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The reaction of imidazo[1,5-*a*]pyridines with ninhydrin revisited

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Abstract: The synthesis of 2,2′-(Imidazo[1,5-*a*]pyridine-1,3-diyl)bis(2-hydroxy-1*H*-indene-1,3(2*H*)-dione) (**11**) is achieved by reaction of imidazo[1,5-*a*]pyridine (**7**) with two equivalents of ninhydrin (**1**) at room temperature. The structure of this new 1,3-bis-adduct **11** is evidenced from HRMS and NMR spectral data and confirmed by single-crystal X-ray crystallography. Employment of equimolar amounts of **1** and **7** gave a separable mixture of the respective 1- and 3-monomeric adducts (**9**, **10**).

Keywords: 1-methylimidazo[1,5-*a*]pyridine; imidazo[1,5-*a*] pyridine; ninhydrin; nucleophilic addition at C-1/C-3; X-ray structures.

1 Introduction

The parent imidazo[1,5-*a*]pyridine is an π-excessive aza-aromatic system in which the bridgehead *N*-4 contributes to the aromaticity with its lone pair. Hence, this nitrogen is not nuclophilic and the attack occurs at *N*-2 position. This parent compound is known to undergo electrophilic substitution (S_E–Ar) with various electrophiles at C-1, but also at C-3 or both, depending, at least in part, on the reaction conditions used [1–10]. Thus, imidazo[1,5-*a*]pyridine is acetylated at C-1 [1] or at C-3 [2], nitrosated (followed by rearrangement) at C-1 [3], mono-formylated at C-1 (70%) and C-3 (30%) [4]. On the other hand, lithiation (and related means of generation of carbanion) takes place preferentially at C-3 [4, 5]. As expected, electrophilic substitution occurs mainly at C-3 if C-1 is bloked [6–10]. Recently, we have reported on the reaction of ninhydrin (**1**) with 3-(substituted)imidazo[1,5-*a*]pyridines (**2**) whereby nuclophilic addition of C-1 occurs at the central carbonyl carbon (C-2′) of ninhydrin to deliver the respected products **3** (Scheme 1) [11].

In light of the preceding information, we sought it would be worthwhile to investigate the reaction of ninhydrin with the parent imidazo[1,5-*a*]pyridine and its 1-methyl derivative under neutral conditions. Herein we report on our findings related to both reactions as illustrated in Schemes 2 and 3 (*vide infra*).

Further work regarding the electronic effect of substituents onto the nucleophilic character of carbon atoms 1 and 3 is in progress. The results will be communicated elsewhere.

2 Results and discussion

2.1 Chemistry

Imidazo[1,5-a]pyridine (**7**) and its 1-methyl derivative (**6**), required in this study, were prepared by cyclization of the respective *N*-[(1-pyridin-2-yl)alkylformamides (**5**, **4**) [1] as noted in the experimental section. Direct interaction of ninhydrin (**1**) with the 1-methyl derivative (**6**) in dichloromethane at room temperature delivered, as expected, the respective adduct namely 2-hydroxy-2-(1-methylimidazo [1,5-*a*]pyridin-3-yl)-1*H*-indene-1,3(2*H*)-dione (**8**) in high yield. Under similar conditions, the reaction of equimolar amounts of (**1**) with the parent compound (**7**) produced a separable mixture of the mono adducts 2-hydroxy-2-(imidazo[1,5-*a*]pyridin-1-yl)-1*H*-indene-1,3(2*H*)-dione (**9**) and 2-hydroxy-2-(imidazo[1,5-*a*]pyridin-3-yl)-1*H*-indene-1,3(2*H*)-dione (**10**) in an approximate ratio of 4:1 (Scheme 3). On the other hand, employment of two equivalents of (**1**) and just one equivalent of (**7**) gave the bis-1,3-adduct 2,2′-(imidazo [1,5-*a*]pyridine-1,3-diyl)bis(2-hydroxy-1*H*-indene-1,3(2*H*)-dione) (**11**) as the main product (Scheme 3).

The new compounds **8** (Scheme 2) and **9**–**11** (Scheme 3) were characterized by IR, MS, and NMR spectral data. These data, detailed in the experimental section, are compatible with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good

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agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H and ^{13}C signal assignments to the different carbons and their attached and/or neighbouring hydrogens. Eventually, the structures of **10** and **11** were confirmed by single-crystal X-ray crystallography (Figures 1 and 2; *vide infra*).

2.2 Crystal structures

The X-ray crystal structures of compounds **10** and **11** were determined at room temperature. A summary of data collection and refinement parameters for **10** and **11** is given in Table 1, whilst selected bond distances and angles are listed in Tables 2 and 3. The molecular structures of the two compounds are shown in Figures 1 and 2. The molecular structure of **11** adheres to crystallographic two-fold symmetry, the axis of rotation bisecting C5–C5A/C3–N3 and passing through N1. It results in a 50 : 50 split occupancy of C3 and N3. Only one of the components is shown in Figure 2.

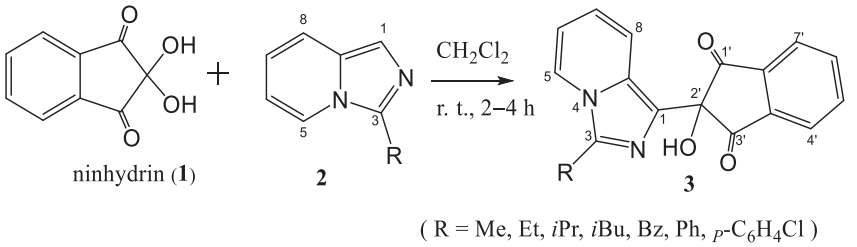
As expected, imidazo[1,5-*a*]pyridine rings are planar in the two compounds, the mean deviation of atoms from the plane are 0.014 Å in **10**, and 0.006 Å in **11**. Similarly, the carbon atoms of the ninhydrin rings are planar in **10**, the mean deviation of atoms from the plane is 0.024 Å. However, the planarity of the carbon atoms in ninhydrin system is less pronounced in **11**, the mean deviations of carbon atoms from the plane is 0.04 Å, whilst C-7 is significantly deviated from the aromatic plane of the ninhydrin system by 0.12 Å. It is noteworthy that the oxygen atoms of the carbonyl groups of ninhydrin system are more significantly deviated from the aromatic planes in **11** than in **10**; the distances between the aromatic plane and the oxygen atoms are 0.01 Å and 0.20 Å for the respective O20 and O21 in **10**, 0.41 Å and 0.21 Å for the respective O15 and O17 in **11**. O–H···N hydrogen bonding interactions link the molecular units of **10** to form a chain structure parallel to the crystallographic *c*–axis (Figure 3). On the other hand, O–H···O hydrogen bonding interactions link the molecular units of **11** to form a layer structure in the *ab*–crystallographic plane (Figure 4). The parameters of hydrogen bonding interactions are listed in Table 4.

3 Conclusion

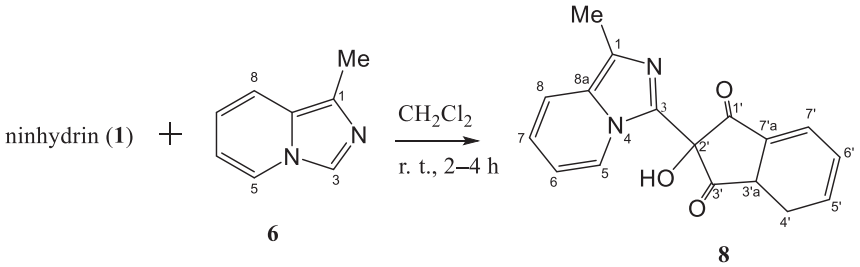
The reaction of 1-methylimidazo[1,5-*a*]pyridine afforded high yield of the respective 3-monomeric adduct, namely 2-hydroxy-2-(1-methylimidazo[1,5-*a*]pyridin-3-yl)-1*H*-indene-1,3(2*H*)-dione (**8**). On the other hand, interaction of the parent imidazo[1,5-*a*]pyridine (**7**) can be utilized and directed towards preparation of novel 1,3-bis-adduct (**11**) as well as the 1- and 3-monomeric adducts (**9**, **10**). These adducts (**8**-**11**) are hybrids of bioactive imidazo[1,5-*a*]pyridine and indene-1,3(2*H*)-dione entities and might display interesting bioactivity.

4 Experimental

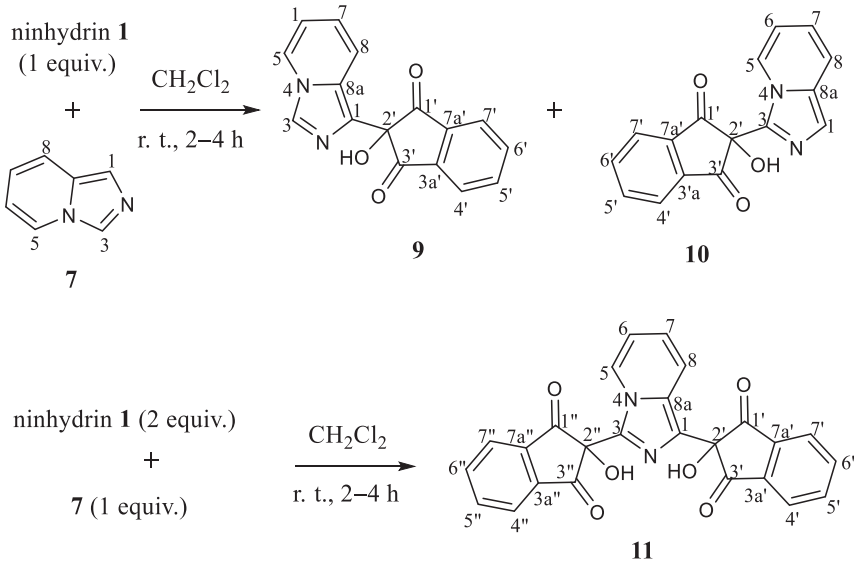
(2-Pyridyl)methylamine, ninhydrin, 2-acetylpyridine, formic acid, phosphorous oxychloride and dry dichloromethane were purchased from Acros. Melting points (uncorrected) were determined on a Stuart scientific melting temperature apparatus in open capillary tubes. IR spectra were measured with a Thermo Nicolet Nexus 670 FT-IR instrument. NMR spectra were recorded on a 500 MHz spectrometer (Bruker



Scheme 1: Formation of 2-hydroxy-2-(imidazo[1,5-*a*]pyridin-1-yl)indene-1,3(2*H*)-diones (**3**).



Scheme 2: Synthesis of 2-hydroxy-2-(1-methylimidazo[1,5-*a*]pyridin-3-yl)indene-1,3(2*H*)-dione (**8**).



Scheme 3: Formation of compounds **9**–**11**.

Avance-III) with TMS as internal standard. High resolution mass spectra (HRMS) were measured on a Bruker APEX-IV mass spectrometer using ESI technique.

The NMR spectral data for the intermediate compounds **4**–**7** are hitherto unreported, and are thus produced herewith.

4.1 *N*-[(1-Pyridin-2-yl)ethyl)]formamide (4)

This compound was obtained by interaction of 1-(pyridin-2-yl)ethanamine with formic acid following a literature procedure [1]. The required 1-(pyridin-2-yl)ethanamine, in turn, is prepared by reduction of 1-(pyridin-2-yl)ethanone oxime [1] with zinc powder and acetic acid, following a reported method [1]. Yellow oil; yield 68%. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.8 Hz, 3H, CH_3), 5.22 (m, 1H, –C*H*Me), 7.23 (pseudo t, 1H, 5-H), 7.26 (d, J = 7.8 Hz, 1H, 3-H), 7.39 (br s, 1H, CON*H*, exchangeable with D_2O), 7.67 (pseudo t, 1H, 4-H), 8.20 (s, 1H, –CHO), 8.51 (d, J = 4.4 Hz, 1H, 6-H) ppm. – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.1 (*C*H_3), 52.5 (–*C*HMe), 120.4 (C-5), 122.3 (C-3), 137.0 (C-4), 148.9 (C-6), 157.4 (C-2), 166.9 (*C*OCH) ppm.

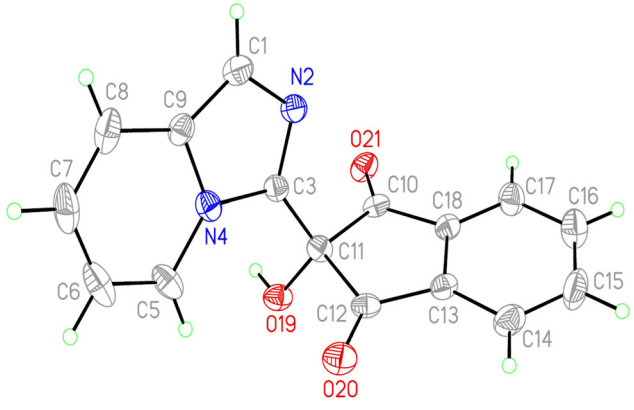


Figure 1: ORTEP view of the molecular structure and atom numbering scheme of **10**. (displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii).

4.2 *N*-((Pyridin-2-yl)methyl)formamide (5)

This compound was obtained by formylation of the amino group of (2-pyridy)methylamine according to a literature procedure [1]. Yellow oil; yield 70%. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40 (d, J = 5.7 Hz, 2H, CH_2), 7.03 (pseudo t, 1H, 5-H), 7.13 (d, J = 7.8 Hz, 1H, 3-H), 7.71 (br s, 1H, CON*H*, exchangeable with D_2O), 7.50 (pseudo t, 1H, 4-H), 8.10 (s, 1H, –CHO), 8.32 (d, J = 4.5 Hz,1H, 6-H) ppm. – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.0 (*C*H_2), 122.2 (C-5), 122.5 (C-3), 137.0 (C-4), 148.8 (C-6), 156.4 (C-2), 161.8 (HC=O) ppm.

4.3 1-Methylimidazo[1,5-*a*]pyridine (6)

This compound was obtained as sticky greenish solid *via* cyclization of *N*-[(1-pyridin-2-yl)ethyl]formamide (**4**) using phosphours oxychloride according to a previously reported procedure [1]. The title compound is purified by recrystallization in chloroform + hexane. Yellow solid; yield 55%; m.p. 63–64 °C, (Lit. [1] m.p. 64–65 °C). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 7.02 (2 overlapped pseudo t, 2H, 6-H, 7-H), 9.38 (s, 1H, 3-H), 7.80 (d, J = 9.1 Hz, 1H, 8-H), 8.47 (d, J = 6.9 Hz, 1H, 5-H) ppm. – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.9 (CH_3), 116.7 (C-6), 118.5 (C-7), 121.9 (C- 8), 121.8 (C-1), 124.4 (C-5), 124.7 (C-3), 126.4 (C-8a) ppm.

Table 1: Crystal data and structure refinement for compounds **10** and **11**.

Compound	10	11
Empirical formula	$C_{16}H_{10}N_2O_3$	$C_{25}H_{14}N_2O_6$
Formula weight, g mol^{-1}	278.26	438.38
Temperature, K	293(2)	293(2)
Wavelength λ, Å	0.71073	0.71073
Crystal system	Monoclinic	Tetragonal
Space group	$P2_1/c$	$I4_1/a$
a, Å	11.762(5)	10.6457(5)
b, Å	13.642(3)	10.6457(5)
c, Å	8.676(3)	34.547(3)
γ, deg.	111.05(4)	90
Volume, Å^3	1299.3(7)	3915.2(4)
Z	4	8
Density (calcd.), g cm^{-3}	1.423	1.487
μ (MoKα), mm^{-1}	0.101	0.108
F(000), e	576	1808
θ range data collection, deg	2.94–25.00	2.95–26.00
Index ranges hkl	$-6 \le h \le 13$	$-13 \le h \le 8$
	$-14 \le k \le 16$	$-13 \le k \le 11$
	$-9 \le l \le 10$	$-42 \le l \le 35$
Refl. collected	4927	8327
Refl. unique/R_{int} (F^2)	2147/0.0475	1928/0.0231
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data/refined parameters	2147/191	1928/157
Final $R1$[a]/$wR2$[b] [$I > 2\,\sigma(I)$]	0.0754/0.2140	0.0507/0.1228
Final $R1$[a]/$wR2$[b] (all data)	0.1198/0.2309	0.0611/0.1292
Goodness-of-Fit[c] on (F^2)	1.112	1.066
Largest diff. peak/hole, e Å^{-3}	0.272/−0.265	0.360/−0.582

[a] $R1 = \Sigma\,||Fo| - |Fc||/\Sigma\,|Fo|$.
[b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$.
[c] $\mathrm{GoF} = S = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

Table 2: Selected bond lengths (Å) and angles (deg) for compound **10**.

C(3)–C(11)	1.484(7)	N(2)–C(3)–N(4)	109.9(4)
O(19)–C(11)	1.404(5)	N(2)–C(3)–C(11)	125.7(4)
C(12)–C(11)	1.558(6)	O(19)–C(11)–C(3)	113.0(4)
C(11)–C(10)	1.542(7)	O(19)–C(11)–C(10)	112.9(4)
O(20)–C(12)	1.217(5)	C(10)–C(11)–C(12)	102.6(4)
O(21)–C(10)	1.207|(5)	C(18)–C(10)–C(11)	108.3(4)
C(18)–C(10)	1.483(7)	C(13)–C(18)–C(10)	110.1(4)
C(18)–C(13)	1.401(6)	C(14)–C(13)–C(12)	129.8(5)
C(13)–C(12)	1.470(7)	O(21)–C(10)–C(11)	124.9(4)
C(9)–C(1)	1.384(7)	C(17)–C(18)–C(10)	128.8(4)
N(2)–C(1)	1.366(6)	O(20)–C(12)–C(11)	124.2(4)
N(2)–C(3)	1.332(6)	C(3)–N(2)–C(1)	107.0(4)
N(4)–C(3)	1.384(6)	N(2)–C(1)–C(9)	110.7(5)
N(4)–C(9)	1.400(6)	C(3)–N(4)–C(9)	107.6(4)

4.4 Imidazo[1,5-*a*]pyridine (7)

This compound is prepared from 2-pyridylmethylamine *via* *N*-formylation, followed by cyclization with phosphorous oxychloride following a reported procedure [1]. Yellow solid; yield 58%; m.p. 53–54 °C (Lit. [1] m.p. 54–55 °C). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.57 (pseudo t, 1H, 6-H), 6.70 (dd, J = 6.6, 9.0 Hz,1H, 7-H), 7.31 (s, 1H, 1-H), 7.48 (d, J = 9.0 Hz, 1H, 8-H), 8.27 (d, J = 7.0 Hz, 1H, 5-H), 8.33 (s, 1H, 3-H) ppm. – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 112.7 (C-6), 118.2 (C-7), 119.4 (C-1), 119.6 (C-8), 123.6 (C-5), 128.7 (C-3), 130.1 (C-8a) ppm.

4.5 2-Hydroxy-2-(1-methylimidazo[1,5-*a*]pyridin-3-yl)-1*H*-indene-1,3(2*H*)-dione (8)

A solution of 1-methylimidazo[1,5-*a*]pyridine **5** (5 mmol) in anhydrous dichloromethane (30 mL) was added to a stirred solution of ninhydrin **1** (5 mmol) in dichloromethane (25 mL) at room temperature. The resulting reaction mixture was stirred further for 3–4 h at rt. Thereafter, the solvent was evaporated in vacuo and the residual crude product was purified by preparative silica gel TLC plates eluting with *n*-hexane-ethyl acetate (3:1, *v*/*v*). Yellow solid; yield 84%; m.p. 208–210 °C. – IR: ν_{max} = 3418, 3360, 3028, 2955, 2916, 1754, 1714, 1593, 1551, 1419, 1367, 1320, 1259, 1174, 1146, 1107 cm^{-1}. – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 4.30 (s, 1H, 2′–OH, exchangeable with D_2O), 6.73 (pseudo t, 1H, 6-H), 6.77 (pseudo t, 1H, 7-H), 7.49 (d, J = 8.9 Hz, 1H, 8-H), 8.03 (overlapped 2d, 4H, 4′-H, 7′-H/5′-H, 6′-H), 8.80 (d, J = 7.1 Hz, 1H, 5-H) ppm. – ^{13}C NMR (125 MHz, DMSO-d_6):δ = 12.5 (CH_3), 78.7 (C-2′), 112.9 (C-6),

Table 3: Selected bond lengths (Å) and angles (deg) for compound **11**.

N(1)–C(2)	1.343(2)	C(2)–N(1)–C(2A)	106.1(2)
N(3)–C(2)	1.377(2)	N(1)–C(2)–C(3)	111.01(15)
N(3)–C(3)	1.391(3)	N(1)–C(2)–C(7)	125.56(17)
C(3)–C(4)	1.404(2)	C(2)–C(3)–C(4)	134.34(16)
C(5)–C(4)	1.341(3)	C(2)–C(3)–N(3)	105.90(9)
C(5)–C(5A)	1.405(5)	N(3)–C(3)–C(4)	119.75(11)
C(7)–C(2)	1.508(2)	C(6)–C(7)–C(8)	102.07(15)
C(7)–C(6)	1.529(3)	C(9)–C(8)–C(7)	106.99(16)
C(7)–C(8)	1.556(3)	C(14)–C(6)–C(7)	108.21(16)
C(8)–C(9)	1.467(3)	O(15)–C(6)–C(7)	124.23(19)
C(7)–O(16)	1.413(2)	O(17)–C(8)–C(7)	125.2(2)
O(15)–C(6)	1.210(2)	O(17)–C(8)–C(9)	127.80(19)
C(8)–O(17)	1.206(2)	O(15)–C(6)–C(14)	127.2(2)

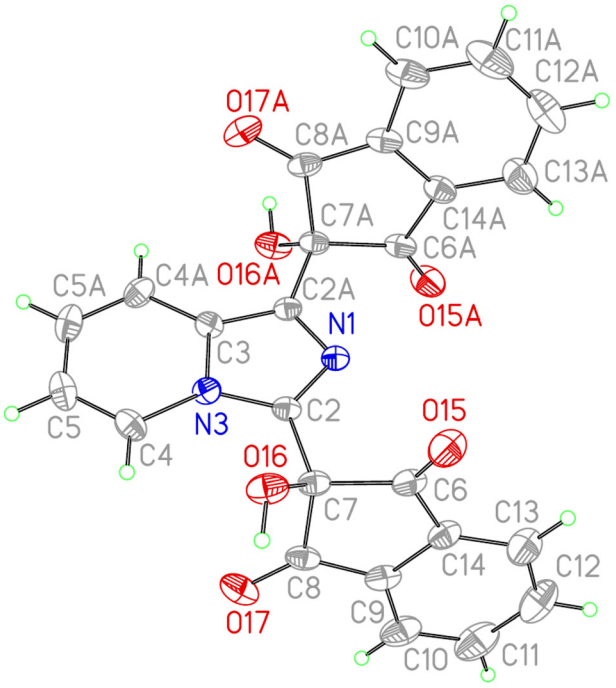


Figure 2: ORTEP view of the molecular structure and atom numbering scheme of **11**. (displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii). The molecular structure adheres to crystallographic two-fold symmetry, the axis of rotation bisecting C5–C5A/C3–N3 and passing through N1. Only one alternative of C3 and N3 is shown.

118.0 (C-8), 119.1 (C-7), 124.3 (C-5′/C-6′), 124.6 (C-5), 127.8 (C-1), 128.5 (C-8a), 130.7 (C-3), 137.5 (C-4′/C-7′), 140.1 (C-3′a/C-7′a), 196.5 (C-1′/C-3′) ppm. – HRMS (ESI): *m/z* = 293.09234 (calcd. 293.09207 for $C_{17}H_{13}N_2O_3$, $[M + H]^+$).

4.6 2-Hydroxy-2-(imidazo[1,5-*a*]pyridin-1-yl)-1*H*-indene-1,3(2*H*)-dione (9)

This compound was prepared from imidazo[1,5-*a*]pyridine **7** (5 mmol) and ninhydrin **1** (5 mmol) by following the same procedure described above for compound **8**. The crude product was a composite mixture of the title compound **9** together with its 3-monomeric adduct **10**. The two components were separated by preparative silica gel plates, eluting with *n*-hexane-ethyl acetate (4:1, *v*/*v*). Yellow solid; yield 55%; m.p. 201–203 °C. – IR: ν_{max} = 3412, 3048, 1750, 1710, 1637, 1590, 1560, 1508, 1458, 1463, 1267, 1170, 1152, 1130, 1085, 1003 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$) δ: 3.95 (br s, 1H, 2′–OH, exchangeable with D_2O), 6.65 (pseudo t, 1H, 6-H), 6.88 (dd, *J* = 9.1, 6.6 Hz 1H, 7-H), 7.84 (d, *J* = 9.1 Hz, 1H, 8-H), 7.90, 7.92 (2d, *J* = 5.6 Hz, 2H, 5′-H/6′-H), 8.08, 8.09

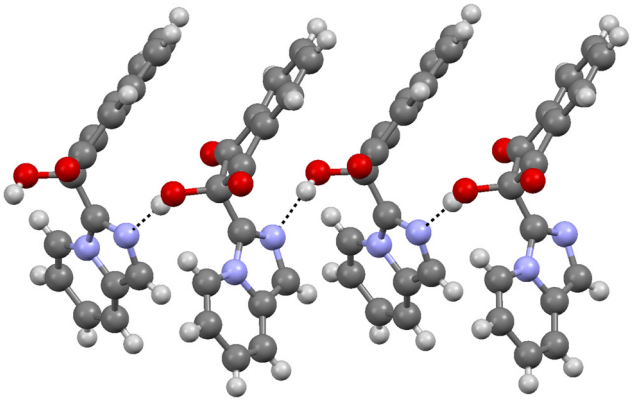


Figure 3: Chain formation of compound **10** in the crystal through hydrogen bonding.

(2d, *J* = 5.6 Hz, 2H, 4′-H/7′-H), 8.52 (d, *J* = 7.0 Hz, 1H, 5-H), 9.18 (s, 1H, 3-H) ppm. – ^{13}C NMR (125 MHz, CDCl3) δ: 78.3 (C-2′), 113.2 (C6), 119.1 (C-8), 119.5 (C-7), 121.0 (C-5), 124.3 (C-4′/C-7′), 124.8 (C-1), 126.1 (C-3), 129.1 (C-8a), 136.2 (C-5′/C-6′), 141.0 (C-3′a/C-7′a), 196.9 (C-1′/C-3′) ppm. – HRMS (ESI): *m/z* = 279.07614 (calcd. 279.07642 for $C_{16}H_{11}N_2O_3$, $[M + H]^+$).

4.7 2-Hydroxy-2-(imidazo[1,5-*a*]pyridin-3-yl)-1*H*-indene-1,3(2*H*)-dione (10)

This compound was obtained from the reaction of **1** and **7** (as noted above in the preparation of **9**). Yellow solid; yield 14%; m.p. 211–212 °C. – IR: ν_{max} = 3426, 3061, 1740, 1718, 1603, 1594, 1558, 1487, 1450, 1362, 1277, 1211, 1150, 1014 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$) δ: 4.01 (br s, 1H, 2′–OH, exchangeable with D_2O), 6.74 (pseudo t, 1H, 6-H), 6.87 (pseudo t, 1H, 7-H), 7.33 (s, 1H, 3-H), 7.43 (d, *J* = 9.1 Hz, 1H, 8-H), 7.92 (d, *J* = 5.7 Hz, 2H, 5′-H/6′-H), 8.09 (d, *J* = 5.7 Hz, 2H, 4′-H/7′-H), 8.97 (d, *J* = 7.0 Hz, 1H, 5-H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.9 (C-2′), 113.3 (C-6), 118.0 (C-8), 120.4 (C-3), 120.6 (C-7), 124.4 (C-5), 124.6 (C-4′/C-7′), 131.4 (C-1), 132.4 (C-8a), 136.7 (C-5′/C-6′), 140.5 (C-3′a/C-7′a), 194.2 (C-1′/C-3′).

Table 4: O–H···A Hydrogen bonding interactions distances (Å) and angles (deg).[a]

	10	11
O···A	2.771(5)	2.883(2)
H···A	1.83(6)	2.13(3)
O–H···A	170(5)	155(3)

[a]A = N in **10**, A = O in **11**.

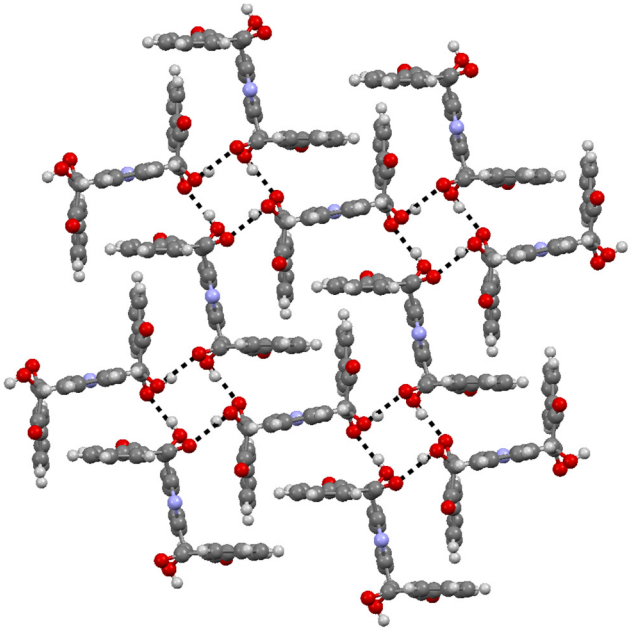


Figure 4: Layer formation in the crystal structure of compound **11** through hydrogen bonding.

– HRMS (ESI): *m/z* = 279.07605 (calcd. 279.07642 for $C_{16}H_{11}N_2O_3$, $[M + H]^+$).

Yellow needle crystals of **10**, suitable for X-ray crystallography, were obtained by recrystallization from acetonitrile.

4.8 2,2′-(Imidazo[1,5-*a*]pyridine-1,3-diyl) bis(2-hydroxy-1*H*-indene-1,3(2*H*)-dione) (11)

This compound was prepared from imidazo[1,5-*a*]pyridine 7 (5 mmol) and ninhydrin 1 (10 mmol) by following the same procedure described for 8 above. Orange solid; yield 63%; m.p. 217–219 °C (dec). – ^{1}H NMR (500 MHz, MeOD): δ = 4.80 (s, 2H, 2″–OH/2′–OH, exchangeable with D_2O), 6.76 (pseudo t, 1H, 6-H), 6.94 (dd, J = 9.3, 6.7 Hz, 1H, 7-H), 7.81 (m, 4H, 4′-H, 7′-H/4″-H, 7″-H), 7.83 (m, 4H, 5′-H, 6′-H/5″-H, 6″-H), 7.96 (d, J = 9.3 Hz, 1H, 8-H), 8.86 (d, J = 7.3 Hz, 1H, 5-H) ppm. – ^{13}C NMR (125 MHz, MeOD): δ = 78.1 (C-2′/C-2″), 113.1 (C-6), 119.0 (C-8), 121.0 (C-7), 123.1, 123.3 (C-4′, C-7′/C-4″, C-7″), 124.5 (C-5), 126.9 (C-3), 130.8 (C-8a), 131.1 (C-1), 135.9, 136.2 (C-5′, C-6′/C-5″, C-6″), 139.9, 140.6 (C-3a′, C-7a′/C-3a″, C-7a″), 195.1, 197.5 (C-1′, C-3′/C-1″, C-3″) ppm. – HRMS (ESI): *m/z* = 461.07392 (calcd. 461.07441 for $C_{25}H_{14}N_2NaO_6$, $[M + Na]^+$).

Brown parallelepiped crystals of **11**, suitable for X-ray crystallography, were obtained by recrystallization in methanol-tetrahydrofuran.

5 Collection of X-ray diffraction data and structure analyses of compounds 10 and 11

Suitable single crystals of **10** (approximate dimensions of 0.4 × 0.1 × 0.1 mm^3) and **11** with approximate dimensions of 0.4 × 0.2 × 0.1 mm^3 were epoxy-mounted on glass fibres. Data for **10** and **11** were then collected at room temperature (T = 293 K) using an Oxford Calibur Diffractometer. Data were acquired and processed to give SHELX-format *hkl* files using CRYSALIS PRO software [12]. Cell parameters were determined and refined using CRYSALIS PRO [12]. A multiscan absorption collection was applied with maximum and minimum transmission factors of 1.00000 and 0.79561, 1.00000 and 0.95256 for **10** and **11**, respectively. The structures were solved by Direct Methods and refined by full-matrix least-squares on F^2 using all unique data [13]. All nonhydrogen atoms were refined anisotropically with the hydrogen atoms placed in calculated positions and refined using a riding model.

The molecular structure of **11** adheres to crystallographic two-fold symmetry, the axis of rotation bisecting C5–C5A/C3–N3 and passing through N1. It results in a 50:50 split occupancy of C3 and N3.

CCDC 945167 and 1945168 for **10** and **11**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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