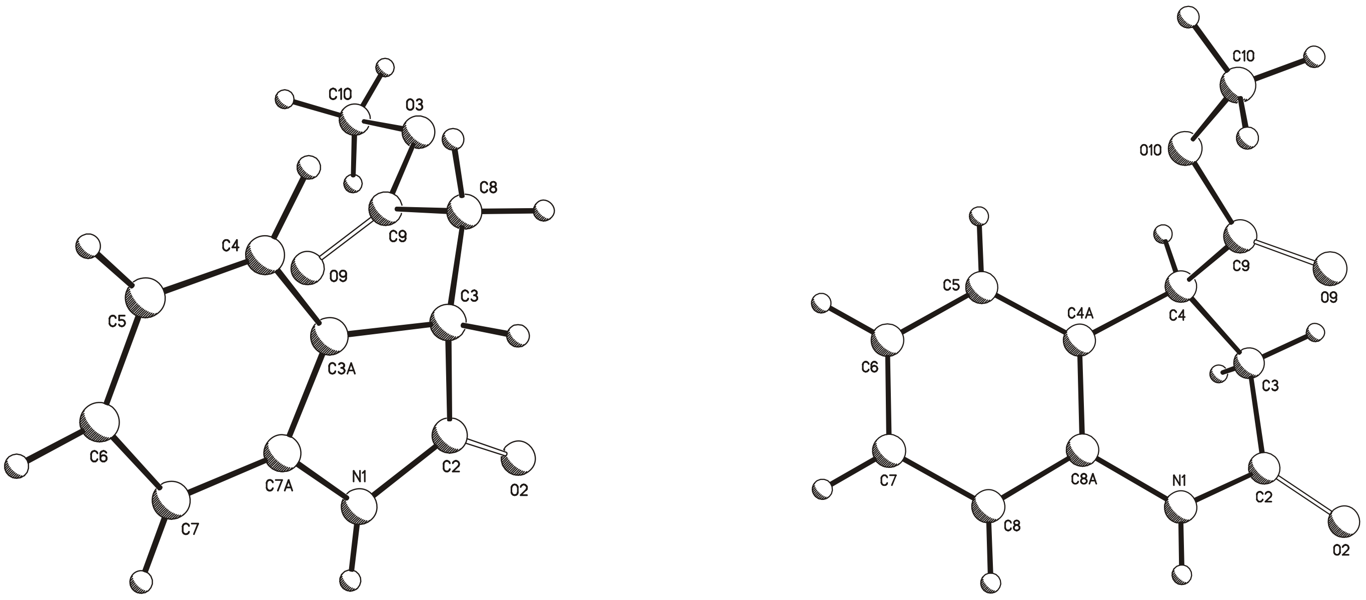


Figure 1. PLUTO drawing of methyl 2-(2-oxo-3-indolyl)acetate (**1**) and methyl 1-(2-oxo-4-quinolyl)-formate (**2**)

Table 1. Selected Bond Distances (Å), Angles (deg) and Dihedral Angles (deg) for **1** and **2**

1		**2**	
Bond Distances		Bond Distances	
C(3a)-C(3)	1.502(4)	C(4a)-C(4)	1.513(3)
C(3)-C(2)	1.524(4)	C(4)-C(3)	1.527(3)
C(2)-N(1)	1.345(4)	C(3)-C(2)	1.505(3)
C(3)-C(8)	1.527(4)	C(2)-N(1)	1.347(3)
C(8)-C(9)	1.497(4)	C(4)-C(9)	1.508(3)
Bond Angles		Bond Angles	
C(3a)-C(3)-C(2)	102.4(2)	C(4a)-C(4)-C(3)	110.5(2)
C(3)-C(2)-N(1)	107.9(2)	C(4)-C(3)-C(2)	113.7(2)
C(2)-N(1)-C(7a)	111.8(2)	C(3)-C(2)-N(1)	116.0(2)
C(3)-C(8)-C(9)	114.1(2)	C(2)-N(1)-C(8a)	124.7(2)
		C(4)-C(9)-O(10)	112.1(2)
Dihedral Angles		Dihedral Angles	
C(3)-C(8)-C(9)-O(3)	-168.7(3)	C(3)-C(4)-C(9)-O(10)	169.9(2)
C(7a)-N(1)-C(2)-C(3)	5.0(3)	C(8a)-N(1)-C(2)-C(3)	-1.9(3)
C(7a)-C(3a)-C(3)-C(2)	5.8(3)	C(8a)-C(4a)-C(4)-C(3)	32.6(2)
C(3a)-C(3)-C(2)-N(1)	-6.5(3)	C(4a)-C(4)-C(3)-C(2)	-47.3(2)
		C(4)-C(3)-C(2)-N(1)	33.5(2)

Table 2. Crystallographic Data for **1** and **2**

	1	**2**
Formula	$C_{11}H_{11}NO_3$	$C_{11}H_{11}NO_3$
Size (mm^3)	0.30 x 0.28 x 0.28	0.40 x 0.34 x 0.30
Crystal system	trigonal	monoclinic
Space group	$P3_1$	C2/c
a (Å)	8.701(1)	23.217(5)
b (Å)	8.701(1)	5.347(1)
c (Å)	11.671(2)	15.980(3)
β(°)	90	103.54(3)
V(Å)	765.1(2)	1928.5(7)
D_{calcd} (g cm^{-3})	1.34	1.41
Z	3	8
μ (mm^{-1})	0.82 (Cu Kα)	0.86 (Cu Kα)
T (K)	293	293
2 θ_{range} (°)	5.87-59.86	3.92-59.94
Total reflections	2465	1867
Unique reflections	794	1374
R_{int}(%)	0.01	4.2
Observed reflections	793 $I \geq 4\sigma(I)$	1297 $I \geq 4\sigma(I)$
Parameters	161	145
R (%), R_w (%)	2.7, 7.6	4.7, 13.1
E_{max} (e $Å^{-3}$)	0.10	0.20

On the bases of this work, we clarify the discrepancies in physical and spectroscopic data previously reported for **1** and **2**, which we rationalized as due to the following: compound (**1**) shows two polymorphs with a significant difference in melting points; the coincident melting point between the amorphous form of oxindole (**1**) and quinolone (**2**); the equilibrium between **1** and **2** through an acid-catalyzed alkoxylation/dealkoxylation; and that **1** and **2** share structural features which seriously impeded their spectroscopic recognition. The identity of **1** and **2** was unambiguously confirmed by X-Ray crystallographic analysis.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were obtained using a Buck Scientific 500 spectrophotometer. NMR spectra were recorded in $CDCl_3$ solutions on a Varian Mercury spectrometer working at 300 and 75.4 MHz, for ^1H and ^{13}C, respectively. Chemical shifts are reported in parts per million downfield from tetramethylsilane. The spectral assignments were confirmed by standard procedures (gHSQC, gHMBC). Electron impact mass spectra (EIMS) were recorded on a Hewlett-Packard 5989A spectrometer at an ionizing voltage of 70 eV. Flash chromatography was performed using silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). All commercial grade reagents were used without further purification.

Methyl 2-(2-oxo-3-indolyl)acetate (**1**). This compound was prepared by esterification of 2-(2-oxo-3-indolyl)acetic acid with diazomethane following the procedure described before.[12] The colorless trigonal crystals of **1** were prepared by slow crystallization from acetone or methanol, mp 187-188 °C. From these crystals an amorphous solid was obtained by rapid cooling of hot acetone or methanol solutions, mp 171-173 °C. TLC: R_f 0.54 (3:7 hexane-EtOAc). IR ($CHCl_3$) υ_{max} 3443 (w), 3210 (w), 1727 (s), 1625 (m) cm^{-1}. IR (KBr) υ_{max} 3442 (w), 3154 (m), 1728 (s), 1703 (s), 1678 (m), 1623 (m), 1603 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.77 (1H, br s, NH), 7.23 (1H, d, J = 7.4 Hz, H-4), 7.22 (1H, t, J = 7.7 Hz, H-6), 7.01 (1H, td, J = 7.5, 1.0 Hz, H-5), 6.91 (1H, d, J = 8.0 Hz, H-7), 3.82 (1H, dd, J = 8.0, 4.6 Hz, H-3), 3.70 (3H, s, CH_3), 3.10 (1H, dd, J = 17.0, 4.6 Hz, H-8), 2.84 (1H, dd, J = 17.0, 8.0 Hz, H-8'); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 179.0 (C, C-2), 171.4 (C, *C*$OOCH_3$), 141.4 (C, C-7a), 128.6 (C, C-3a), 128.2 (CH, C-6), 124.0 (CH, C-4), 122.4 (CH, C-5), 109.8 (CH, C-7), 52.1 (CH_3), 42.3 (CH, C-3), 34.6 (C-8); EIMS *m*/*z* 205 $[M]^+$ (38), 173 (25), 146 (41), 145 (100), 128 (19), 117 (44).

Methyl 1-(2-oxo-4-quinolyl)formate (2). A solution of 2-(2-oxo-3-indolyl)acetic acid (191 mg, 1 mmol) in 2 mL of MeOH/HCl (prepared by bubbling dry HCl into anhydrous methanol during 15 min) was stirred for 30 h at rt, after which TLC analysis indicated the presence of two spots in an equilibrated ratio of ca. 1:8. The solution was diluted with EtOAc (20 mL), washed with brine (2 x 2 mL), dried over sodium sulfate and evaporated to dryness. The isomeric mixture contained in the residue was separated carefully by flash column chromatography using silica gel (4:1 hexane/EtOAc, then 7:3 hexane/EtOAc, and 3:2 hexane-EtOAc) to afford 21 mg (0.102 mmol) of the minor oxindole (**1**) in 10% yield and of the major quinolone (**2**) in 83% yield (170 mg, 0.829 mmol). Quinolone (**2**) was isolated as colorless crystals, mp 170-171 °C from DMSO (lit.,[10] mp 145-165 °C). TLC: R_f 0.42 (3:7 hexane-EtOAc). IR ($CHCl_3$) υ_{max} 3408 (w), 3223 (w), 1739 (s), 1690 (s), 1612 (w), 1600 (m) cm^{-1}. IR (KBr) υ_{max} 3442 (w), 3222 (m), 1728 (s), 1689 (s), 1679 (m), 1596 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.01 (1H, br s, NH), 7.28 (1H, d, J = 7.3 Hz, H-5), 7.24 (1H, td, J = 7.7, 1.5 Hz, H-7), 7.03 (1H, td, J = 7.5, 1.2 Hz, H-6), 6.86 (1H, dd, J = 7.9, 1.2 Hz, H-8), 3.95 (1H, dd, J = 6.7, 4.0 Hz, H-4), 3.70 (3H, s, CH_3), 2.99 (1H, dd, J = 16.5, 4.0 Hz, H-3), 2.79 (1H, dd, J = 16.5, 6.7 Hz, H-3'); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 171.9 (C, *C*$OOCH_3$), 169.6 (C, C-2), 136.9 (C, C-8a), 128.9 (CH, C-7), 128.7 (CH, C-5), 123.2 (CH, C-6), 119.9 (C, C-4a), 116.0 (CH, C-8), 52.6 (CH_3), 42.3 (CH, C-4), 32.9 (C-3); EIMS *m*/*z* 205 $[M]^+$ (56), 146 (100), 145 (5), 128 (47), 117 (8).

X-Ray diffraction analysis of 1 and 2. The X-Ray data were collected on a Bruker Nonius CAD4 diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å). The data were collected at 298 K in the ω-2θ scan mode. Unit cell refinements were done using the CAD4 Express v2.0 software. The structures were solved by direct methods using the SHELXS-97 program included in the WinGX v1.64.05 crystallographic software package. The structural refinement was carried out by full-matrix least squares on F^2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. The Cambridge Crystallographic Data Centre deposition number for **1** is 608113, and that for **2** is 608114.

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