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SYNTHESIS AND STRUCTURAL STUDIES OF (2-OXO-2,3-DIHYDROIMIDAZO[1,2-*a*]PYRIDIN-3-YL)ACETIC ACIDS

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Abstract – (2-Oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids (**4a-c**, **9a-c**) were prepared from 2-aminopyridines by acylation with maleic or citraconic anhydrides and followed by Michael addition. Formation of 3-methyl substituted derivatives (**9a-c**) from citraconic anhydride was found to be regioselective. The molecular conformations of the products in the solution and in the crystal form were discussed based on ^{1}H NMR spectral and X-Ray data.

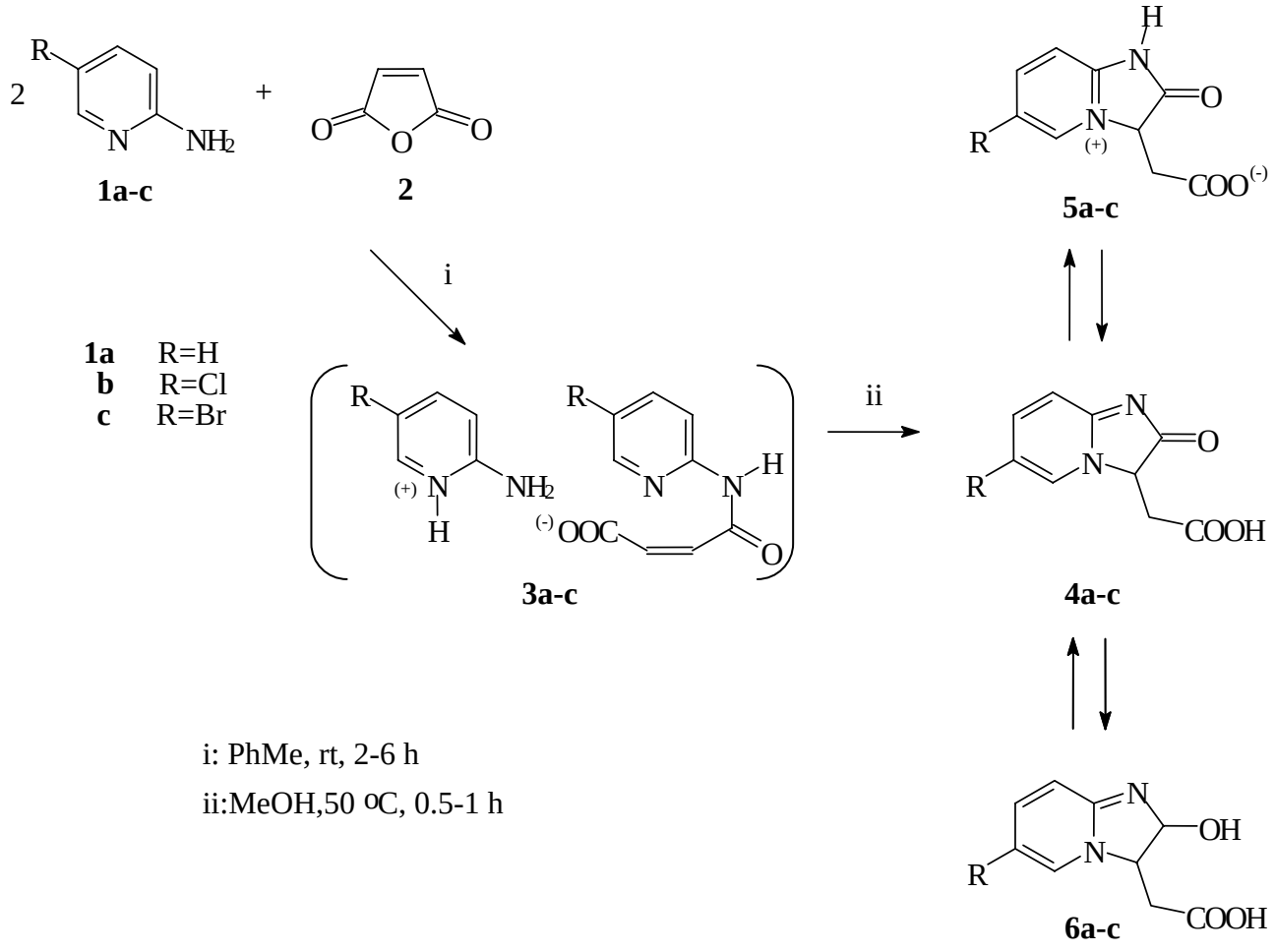
INTRODUCTION

2-Oxo-2,3-dihydroimidazo[1,2-*a*]pyridines are known to possess a good synthetic potential, especially in the preparation of disubstituted maleic anhydrides and maleimides.[1-8] It has been shown that several 2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines and, in particular, 3,3-dibenzylimidazo-2-(3*H*)-one (ZSET845) are able to improve the cerebral function and may be of therapeutic value for the cognitive and memory disorders such as Alzheimer's disease.[9-11] In addition, fluorescent properties of 3,3-disubstituted 2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridines have been reported.[12] Clearly, this is considerable importance of this class of compounds and this study reports on the synthesis and structural analysis of some (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids.

RESULTS AND DISCUSSION

The reaction of 2-aminopyridines (**1a-c**) with maleic anhydride (**2**) in the ratio of 2:1 afforded salts (**3a-c**) that readily cyclized to form (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids (**4a-c**) through intramolecular Michael addition (Scheme 1). X-Ray crystallographic data of **4a** showed that the crystal existed as tautomers (**4a**) and (**5a**) in equal proportion.[5] In aqueous solution, only form (**5a**) was found (^{1}H NMR spectral data, Table 1). However in DMSO solution, enolic form (**6a**) appeared together with zwitterion (**5a**) (Table 2). 6-Halogen-substituted analogues of **4a** were presented in DMSO only as enols (**6b,c**) that was confirmed by singlet at 3.85 ppm in ^{1}H NMR spectra related to protons of the methylenic group next to the carboxyl (Table 1).

Scheme 1



Interestingly, the addition of trifluoroacetic acid (TFA) into DMSO solution of **4a** changed the ratio of the tautomers (**5a** and **6a**) that was observed as decreasing intensity of the enol signals in ^{1}H NMR spectrum with concerted increasing intensity of the zwitterion signals (Table 2). When the same methodology was applied to (6-halogeno-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids (**4b,c**) two pairs of doublets related to diastereotopic protons of the methylenic group pertinent to forms (**5b,c**) were indicated in ^{1}H NMR spectra together with characteristic signals of enols (**6b,c**).

Table 1. ^{1}H NMR spectral data of individual forms of (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)-acetic acids.

Compd	R	^{1}H NMR (300 MHz, DMSO-d_6, TMS)					
		CH_2	C^5H	C^6H	C^7H	C^8H	NH
5a*	H	dd, 3.32, 3.37 (J_{AB}=18.08 Hz)	d, 8.57 (J=6.31 Hz)	m, 7.49-7.59	t, 8.35 (J=8.10 Hz)	m, 7.49-7.59	-
6b	Cl	s, 3.85	s, 8.41	-	d, 7.33 (J=9.42 Hz)	d, 7.16 (J=9.41 Hz)	br s, 11.59
6c	Br	s, 3.85	s, 8.46	-	d, 7.28 (J=9.04 Hz)	d, 7.23 (J=9.04 Hz)	br s, 11.57

*- spectrum in D_2O, DSS as internal standard

Table 2. ^{1}H NMR spectral data of the acid tautomerized (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)-acetic acids.

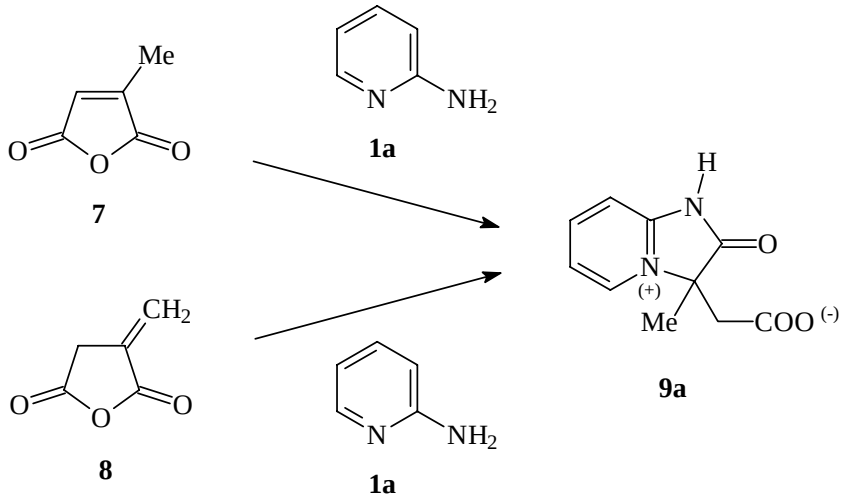
Compd	R	Isomer	^{1}H NMR (300 MHz, DMSO-d_6 +TFA, TMS)					
			CH_2	C^3H	C^5H	C^6H	C^7H	C^8H
4a	H	**5a***	dd, 3.01, dd, 3.20 (J_{AB}=16.95 Hz, J_{AX}=4.14 Hz)	t, 4.70 (J=4.71 Hz)	d, 8.21 (J=6.03 Hz)	t, 6.78 (J=6.78 Hz)	t, 7.76 (J=7.91 Hz)	d, 7.05 (J=8.29 Hz)
		6a*	s, 3.80	-	d, 8.11 (J=6.41 Hz)	t, 6.88 (J=6.60 Hz)	t, 7.14 (J=7.91 Hz)	d, 7.28 (J=8.29 Hz)
		5a	dd, 3.45, dd, 3.71 (J_{AB}=18.84 Hz, J_{AX}=4.14 Hz)	t, 5.53 (J=3.77 Hz)	d, 8.92 (J=6.45 Hz)	m, 7.55-7.69	t, 8.44 (J=7.91 Hz)	m, 7.55-7.69
		6a	s, 4.09	-	d, 8.69 (J=6.78 Hz)	t, 7.45 (J=9.78 Hz)	m, 7.71-7.86	
4b	Cl	**5b**	dd, 3.46, dd, 3.75 (J_{AB}=18.84 Hz, J_{AX}=4.52 Hz)	t, 5.54 (J=3.77 Hz)	s, 9.29	-	d, 8.56 (J=9.04 Hz)	d, 7.68 (J=9.04 Hz)
		6b	s, 4.08	-	s, 9.09	-	d, 7.85 (J=9.42 Hz)	d, 7.77 (J=9.42 Hz)
4c	Br	**5c**	dd, 3.46, dd, 3.76 (J_{AB}=18.84 Hz, J_{AX}=4.52 Hz)	t, 5.53 (J=3.77 Hz)	s, 9.32	-	d, 8.64 (J=9.04 Hz)	d, 7.61 (J=9.04 Hz)
		6c	s, 4.09	-	s, 9.14	-	d, 7.93 (J=9.42 Hz)	d, 7.70 (J=9.42 Hz)

* - spectrum in DMSO without acid

The reaction of citraconic anhydride (**7**) with 2-aminopyridine (**1a**) in ratio of 1:1 in ethyl acetate in the mild condition proceeded in a regioselective way to afford **9a** directly in a good yield (Scheme 2). The same product (**9a**) could be prepared from tautomer of **7** – itaconic anhydride (**8**). It was assumed that cycloaddition of itaconic anhydride (**8**) to 2-aminopyridine (**1a**) involved the tautomerization of **8** to **7**, catalyzed by **1a,** in the manner described for amines.[13] (3-Methyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]-

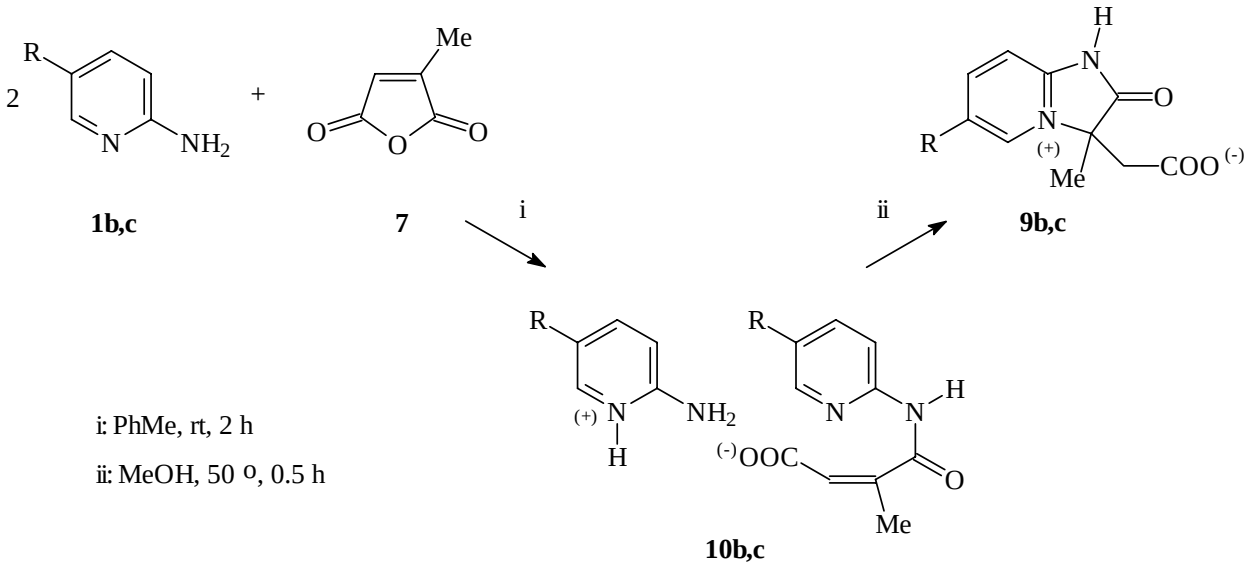
pyridin-3-yl)acetic acid (**9a**) in solution as well as in crystal form (*vide infra*) existed only in the zwitterion form.

Scheme 2



5-Halogeno-2-aminopyridines (**1b,c**), however, did not afford the corresponding (3-methyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids (**9b,c**) in the conditions that led to **9a**. Compounds (**9b,c**) were obtained instead using the methodology applied for the preparation of **4a-c** (Scheme 3).

Scheme 3



X-Ray crystallographic structural analysis unambiguously showed that (3-methyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acid (**9a)** was a zwitterion with a positive charge delocalized at fragment N1-C9-N4 [$^{(+)}$N1=C9-N4 ↔ N1-C9=N4$^{(+)}$] and a negative charge delocalized at carboxylic group O2-C11-O3 [O2=C11-O3$^{(-)}$ ↔ $^{(-)}$O2-C11=O3] (Figure 1). Compound (**9a**) could be considered as internal salt. Molecule of **9a** has a long chain of conjugated bonds and it is practically flat except for the substitutes at the asymmetric carbon atom C3. X-Ray crystallographic data showed the

torsion angle C12-C3-C10-C11 equal 173.9(1)° indicating that steric hindrance between the carboxylic group and the methyl group was minimal.

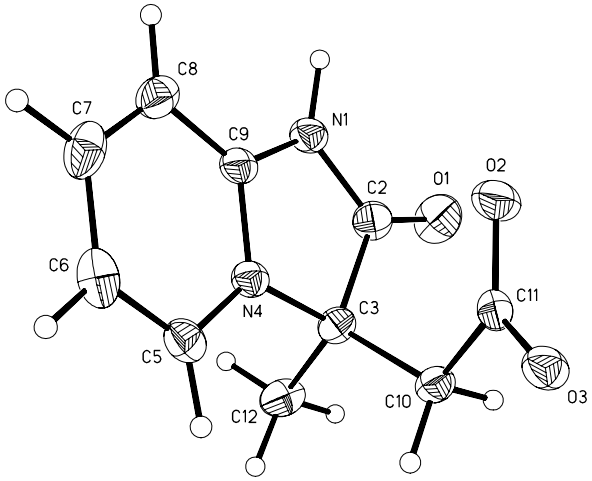


Figure 1. Molecular structure of **9a**, showing the atom labeling. Displacement ellipsoids of atoms are drawn at 50 % probability.

Crystal of **9a** was a racemate. The molecules were linked through very strong hydrogen bounds N1-H1N**...**O3 [-x+1/2, y+1/2, -z+1/2] (N-H 0.98(3), N...O 2.586(2), H...O 1.60(3) Å, angle N-H...O 176(1)°).

It was also found that solutions of the synthesized (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids (**4a-c, 9a-c**) possessed fluorescent properties in UV light. The fluorescence of the compounds with angular methyl group (**9a-c**) was stronger than the one of corresponding **4a-c** that might be due to the characteristics of zwitterion forms. These phenomena could be a subject of further investigations.

EXPERIMENTAL

General Methods. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 spectrometer using TMS or DSS as internal references. MS spectral data were obtained using a Kratos MS-30 spectrometer at 70 eV. IR spectra were performed on a Jasco FT-IR-430 spectrophotometer in KBr pellets.

Collection of X-Ray Diffraction Data and the Structure Analysis of 9a. Unit cell parameters were measured and 6595 reflections were collected with a Bruker SMART CCD 1000 diffractometer [T = 110 K, λ(Mo-K$_\alpha$), graphite monochromator, θ/10-scan, θ_{max} = 28°] operating in the ω-mode (0.3°). The structure was solved by direct method using SHELXTL PLUS programs.[14] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedure. The coordinates of the hydrogen atoms located from the difference Fourier electron density synthesis and were then refined isotropically.

Convergence was reached at $R_1 = 0.0460$ for 1826 reflections having $I > 2\sigma(I)$ and $wR_2 = 0.1293$ for 2262 independent reflections.

(2-Oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (4a)

To a solution of 2-aminopyridine (**1a**, 1.88 g, 0.02 mol) in toluene (20 mL) was slowly added at 0 °C a solution of maleic anhydride (**2**, 0.98 g, 0.01 mol) in toluene (10 mL). The mixture was stirred for 2 h at rt. The precipitated salt (**3a**) was filtered and washed with ether. Salt (**3a**) was dissolved in methanol (30 mL) and refluxed for 30 min. Resulting solid was filtered, dried and recrystallized from 70 % ethanol to give **4a**. Yield 1.11 g (58 %) (from **1a** and **2**); mp 221 °C (decomp) (lit.,[5] 220 °C); IR (KBr, ν cm^{-1}): 1765, 1709, 1644, 1493; Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.06; H, 4.23; N, 14.61.

(6-Chloro-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (4b)

A mixture of 2-amino-5-chloropyridine (**1b**, 2.57 g, 0.02 mol) and maleic anhydride (**2**, 0.98 g, 0.01 mol) in toluene (20 mL) was stirred for 4 h at rt. The precipitated salt (**3b**) was filtered and washed with ether. Salt (**3b**) was dissolved in methanol (30 mL) and refluxed for 1 h. Resulting solid was filtered, washed with water and dried to give pure **4b**. Yield 1.18 g (52 %); mp 246 °C (decomp); IR (KBr, ν cm^{-1}): 1692, 1660, 1600, 1514, 1087; Anal. Calcd for $C_9H_7N_2O_3Cl$: C, 47.70; H, 3.11; N, 12.36. Found: C, 47.56; H, 3.18; N, 12.31.

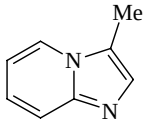
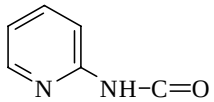
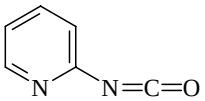
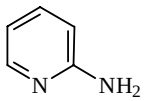
(6-Bromo-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (4c)

A mixture of 2-amino-5-bromopyridine (**1c**, 3.46 g, 0.02 mol) and maleic anhydride (**2**, 0.98 g, 0.01 mol) in toluene (20mL) was stirred for 6 h at rt. The precipitated salt (**3c**) was filtered, washed with ether and treated following the procedure and experimental conditions described above for **4b**. Yield of **4c** was 1.22 g (45 %); mp 243 °C (decomp); IR (KBr, ν cm^{-1}): 1693, 1658, 1608, 1512, 1071. Anal. Calcd for $C_9H_7N_2O_3Br$: C, 39.88; H, 2.60; N, 10.33. Found: C, 39.77; H, 2.64; N, 10.39.

(3-Methyl-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (9a)

Method A. To a solution of 2-aminopyridine (**1a**, 0.94 g, 0.01 mol) in ethyl acetate (15 mL) was slowly added a solution of citraconic anhydride (**7**, 1.12 g, 0.01 mol) in ethyl acetate (15 mL). The mixture was stirred for 2 h at rt. The precipitated solid (**9a**) was filtered and recrystallized from 70 % ethanol. Yield 1.75 g (85 %); mp 228 °C (decomp).

Method B. The methodology mentioned above in *Method A* was applied for the reaction of 2-aminopyridine (**1a**, 0.94 g, 0.01 mol) and itaconic anhydride (**8**, 1.12 g, 0.01 mol). Yield 0.93 g, 42 %;

mp 228 °C (decomp); IR (KBr, ν cm^{-1}): 1757, 1647, 1526; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 1.38 (3H, s, Me), 2.92, 3.21 (2H, dd, J_{AB} = 17.33 Hz, CH_2), 6.81 (1H, t, *J* = 6.78 Hz, C^6H), 7.06 (1H, d, *J* = 8.67 Hz, C^8H), 7.75 (1H, t, *J* = 7.92 Hz, C^7H), 8.34 (1H, d, *J* = 6.40 Hz, C^5H), 12.37 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ 24.4 (Me), 39.8 (CH_2), 65.2 (C-3), 111.7 (C-8), 114.3 (C-6), 134.7 (C-5), 142.1 (C-7), 166.3 (C-9), 169.6 (C-2), 187.6 (COO^-); MS, m/z (I (%)), for I > 5%: 206 (40) $[M]^+$, 189 (5) $[M - OH]^+$, 188 $[M - H_2O]^+$, 162 (16) $[M - CO_2]^+$, 161 (100) $[M - CO_2 - H]^+$, 160 (28) $[M - CO_2 - 2\ H]^+$, 133 (6) $[M - CO_2 - H - CO]^+$, 132 (23) $[M - CO_2 - 2\ H - CO]^+$, 131 (21) []$^+$, 121 (57) []$^+$, 120 (27) []$^+$, 94 (31) []$^+$, 92 (12), 79 (8), 78 (54), 69 (9), 68 (15), 67 (18). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.09; H, 4.96; N, 13.48.

Crystal data[15]: $C_{10}H_{10}N_2O_3$; M = 206.2; monoclinic; space group C2/c, at T = 110 K: a = 18.3912(19), b = 10.2569(11), c = 13.1911(14) Å, β = 130.923(2)°, V = 1880.2(3) Å3, Z = 8, d_{calc} = 1.457 g cm^{-3}, F(000) = 864, μ = 0.11 mm^{-1}.

(6-Chloro-3-methyl-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (9b)

This compound was prepared from **1b** (2.57 g, 0.02 mol) and **7** (1.12 g, 0.01 mol) following the procedure and experimental conditions described above for **4a**. Yield 1.61 g, 67 %; mp 231 °C (decomp); IR (KBr, ν cm^{-1}): 1716, 1629, 1549, 1055; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 1.39 (3H, s, Me), 2.93, 3.26 (2H, dd, J_{AB} = 17.33 Hz, CH_2), 7.11 (1H, d, *J* = 9.41 Hz, C^8H), 7.83 (1H, dd, *J* = 9.42 and 2.26 Hz, C^7H), 8.70 (1H, d, *J* = 2.27 Hz, C^5H), 12.46 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ 24.2 (Me), 39.7 (CH_2), 66.2 (C-3), 115.5 (C-8), 117.2 (C-6), 133.2 (C-5), 142.4 (C-7), 165.5 (C-9), 169.6 (C-2), 187.8 (COO^-); Anal. Calcd for $C_{10}H_9N_2O_3Cl$: C, 49.91; H, 3.77; N, 11.64. Found: C, 49.72; H, 3.84; N, 11.60.

(6-Bromo-3-methyl-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetic acid (9c)

This compound was prepared from **1c** (3.46 g, 0.02 mol) and **7** (1.12 g, 0.01 mol) following the procedure and experimental conditions described above for **4a**. Yield 1.54 g, 54 % mp 214 °C (decomp); IR (KBr, ν cm^{-1}): 1714, 1622, 1538, 1061; ^{1}H NMR (300 MHz, DMSO-d_6, TMS): δ 1.40 (3H, s, Me), 2.93, 3.27 (2H, dd, J_{AB} = 17.33 Hz, CH_2), 7.05 (1H, d, *J* = 9.42 Hz, C^8H), 7.89 (1H, dd, *J* = 9.42 and 1.88 Hz, C^7H), 8.74 (1H, d, *J* = 2.27 Hz, C^5H), 12.46 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6, TMS): δ 24.3 (Me), 39.7

(CH_2), 66.1 (C-3), 103.5 (C-8), 115.8 (C-6), 135.2 (C-5), 144.6 (C-7), 165.5 (C-9), 169.6 (C-2), 187.6 (COO^-); Anal. Calcd for $C_{10}H_9N_2O_3Br$: C, 42.13; H, 3.18; N, 9.83. Found: C, 41.96; H, 3.26; N, 9.76.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. N. P. Argade and R. H. Naik, *Bioorg. Med. Chem.*, 1996, **4**, 881.
2. C. Florac, M. Baudy-Floc'h, and A. Robert, *Tetrahedron*, 1990, **46**, 445.
3. M. E. Baumann, H. Bosshard, W. Breitenstein, and G. Rist, *Helv. Chim. Acta*, 1986, **69**, 396.
4. M. Baumann, H. Bosshard, W. Breitenstein, and H. Greuter, Org. Synth.: Interdiscip. Challenge, Proc. IUPAC Symp., 5th, ed. by J. Streith, H. Prinzbach, G. Schill, Blackwell, Oxford, UK, 1985, pp.157-166.
5. M. E. Baumann, H. Bosshard, W. Breitenstein, G. Ribs, and T. Winkler, *Helv. Chim. Acta*, 1984, **67**, 1897.
6. P. Wenk, W. Breitenstein, M. Baumann, *Pat. EP*, 78240, 1983 (*Chem. Abstr*., 1983, **99**, 158229).
7. W. Breitenstein, M. Baumann, and H. Bosshard, *Pat. EP*, 78239, 1983 (*Chem. Abstr*., 1983, **99**, 158221).
8. P. Wenk, W. Breitenstein, and M. Baumann, *Pat. EP*, 78241, 1983 (*Chem. Abstr*., 1983, **99**, 139751).
9. S. Kawashima, T. Matsuno, N. Fukuda, K. Saitoh, Y. Yamaguchi, and M. Higashi, *Pat. WO*, 0260907, 2002 (*Chem. Abstr*., 2002, **137**, 154933).
10. Y. Yamaguchi, T. Matsuno, and S. Kawashima, *Brain Res*., 2002, **945**, 259.
11. Y. Yamaguchi, M. Higashi, T. Matsuno, and S. Kawashima, *Jpn. J. Pharmacol.*, 2001, **87**, 240.
12. V. V. Zalesov and S. S. Kataev, *Pat. RU*, 2137772, 1999 (*Chem. Abstr*., 2000, **133**, 252432).
13. A. V. Galanti, B. T. Keen, R. H. Pater, and D. A. Scola, *J. Polymer Sci., Polymer Chem. Ed.*, 1981, **19**, 2243.
14. G. M. Sheldrick, SHELXTL, V5.10, Bruker AXS Inc., Madison, WI-53719, USA, 1997.
15. Crystallographic data for the structural analysis of **9a** have been deposited with the Cambridge Crystallographic Data Center and may be obtained free of charge (CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).