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FACILE SYNTHESIS OF 3-(SUCCINIMID-3-YL)-2-OXO-2,3-DIHYDRO-IMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES BY SEQUENTIAL INTRA- AND INTERMOLECULAR MICHAEL REACTIONS BETWEEN 2-AMINOPYRIDINES AND MALEIMIDES

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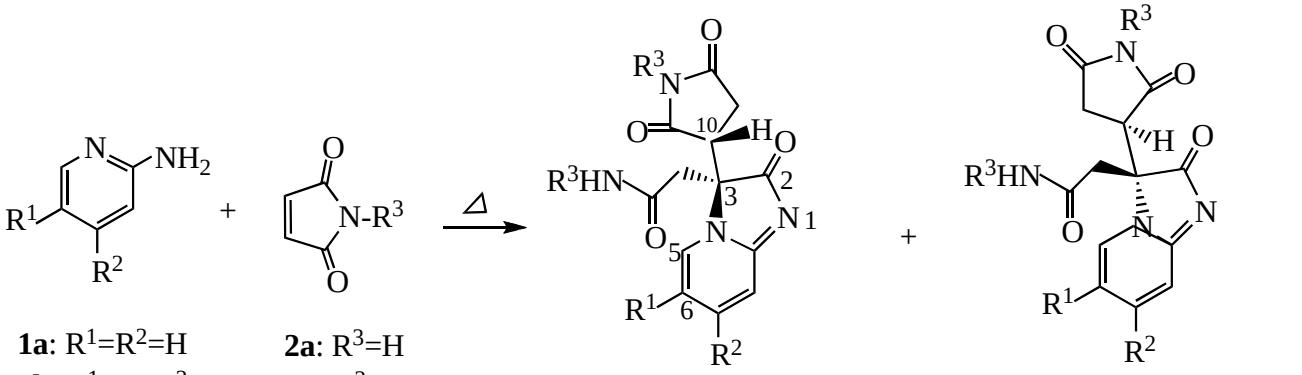
Abstract – 3-(Succinimid-3-yl)-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridine derivatives (**3** and **4**) were prepared through a one-pot reaction from 2-amino-pyridines (**1**) by acylation with maleimides (**2**) and followed by an intramolecular Michael addition, and a subsequent second Michael addition with another molecule of **2**. The diastereomeric configurations of the products were confirmed by X-ray crystal analyses. The reaction mechanism of the accumulated three types of additions between **1** and two equimolar amounts of **2** was calculated using MOPAC-PM6 molecular simulations and the competing addition reactions as hard and soft reactions were explained by HSAB theory.

In recent years, significant attention has been paid to the synthesis or further transformations of fused [5,6] herero-ring systems. In particular, noticeable interest has focused on imidazo[1,2-*a*]pyridines, fused bicyclic [5,6] heterocycles with a one-ring-junction nitrogen atom and one extra nitrogen atom in the five-membered ring, because these compounds show high binding affinity to multiple receptors. The

high binding affinity towards receptors indicates that these heterocycles may represent useful therapeutic compounds, such as antifungal, antibacterial and local anesthetic agents.[1] There are several methods that describe the synthesis of 2-substituted or 3-substituted imidazo[1,2-*a*]pyridines. These methods depend primarily on condensation reactions of 2-aminopyridines with α-halocarbonyl compounds,[2] glyoxal trimer dihydrate,[3] or aldehydes and isonitriles[4] to form the five-membered cyclic systems. It has been reported that several 2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines and, especially, 3,3-dibenzoyl-2-oxo-2,3-dihydro-imidazo[1,2-*a*]pyridine (ZSET 845) improve cerebral function, and therefore may represent therapeutic treatments for cognitive and memory disorders including Altzheimer's desease.[5] Since these types of compounds are important, we describe herein a facile synthesis and structural analysis of particular [3-(succinimid-3-yl)-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3yl]acetamides through a one-pot reaction of 2-aminopyridines with maleimides. The reaction mechanism of accumulated three types of additions between 2-aminopyridines and two equimolar amounts of maleimides were found to be very interesting, because the additions are competing for acylation and hard and soft Michael addition reactions. Such types of selective reactions are present in many biochemical reactions.[6] We have previously reported many thermal[7] and photochemical[8] bimolecular addition and isomerization reactions. The reaction mechanisms were analyzed by a molecular orbital method containing frontier molecular orbital (FMO) theory[8] and the transition state (TS) analysis.[9] The reaction mechanism of the accumulated processes for products **3** and **4** may be analyzed using the recent MOPAC2009-PM6 level.[10] The PM6 accuracy by average unsigned error (AUE) of heat of formation (HOF) for 1493 organic molecules was found to be higher than that of B3LYP/6-31G* levels.

A solution of 4-methyl-2-amiopyridine (**1b**) (1.6 mmol) and maleimide (**2a**) (3.2 mmol) in acetonitrile (10ml) was refluxed for 8 h under nitrogen atmosphere. Upon cooling to room temperature, the product **3ba** (40% yield) crystallized out of solution. The filtrate was left standing overnight to give **4ba** in 25% yield (Scheme 1 and entry 2 in Table 1). Product **3ba** was estimated as a diastereomer of **4ba** from X-ray crystallographic analysis of **4ba**. The ^{1}H NMR spectral data between **3ba** and **4ba** were similar to each other.[11] The results of the similar reactions of **1a-c** with **2a**,**b** are summarized in Table 1. The yields of products **4ca** and **4cb** were calculated by ^{1}H NMR analyses (entry 6,7) because it was difficult to isolate these compounds from the recrystallization. Products **3ca,** which was obtained from the reaction of 5-methyl-2-aminopyridine (**1c**) with **2a** (entry 6), and **4ba** were recrystallized from water to give single

crystals, and the structures of **3ca** and **4ba** (Figure 1)[12] were established by X-ray crystallographyic analyses as 3S,10R- and 3R,10R-[3-(succinimid-3-yl)-2-oxo-2,3-dihydroimidazo- [1,2-*a*]pyridin-3-yl]-acetamides, respectively. The assignments of the same structures (**3** and **4**) were based on their ^{1}H-NMR , IR and MS spectra that were analogous to those of **3ca** and **4ba**.[11]



1a: R^1=R^2=H
1b: R^1=H, R^2=Me
1c: R^1=Me, R^2=H

2a: R^3=H
2b: R^3=Ph

3aa: R^1=R^2=R^3=H
3ba: R^1=R^3=H, R^2=Me
3bb: R^1=H, R^2=Me, R^3=Ph
3ca: R^1=Me, R^2=R^3=H
3cb: R^1=Me, R^2=H, R^3=Ph

4aa: R^1=R^2=R^3=H
4ba: R^1=R^3=H, R^2=Me
4bb: R^1=H, R^2=Me, R^3=Ph
4ca: R^1=Me, R^2=R^3=H,
4cb: R^1=Me, R^2=H, R^3=Ph

Scheme 1

Table 1. Reactions of 2-Aminopyridines (**1**) with Maleimides (**2**)[a]

Entry	2-Aminopyridine	Maleimide	Yield(%)[b]		
1	**1a**	**2a**	**3aa** (52)	**4aa** (12)	**2a** (36)
2	**1b**	**2a**	**3ba** (44)	**4ba** (28)	**2a** (28)
3	**1b**[c]	**2a**[c]	**3ba** (7)	**4ba** (17)	**2a** (76)
4	**1b**[d]	**2a**[d]	**3ba** (12)	**4ba** (12)	**2a** (76)
5	**1b**	**2b**	**3bb** (37)	**4bb** (16)	**2b** (47)
6	**1c**	**2a**	**3ca** (43)	**4ca** (26)[e]	**2a** (31)
7	**1c**	**2b**	**3cb** (56)	**4cb** (35)[e]	**2b** (9)

[a]A mixture of **1** and two equimolar **2** was refluxed for 8 h in MeCN (0.48 M solution). Isolated yields of **3** and **4** in the same conditions were as follows; **3aa** (45%), **4aa** (5%), **3ba** (40%), **4ba** (25%), **3bb** (14%), **4bb** (1%), **3ca** (19%), **3cb** (18%). [b]Estimated from ^{1}H NMR analyses based on total integral of **2**, **3** and **4**.[c]MeCN solution of **1b** and equimolar **2a** was allowed to stand for 24 h at room temperature. [d]A mixture of **1b** and equimolar **2a** was ground for 10 min and heated at 80 ℃ for 8 h without solvent. [e]It was difficult to isolate by recrystallization.

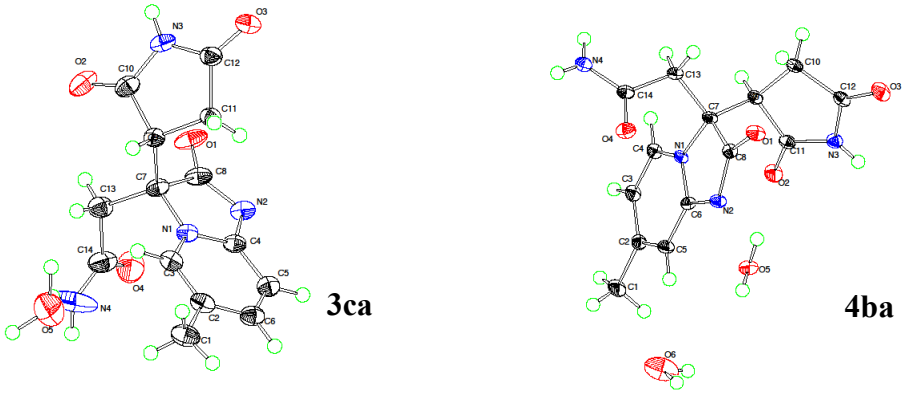
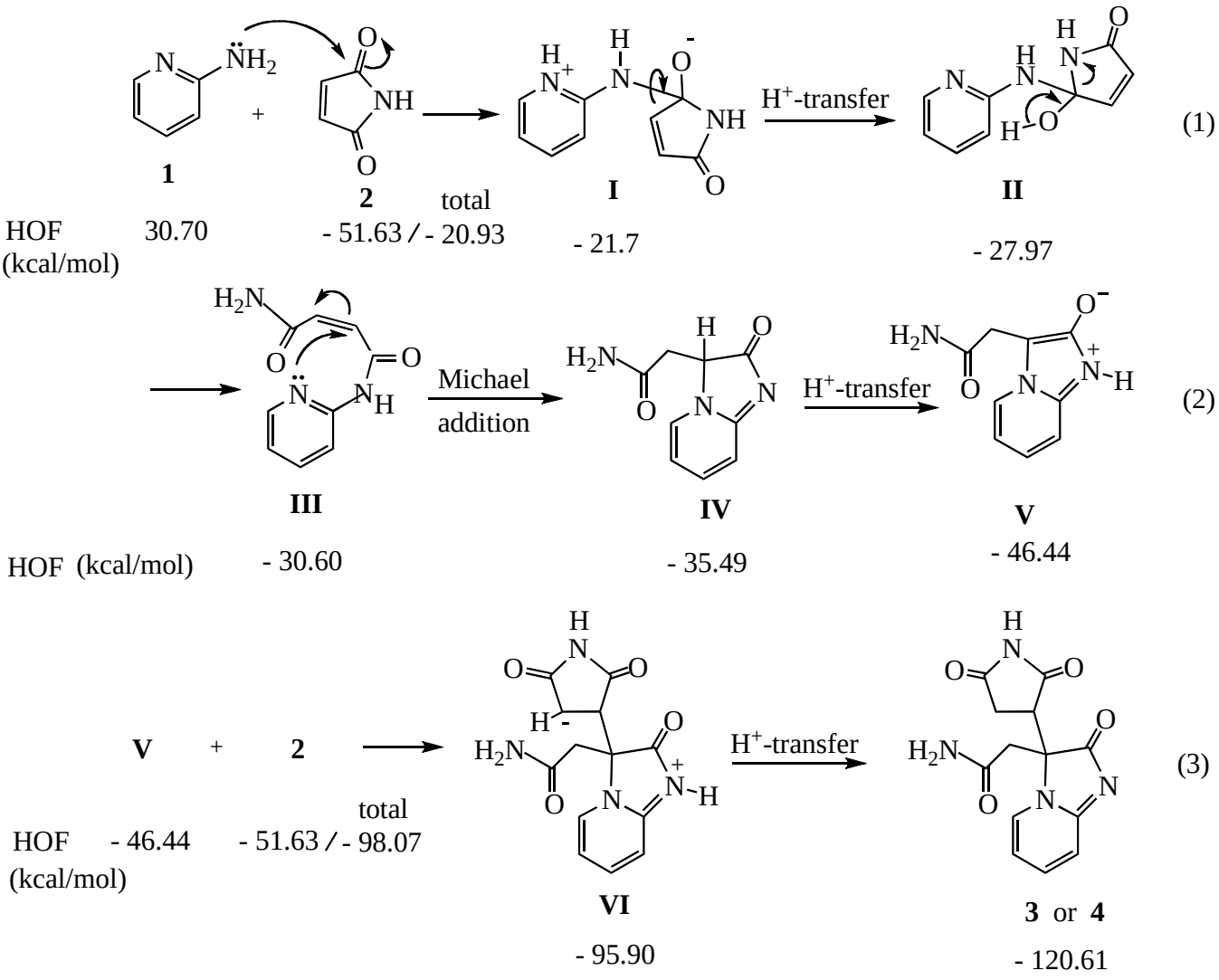


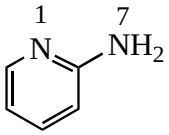
Figure 1. ORTEP drawings of **3ca** and **4ba**

The reaction of **1** with two equimolar amount of **2** gave **3** and **4** *via* two types of intermolecular reactions at the carbonyl group and the C-C double bond of **2**. The reaction mechanism was estimated to proceed *via* acylation, two types of Michael additions and a proton transfer, as estimated from MO calculations using the accurate MOPAC PM6 level (Scheme 2).[10] The values of the heat of formation

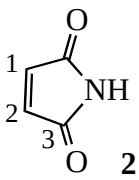


Scheme 2

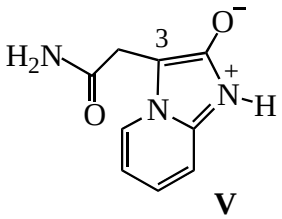
Table 2. Ionization potential (IP), frontier orbital coefficients and atomic charges (AC) of **1**, **2** and **V**



1



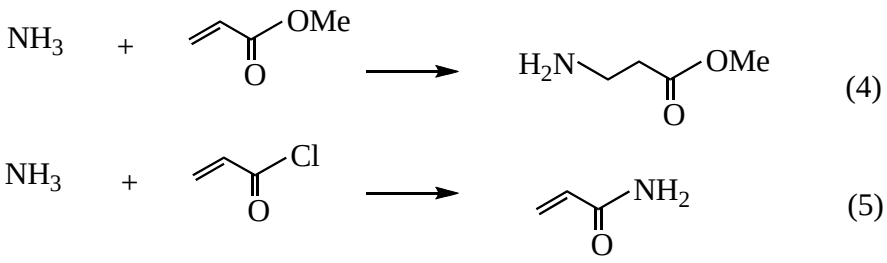
2



V

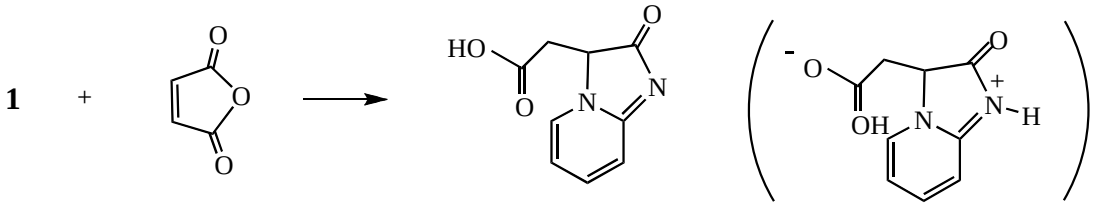
	1			**2**			**V**	
	1-position	7-position			1-position	3-position		3-position
IP (eV)	8.78			11.06				8.53
HOMO	0.30	**0.57**		LUMO	0.51	0.38	HOMO	**0.66**
AC	- 0.45	- **0.52**			- 0.22	+ **0.60**		- 0.40

(HOF) (**1-4**, **I-VI**) are shown in Scheme 2, and those of the ionization potential (IP), frontier orbital coefficients (HOMO, LUMO) and atomic charge (AC) of **1**, **2** and **V** are listed in Table 2. The changes of HOF values (kcal/mol) (- 20.93 → - 21.7 → - 27.97 in the reaction (1), - 30.60 → - 35.49 → - 46.44 in the reaction (2) and – 98.07 → - 95.90 → - 120.61 in the reaction (3) in Scheme 2) are reasonable and suggest that these reactions proceed smoothly. The reactions (1) and (3) are also competing reactions for maleimide (**2**). They are similar to following soft and hard reactions ((4) and (5) in Scheme 3)[13] of HSAB theory. The reaction of each step between **1** and **2** was reasonably explained as follows. Since the AC value at the 7-position (NH_2) of **1** was more negative than at the 1-position of **1** (also the HOMO coefficient at the 7-position was larger than at the 1-position) and the AC value at the 3-position (C=O) of **2** was more positive than at the 1-position (Table 2), the reaction of **1** at the 7-position with **2** at the 3-position has been proceeded by the hard reaction to give **I**, according to the hard and soft acids and bases (HSAB) theory. Intermediate **I** afforded **II** *via* a proton transfer and followed by the ring opening reaction of the γ-lactam to give **III**. **III** underwent intramolecular.



Scheme 3

Michael addition to give **V** having lower HOF than that of **IV**. Since the IP value of **V** was smaller than that of **1** and the HOMO coefficient at the 3-position of **V** was the largest value (Table 2), **V** reacted with another molecule of **2** at the olefinic part by the soft reaction to afford **3** or **4** *via* **VI**. The activation energy (ΔEa) of the reaction between **V** and **2** to give **VI** was estimated to 12.23 kcal/mol (vibration analysis: - 486.7 cm^{-1}) using PM6 methods. It was found that intermediate **IV**, whose skeleton is known,[14] was a very active species because trials to obtain **IV** derived from the reaction of **1b** with **2a** were unsuccessful in giving **3ba** and **4ba,** even under mild conditions (solution reaction at room temperature) or solid-state conditions (reaction at 80 ℃ without solvent) (Table 1, entry 3, 4). It was assumed that the structure of the intermediate **IV**, obtained by the reaction between **1** and maleic anhydride, was stable owing to the formation of an inner salt as shown in Scheme 4.[14]



Scheme 4

The reaction (3) is competing with the reaction (1) and the formation of **3** and **4** as diastereomers suggests that the soft reaction (3) by the intermediate **V** is faster than the reaction (1).

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11. All the new compounds gave the correct analytical and MS data. Selected spectral data are given below. **3aa**: mp 243-246 ℃; ^{1}H NMR (DMSO-d_6) δ 1.73 (1H, dd, *J*=18.0, 4.0 Hz), 2.53 (1H, dd, *J*=18.0, 9.2 Hz), 3.18, 3.30 (each 1H, d, *J*=17.3 Hz), 3.74 (1H, dd, *J*=9.2, 4.0 Hz), 6.83, 7.43, 11.33 (each 1H, s), 6.85 (1H, dd, *J*=7.6, 6.4 Hz), 7.07 (1H, d, *J*=9.2 Hz), 7.79 (1H, dd, *J*=9.2, 7.6 Hz), 8.39 (1H, d, *J*=6.4 Hz). IR (KBr) 1770, 1740, 1673 cm^{-1}. **4aa**: mp 206-207 ℃; ^{1}H NMR (DMSO-d_6) δ 2.75 (1H, dd, *J*=18.0, 9.2 Hz), 2.81, 3.10 (each 1H, d, *J*=16.0 Hz), 3.02 (1H, dd, *J*=18.0, 4.4 Hz), 3.63 (1H, dd, *J*=9.2, 4.4 Hz), 6.86, (1H, dd, *J*=7.6, 6.8 Hz), 6.96, 7.45, 11.20 (each 1H, s), 7.03 (1H, d, *J*=8.8Hz), 7.78 (1H, dd, *J*=8.8, 7.6 Hz), 8.31(1H, d, *J*=6.8 Hz). IR (KBr) 1780, 1720, 1683 cm^{-1}. **3ba**: mp 232-236 ℃; ^{1}H NMR (DMSO-d_6) δ 1.71 (1H, dd, *J*=18.0, 4.0 Hz), 2.33 (3H, s), 2.40 (1H, dd, *J*=18.0, 9.2 Hz), 3.15, 3.22 (each 1H, d, *J*=16.4 Hz), 3.73 (1H, dd, *J*=9.2, 4.0 Hz), 6.72 (1H, d, *J*=6.8 Hz), 6.82, 7.41, 11.30 (each 1H, s), 6.91 (1H, s), 8.24 (1H, d, *J*=6.8 Hz). IR (KBr) 1760, 1735, 1665 cm^{-1}. **4ba**: mp 207- 210 ℃; ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 2.74 (1H, dd, *J*=18.2, 9.2 Hz), 2.76, 3.08 (each 1H, d, *J*=15.6 Hz), 2.97 (1H, dd, *J*=18.2, 4.4 Hz), 3.61 (1H, dd, *J*=9.2, 4.4 Hz), 6.73, (1H, d, *J*=6.8 Hz), 6.85, 7.42, 11.19 (each 1H, s), 6.93 (1H, s), 8.14 (1H, d, *J*=7.2 Hz). IR (KBr) 1775, 1710, 1650 cm^{-1}. **3bb**: mp 181-184 ℃; ^{1}H NMR (DMSO-d_6) δ 1.85 (1H, dd, *J*=18.0, 4.0 Hz), 2.37 (3H, s), 2.83 (1H, dd, *J*=18.0, 6.0 Hz), 3.50, 3.61 (each 1H, d, *J*=17.2 Hz), 3.96 (1H, dd, *J*=6.0, 4.0 Hz), 6.83 (1H, d, *J*=6.0 Hz), 7.00, 7.1-7.5 (10H, m), 7.01 (1H, s), 8.46 (1H, d, *J*=6.0 Hz), 10.16 (1H, s). IR (KBr) 1780, 1710, cm^{-1}. **4bb**: mp 162-165 ℃; ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 2.82 (1H, dd, *J*=15.6, 6.0 Hz), 2.87, 3.05 (each 1H, d, *J*=15.6Hz),

3.02 (each 1H, dd, *J*=15.6, 4.0 Hz), 3.82 (1H, dd, *J*=6.0, 4.0 Hz), 6.65 (1H, d, *J*=6.0 Hz), 6.80 (1H, s), 7.00, 7.1-7.5 (10H, m), 8.32 (1H, d, *J*=6.0 Hz), 10.10 (1H, s). IR (KBr) 1780, 1710 cm^{-1}. **3ca**: mp 240-243 ℃; ^{1}H NMR (DMSO-d_6) δ 1.70 (1H, dd, *J*=18.0, 4.0 Hz), 2.17 (3H, s), 2.50 (1H, dd, *J*=18.0, 9.2 Hz), 3.14, 3.30 (each 1H, d, *J*=16.0 Hz), 3.69 (1H, dd, *J*=9.2, 4.0 Hz), 6.81, 7.42, 11.31 (each 1H, s), 7.02 (1H, d, *J*=9.2 Hz), 7.68 (1H, d, 9.2 Hz), 8.22 (1H, s). IR (KBr) 1780, 1720, 1680 cm^{-1}. **4ca** (not isolated): ^{1}H NMR (DMSO-d_6) δ 2.17 (3H, s), 2.65 (1H, dd, *J*=18.0, 9.2 Hz), 2.80, 3.07 (each 1H, d, *J*=16.4 Hz), 2.96 (1H, dd, *J*=18.0, 4.0 Hz), 3.59 (1H, dd, *J*=9.2, 4.9 Hz), 6.91, 7.80, 11.20 (each 1H, s), 6.98 (1H, d, *J*=9.2 Hz), 7.67 (1H, d, *J*=9.2 Hz), 8.15 (1H, s). **3cb**: mp 252-255 ℃; ^{1}H NMR (DMSO-d_6) δ 1.85 (1H, dd, *J*=18.4, 6.0 Hz), 2.21 (3H, s), 2.84 (1H, dd, *J*=18.4, 9.2 Hz), 3.48, 3.66 (each 1H, d, *J*=16.8Hz), 3.91 (1H, dd, *J*=9.2, 4.4 Hz), 7.1 (1H, d, *J*=9.2 Hz), 7.0-7.5 (10H, m), 7.76 (1H, d, *J*=9.2 Hz), 8.42 (1H, s), 10.15 (1H, s). IR (KBr) 1780, 1710 cm^{-1}. **4cb** (not isolated): ^{1}H NMR (DMSO-d_6) δ 2.14 (3H, s), 2.95 (1H, dd, *J*=18.0, 5.2 Hz), 3.05 (1H, dd, *J*=18.0, 9.2 Hz), 3.20, 3.46 (each 1H, d, *J*=16.8 Hz), 3.80 (1H, dd, *J*=9.6, 4.0 Hz), 7.0-7.5 (11H, m), 7.73 (1H, d, *J*=9.0 Hz), 8.32 (1H, s).

12. X-Ray crystal data for **4ba** ($C_{14}H_{14}N_4O_4$); T=23.0 ℃, Mo-Kα (Rigaku RAXSIS-RAPID imaging plate diffractometer, λ=0.71069 Å), crystal dimensions 0.12 x 0.15 x 0.57 mm^3 (a colorless block crystal), a=7.3922 (4), b=8.8511 (5), c=12.6067 (9) Å, α=94.739 (5), β=93.452 (4), γ=114.591 (2) ° triclinic, space group P-1 (#2), Z=2, $\mu_{MoK\alpha}$=1.02 cm^{-1}, Mr=302.29, V=743.37 (5) $Å^3$, anode power 50 KV x 32 mA, ρ_{calc}=1.350 g/cm^3, $2\theta_{max}$=54.9 °, F (000)=316.00. 6128 reflections measured, 2846 observed (I > 2σ (I)), number of parameters 217. The structure was solved by direct methods and was refined on SIR 97.[15] Data were corrected for Lorentz polarizations. The data/parameter ratio was 13.12. R=0.051, R_w=0.178, GOF=1.46, max/min residual density +0.65/-0.47 $eÅ^{-3}$. **3ca** ($C_{14}H_{14}N_4O_4$); T= - 150 ℃, crystal dimensions 0.57 x 0.57 x 0.13 mm^3 (a colorless platelet crystal), a=21.212 (2), b=5.9784 (4), c=23.791 (1) Å, β=104.188 (2) °, monoclinic, space group C2/c (#15), Z=6, $\mu_{MoK\alpha}$=0.77 cm^{-1}, Mr=302.29, V=2925.1 (3) $Å^3$, ρ_{calc}=1.030 g/cm^3, F (000)=948.00. 13090 reflections measured, 2753 observed (I > 2σ (I)), number of parameters 208. The structure was solved by direct method and was refined on SIR 97. The data/parameter ratio was 13.24. R=0.077, R_w=0.259, GOF=1.87, max/min residual density +0.70/-0.8 $eÅ^{-3}$. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

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