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The synthesis and reactivity of imidazo[1,2-*a*][1,8]naphthyridines are reported. Electrophilic substitution reactions were studied and the site of the reaction was established with the aid of high-field  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra. The experimental C-1 position reaction was correlated with a CNDO/2 calculations.

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### Introduction.

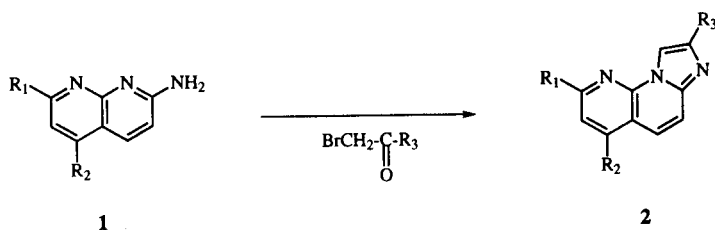
A number of tricyclic heterocycles with a bridgehead nitrogen atom have been recently described for their pharmacological properties [1a-f]. From these, antiinflammatory properties have been frequently noted. In this way, the 2-carboxylic acid ester, substituted with a 2-phenyl or a 2-benzoyl substituant appeared of great interest [2a-c]. In continuation of our studies on these ring systems [3a-b], we report now, the synthesis, structure and reactivity of imidazo[1,2-*a*][1,8]naphthyridines which have not been extensively studied [4a-b]. Thus, the reported compounds have been designed for use against inflammatory disease.

The synthesis of [1,8]naphthyridines was reported by Skraup reaction in good yield [5a] and nucleophilic amination was described to give the 2-amino[1,8]naphthyridine in poor yield [5b], whereas 2,4-dimethyl-7-amino[1,8]naphthyridine was obtained by the Combes Beyer

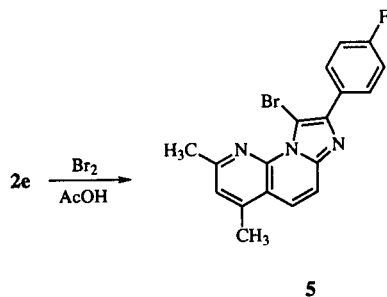
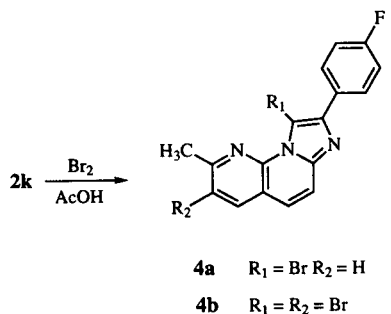
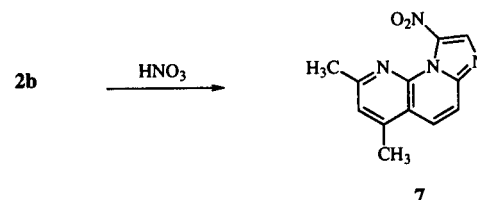
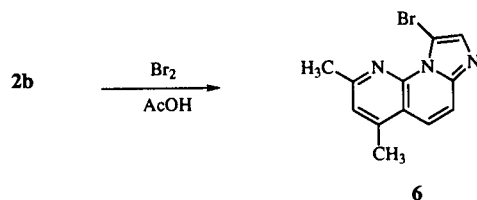
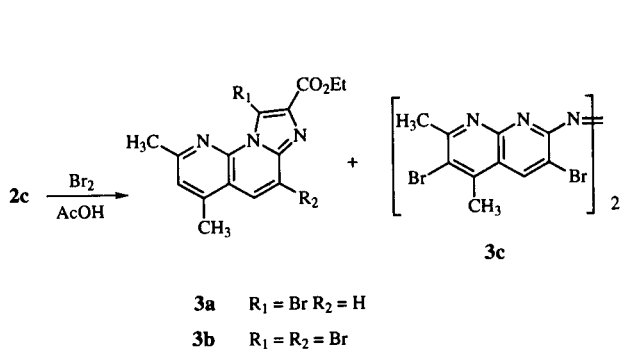
cyclodehydration from 2,6-diaminopyridine [5c]. This second method was used for the synthesis of 2-amino[1,8]naphthyridine (**1a**). In this way, 2,6-diaminopyridine was condensed with 1,1,3,3-tetramethoxypropane in concentrated phosphoric acid to give **1a** in 11% yield (not optimized).

A series of imidazo[1,2-*a*][1,8]naphthyridines **2a-o** were synthesized in 21% to 74% yield by condensation of aminonaphthyridines **1a-e** with different  $\alpha$ -halogenocarbonyl compounds. Structural determinations were based on  $^1\text{H}$  and  $^{13}\text{C}$  nmr from COSY, HETCOR ( $^{13}\text{C}$ - $^1\text{H}$ ) and LR-HETCOR spectra on 6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**2b**).

The COSY spectrum of **2b** showed a singlet at  $\delta$  6.75 attributed to H-7, two doublets at  $\delta$  7.47 and 8.20 with a J value of 1.5 Hz corresponding respectively to H-2 and H-1. The discrimination between the two doublets at  $\delta$  7.19 and 7.26 with a coupling constant of 9 Hz for H-4 and



a	R <sub>1</sub> = R <sub>2</sub> = H	a	R <sub>1</sub> = R <sub>2</sub> = R <sub>3</sub> = H	38%
b	R <sub>1</sub> = R <sub>2</sub> = CH <sub>3</sub>	b	R <sub>1</sub> = R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = H	35%
c	R <sub>1</sub> = Cl R <sub>2</sub> = CH <sub>3</sub>	c	R <sub>1</sub> = R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	26%
d	R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> R <sub>2</sub> = CH <sub>3</sub>	d	R <sub>1</sub> = R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = C <sub>6</sub> H <sub>5</sub>	34%
e	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H	e	R <sub>1</sub> = R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = 4-FC <sub>6</sub> H <sub>4</sub>	43%
		f	R <sub>1</sub> = Cl R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	35%
		g	R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	45%
		h	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H R <sub>3</sub> = C <sub>6</sub> H <sub>5</sub>	65%
		i	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H R <sub>3</sub> = 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	72%
		j	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H R <sub>3</sub> = 2,4-(OCH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	74%
		k	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H R <sub>3</sub> = 4-F-C <sub>6</sub> H <sub>4</sub>	56%
		l	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H R <sub>3</sub> = 4-Cl-C <sub>6</sub> H <sub>4</sub>	67%
		m	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = H R <sub>3</sub> = 4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	59%
		n	R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = CO-C <sub>6</sub> H <sub>5</sub>	21%
		o	R <sub>1</sub> = R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = CO-C <sub>6</sub> H <sub>5</sub>	43%



experiment and a LR-HETCOR [6a-b]. The <sup>13</sup>C spectrum showed resonances of two methyl groups, five methines and five quaternary carbons. The signal which resonates at the high field (δ 111.5) could be easily assigned to C-1 by comparison with the chemical shift of the imidazo[1,2-*a*]pyridine [7a-c] and the imidazo[1,2-*c*]quinazoline series [2a]. The most deshielded signal (δ 131.9) was assigned to C-2 in accordance with the previously cited references. The C-5a resonance at δ 114.1 was in good agreement with the β-effect of N-9 and N-10. From the HETCOR spectrum the signal at δ 121.7 could be assigned to C-7 and in addition the following connectivities were obtained: 7.19-120.0 and 7.26-116.0. The discrimination between the two signals was made by performing the LR-HETCOR experiment; H-5 was assigned at δ 7.19 because it showed a <sup>3</sup>J<sub>CH</sub> with the carbon at δ

Table I

$\pi_z$  Electron Density of Neutral and Protonated Species of 6,8-Dimethylimidazo[1,2-*a*][1,8]naphthyridines **2b,c** Obtained from CNDO/2 Calculations

	<b>2b</b>		<b>2c</b>	
	Neutral	Protonated	Neutral	Protonated
C(1)	1.1784	1.1910	1.1047	1.1336
C(2)	1.0091	0.9669	1.0570	0.9978
N(3)	1.1780	1.1430	1.1904	1.1490
C(3a)	1.0220	1.0211	1.0108	1.0135
C(4)	1.0297	0.9899	1.0360	0.9932
C(5)	0.9898	1.0075	0.9810	1.0047
C(5a)	1.0884	1.0910	1.0870	1.0900
C(6)	0.9035	0.7516	0.9060	0.7630
C(7)	1.0835	1.1094	1.0860	1.1065
C(8)	0.8992	0.8062	0.9010	0.8120
N(9)	1.1604	1.5780	1.1599	1.5595
C(9a)	0.9633	0.9107	0.9540	0.9059
N(10)	1.5330	1.5240	1.4988	1.1400

Table II

Bond Order of Neutral and Protonated Species of **2b,c** Obtained from CNDO/2 Calculations

	<b>2b</b>		<b>2c</b>	
	Neutral species	Protonated species	Neutral species	Protonated species
C(1)-C(2)	0.8004	0.8078	0.7474	0.7489
C(2)-N(3)	0.5306	0.5157	0.4726	0.4525
N(3)-C(3a)	0.7197	0.7374	0.7055	0.6966
C(3a)-C(4)	0.4007	0.4025	0.3755	0.3597
C(4)-C(5)	0.8548	0.8541	0.8431	0.8191
C(5)-C(5a)	0.3916	0.3852	0.3789	0.3726
C(5a)-C(6)	0.5703	0.5482	0.5665	0.5291
C(6)-C(7)	0.6870	0.6245	0.6808	0.6071
C(7)-C(8)	0.6136	0.6880	0.6041	0.6483
C(8)-N(9)	0.6672	0.5299	0.6647	0.5048
N(9)-C(9a)	0.6033	0.4732	0.5963	0.4631
C(9a)-N(10)	0.3623	0.4425	0.3562	0.4163
N(10)-C(1)	0.4276	0.4034	0.4438	0.3846
C(3a)-N(10)	0.4575	0.4152	0.4492	0.4021
C(5a)-C(9a)	0.6067	0.6362	0.5960	0.5936
C(8)-C(11)	0.2272	0.2568	0.2231	0.2506
C(6)-C(12)	0.2259	0.2533	0.2220	0.2267
C(2)-C(13)			0.2639	0.2285
C(13)-O(14)			0.7501	0.6419
C(13)-O(15)			0.3148	0.2974

142.3 (C-9a), while the signal at  $\delta$  7.26 was coupled with C-5a at  $\delta$  114.1. The complete proton and carbon chemical shifts of **2b** are reported in the Experimental.

Condensation of 7-amino-2,4-dimethyl[1,8]naphthyridine (**1b**) with ethyl bromopyruvate gave ethyl 6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**2c**). This structure was confirmed by nmr spectroscopy. The  $^1\text{H}$  nmr spectrum showed a singlet at  $\delta$  8.91 for H-1. This result was confirmed by  $^{13}\text{C}$  nmr with a C-2 resonance at  $\delta$  135.7 whereas C-1 was shifted upfield by

nearly 5 ppm. These values are in good agreement with the data of the imidazo[1,2-*a*]pyridine ring system [7c].

Different electrophilic substitutions have been accomplished. The bromination of **2c** in acetic acid media by the procedure of Matveev [8] gave a mixture of three compounds. Their structural determinations were made by mass spectrometry and nmr. The first compound was shown to be ethyl 1,4-dibromo-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**3b**). In the  $^1\text{H}$  nmr spectrum there are two aromatic singlets at  $\delta$  7.23 and  $\delta$  8.03 assigned to H-7 and H-5, respectively. The second compound **3a** was established as a monobromo derivative by mass spectroscopy. The  $^1\text{H}$  nmr spectrum showed the disappearance of the most deshielded signal (H-1) while in the  $^{13}\text{C}$  nmr spectrum, the C-1 resonates at 102.6 ppm was in good agreement with the 1-bromo derivative. The last compound **3c** was assigned as a dibromo dimer with an azo linkage on the basis of mass spectroscopy with  $m/z/2$ : 331-329-327. The bromination of phenyl derivatives **2e,k** was then studied. The 8-methyl compound **2k** gave a mixture of 1-bromo and 1,7-dibromo derivatives **4a,b** while the dimethyl compound **2e** led to the 1-bromo derivative **5**. The 2-unsubstituted derivative **2b** gave only the 1-bromo derivative **6** on the basis of  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectroscopy.

The nitrosation reaction was also studied. In the imidazo[1,2-*a*]pyridine series, only the 2-phenyl derivatives could be nitrosated by sodium nitrite in acidic media [8], whereas the ethyl 2-carboxylate derivatives reacted only with nitrosyl chloride [9]. We previously reported that the reaction of nitrosyl chloride with **2d** gave 1-halogenation and an addition reaction to C-4/C-5 [10]. The application of the sodium nitrite procedure on some of the compounds was not applicable.

The nitration reaction was studied and gave variable results. Compound **2c** treated with nitric acid (d, 1.38) in concentrated sulfuric acid at 0-20° does not lead to the proposed product. The material was recovered unchanged. Under the same conditions **2b** gave the 1-nitro derivative **7** in 24% yield. The structure proof was accomplished by  $^1\text{H}$  nmr with the disappearance of the H-1 resonance. With the *para*-fluorophenyl derivative **2e**, the reaction was very exothermic and gave a mixture of two dinitro derivatives based on the  $^1\text{H}$  nmr spectra. The products could not be separated.

These experimental results were tentatively correlated using the CNDO/2 method based on a Moldesign calculations [11]. This study showed that the heterocycle was protonated at N-10 and the  $p_z$  electron densities predicted the electrophilic substitutions at C-1. These results are in good agreement with the experimental data.

Pharmacological studies of the reported compounds is currently under investigations.

## EXPERIMENTAL

Melting points were determined on a Büchi capillary apparatus and are not corrected. Elemental analyses were performed by the Microanalytical Center, ENSCM, Montpellier. The  $^1\text{H}$  nmr spectra were recorded on a Varian EM 360 (60 MHz), Bruker MSL 300 or AM 400 WB spectrometers. The  $^{13}\text{C}$  nmr spectra were obtained at  $26^\circ$  with proton noise decoupling on a Bruker MSL 300 instrument operating at 75 MHz or at 100 MHz with a Bruker AM 400 WB spectrometer. The  $^{13}\text{C}$  chemical shifts are reported in ppm from TMS with the center resonance of deuteriochloroform as an internal reference for  $^{13}\text{C}$  (77.0 ppm) and with the small amount of residual chloroform as an internal reference from the  $^1\text{H}$  spectrum (7.24 ppm). The ir spectra were obtained on a Beckman AccuLab 2 spectrometer. Mass spectra were recorded on a LKB 2091 spectrometer at 70 eV [ $\theta_{\text{source}}$ :  $180^\circ$ ]. The compounds were purified by high performance liquid chromatography (hplc) on a preparative alumina column using a Waters M 590 chromatograph. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatography (tlc) was performed on 0.25 mm E. Merck precoated neutral alumina plates. Substituted [1,8]naphthyridines **2b-e** were prepared by described methods [12-13].

2-Amino[1,8]naphthyridine (**1a**).

Thirteen g of 2,6-diaminopyridine (0.12 mole) and 16 g of 1,1,3,3-tetramethoxypropane (0.097 mole) in phosphoric acid (50 ml) were warmed at  $50^\circ$  for 30 minutes. After cooling the solution was poured onto ice and basified with a 50% potassium hydroxide solution. The aqueous media was extracted continuously with chloroform. After drying the extracts were concentrated *in vacuo* and the residue chromatographed on neutral alumina. Elution with dichloromethane gave 2 g of starting diamine and 1.6 g of **1a** (11%) as red plates, mp  $130-132^\circ$  [lit [14]  $135-138^\circ$ ], sufficiently pure to be used without further purification.

Imidazo[1,2-*a*][1,8]naphthyridine (**2a**).

Bromoacetaldehyde diethyl acetal (5.5 g, 27.9 mmoles) was dissolved in water (20 ml) and hydrobromic acid (2 ml) was added. The mixture was refluxed for 30 minutes. After cooling the solution was extracted with ether. The organic layers were dried over sodium sulfate and the ether was removed *in vacuo*. The bromoacetaldehyde was poured into a solution of 1.3 g (9 mmoles) of **1a** in dry ethanol (100 ml). The mixture was refluxed for 3 hours and evaporated under reduced pressure. The residue was dissolved in water, made basic with sodium carbonate and extracted with dichloromethane. After drying the organic layers were concentrated *in vacuo* and chromatographed on neutral alumina. Elution with methylene chloride gave 580 mg of **2a** (38%) as white plates which became green upon exposure to light, mp  $91-93^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform, 300 MHz):  $\delta$  7.32 (d,  $J_{4,5} = 10$  Hz, H-4 or H-5), 7.33 (dd,  $J_{6,7} = 8.25$  Hz,  $J_{7,8} = 4.5$  Hz, H-7), 7.51 (d, H-5 or H-4), 7.59 (d,  $J_{1,2} = 0.75$  Hz, H-2), 8.00 (dd,  $J_{6,7} = 8.25$  Hz,  $J_{6,8} = 1.5$  Hz, H-6), 8.37 (d, H-1), 8.57 (dd,  $J_{7,8} = 4.5$  Hz, H-8);  $^{13}\text{C}$  nmr (deuteriochloroform, 75 MHz):  $\delta$  111.9 (C-1), 117.9 (C-5a), 118.3 (C-4), 120.7 (C-5), 124.0 (C-7), 132.4 (C-2), 136.7 (C-6), 143.5 (C-9a), 144.5 (C-3a), 148.2 (C-8).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_7\text{N}_3$ : C, 71.01; H, 4.14; N, 24.85. Found: C, 71.14; H, 4.16; N, 24.75.

General Procedure for Compounds **2b-o**.

The aminonaphthyridines were refluxed in dry ethanol with a small excess of the  $\alpha$ -halogenocarbonyl compounds for 4 hours. After cooling the solution was evaporated to dryness and the residue dissolved in water. The solution was made basic with sodium carbonate and extracted with methylene chloride. The organic layers were dried over calcium chloride and concentrated *in vacuo*. The residue was chromatographed on neutral alumina and eluted with dichloromethane to give the following compounds.

6,8-Dimethylimidazo[1,2-*a*][1,8]naphthyridine (**2b**).

This compound had mp  $169-171^\circ$  [lit [4b]  $178^\circ$  sublimation];  $^1\text{H}$  nmr (deuteriochloroform, 300 MHz):  $\delta$  2.29 (s,  $\text{CH}_3$ -6), 2.42 (s,  $\text{CH}_3$ -8), 6.75 (s, H-7), 7.19 (d,  $J_{4,5} = 10$  Hz, H-5), 7.26 (d, H-4), 7.47 (d,  $J_{1,2} = 1.5$  Hz, H-2), 8.20 (d, H-1);  $^{13}\text{C}$  nmr (deuteriochloroform, 75 MHz):  $\delta$  18.19 ( $\text{CH}_3$ -6), 24.3 ( $\text{CH}_3$ -8), 111.5 (C-1), 114.1 (C-5a), 116.0 (C-4), 120.0 (C-5), 121.7 (C-7), 131.9 (C-2), 142.3 (C-9a), 144.4 (C-3a), 145.6 (C-6), 157.5 (C-8).

Ethyl 6,8-Dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**2c**).

This compound had mp  $153-155^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform, 300 MHz):  $\delta$  1.41 (t,  $\text{CH}_3$ ), 2.50 (s,  $\text{CH}_3$ -6), 2.62 (s,  $\text{CH}_3$ -8), 4.43 (q,  $\text{CH}_2$ ), 7.07 (s, H-7), 7.42 (d,  $J_{4,5} = 10$  Hz, H-4), 7.52 (d, H-5), 8.91 (s, H-1);  $^{13}\text{C}$  nmr (deuteriochloroform, 75 MHz):  $\delta$  14.4 ( $\text{CH}_3$ ), 18.6 ( $\text{CH}_3$ -6), 24.5 ( $\text{CH}_3$ -8), 60.9 ( $\text{CH}_2$ ), 114.9 (C-5a), 116.8 (C-1 or C-4), 116.8 (C-4 or C-1), 122.6 (C-5), 123.1 (C-7), 135.7 (C-2), 142.8 (C-9a), 144.5 (C-3a), 146.5 (C-6), 158.5 (C-8), 163.1 (C=O).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ : C, 66.91; H, 5.58; N, 15.61. Found: C, 66.99; H, 5.53; N, 15.66.

6,8-Dimethyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridine (**2d**).

This compound had mp  $175-177^\circ$ , [lit [4a]  $174^\circ$ ];  $^1\text{H}$  nmr (deuteriochloroform, 60 MHz):  $\delta$  2.47 (s,  $\text{CH}_3$ -6), 2.60 (s,  $\text{CH}_3$ -8), 6.95 (s, H-7), 7.08 (m, 5H, 3Ph, H-4,5), 8.03 (m, 2H, 2Ph), 8.63 (s, H-1).

6,8-Dimethyl-2-(4-fluorophenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2e**).

This compound had mp  $201-203^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform, 300 MHz):  $\delta$  2.60 (s,  $\text{CH}_3$ -6), 2.68 (s,  $\text{CH}_3$ -8), 7.11 (t,  $J_{2,3} = J_{\text{HF}} = 9$  Hz, H-3',5'), 7.15 (s, H-7), 7.53 (d,  $J_{4,5} = 10$  Hz, H-4 or 5), 7.59 (d, H-5 or 4), 7.99 (dd,  $J_{\text{HF}} = 6$  Hz, H-2',6'), 8.64 (s, H-1);  $^{13}\text{C}$  nmr (deuteriochloroform, 75 MHz):  $\delta$  18.7 ( $\text{CH}_3$ -6), 24.7 ( $\text{CH}_3$ -8), 107.4 (C-1), 114.9 (C-5a), 115.7 ( $J_{\text{CF}} = 21$  Hz, C-3',5'), 116.1 (C-4), 121.9 (C-5), 122.4 (C-7), 127.6 ( $J_{\text{CF}} = 8.65$  Hz, C-2',6'), 130.0 (C-2), 142.8 (C-9a), 143.5 (C-1'), 144.5 (C-3a), 146.5 (C-6), 158.4 (C-8), 162.7 ( $J_{\text{CF}} = 245$  Hz, C-4').

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{14}\text{N}_3\text{F}$ : C, 74.23; H, 4.81; N, 14.43. Found: C, 73.94; H, 4.79; N, 14.46.

Ethyl 8-Chloro-6-methylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**2f**).

This compound had mp  $184-186^\circ$ ;  $^1\text{H}$  nmr (deuteriochloroform, 60 MHz):  $\delta$  1.47 (t,  $\text{CH}_3$ ), 2.67 (s,  $\text{CH}_3$ ), 4.50 (q,  $\text{CH}_2$ ), 7.35 (s, H-7), 7.63 (s, H-4, 5), 8.93 (s, H-1).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{12}\text{ClN}_3\text{O}_2$ : C, 58.03; H, 4.15; N, 14.51. Found: C, 58.20; H, 4.16; N, 14.56.

Ethyl 6-Methyl-8-phenylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**2g**).

This compound had mp 133-135° [lit [4b] 134-136°]; <sup>1</sup>H nmr (deuteriochloroform, 60 MHz): δ 1.47 (t, CH<sub>3</sub>), 2.52 (s, CH<sub>3</sub>), 4.47 (q, CH<sub>2</sub>), 7.43 (m, 6H, 3Ph, H-4,5,7), 8.00 (m, 2H, 2Ph), 8.83 (s, H-1).

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.51; H, 5.14; N, 12.69. Found: C, 72.58; H, 5.16; N, 12.73.

8-Methyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridine (**2h**).

This compound had mp 183-185°; <sup>1</sup>H nmr (deuteriochloroform, 400 MHz): δ 2.78 (s, CH<sub>3</sub>), 7.31 (d, J<sub>6,7</sub> = 8.0 Hz, H-7), 7.34 (m, 1Ph), 7.44 (d, J<sub>4,5</sub> = 9.3 Hz, H-5), 7.45 (m, 2Ph), 7.59 (d, H-4), 8.01 (d, H-6), 8.06 (m, 2Ph), 8.78 (s, H-1); <sup>13</sup>C nmr (deuteriochloroform, 100 MHz): δ<sub>CH</sub> 107.4 (C-1), 117.1 (C-4), 120.9 (C-7), 124.4 (C-5), 125.9 (2C-Ph), 127.7 (C-Ph), 128.7 (2C-H), 137.1 (C-6).

*Anal.* Calcd. for C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>: C, 78.76; H, 5.02; N, 16.22. Found: C, 78.72; H, 5.03; N, 16.25.

8-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2i**).

This compound had mp 219-221°; <sup>1</sup>H nmr (deuteriochloroform, 60 MHz): δ 2.40 (s, CH<sub>3</sub>), 2.73 (s, CH<sub>3</sub>), 7.23 (m, 4H), 7.86 (m, 4H), 8.60 (s, H-1).

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>: C, 79.12; H, 5.49; N, 15.39. Found: C, 79.16; H, 5.50; N, 15.34.

8-Methyl-2-(2,4-dimethoxyphenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2j**).

This compound had mp 181-183°; <sup>1</sup>H nmr (deuteriochloroform, 400 MHz): δ 2.77 (s, CH<sub>3</sub>), 3.88 (s, OCH<sub>3</sub>), 4.05 (s, OCH<sub>3</sub>), 6.61 (d, J<sub>3,5'</sub> = 2.4 Hz, H-3'), 6.66 (dd, J<sub>5,6'</sub> = 8.6 Hz, H-5'), 7.26 (d, J<sub>6,7</sub> = 8.0 Hz, H-7), 7.39 (d, J<sub>4,5</sub> = 9.3 Hz, H-5), 7.56 (d, H-4), 7.98 (d, H-6), 8.32 (d, H-6'), 8.89 (s, H-1).

*Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>: C, 71.47; H, 5.33; N, 13.17. Found: C, 71.32; H, 5.31; N, 13.21.

8-Methyl-2-(4-fluorophenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2k**).

This compound had mp 187-189°; <sup>1</sup>H nmr (deuteriochloroform, 60 MHz): δ 2.70 (s, CH<sub>3</sub>), 7.27 (m, 5H), 8.00 (m, 3H), 8.67 (s, H-1).

*Anal.* Calcd. for C<sub>17</sub>H<sub>12</sub>FN<sub>3</sub>: C, 73.65; H, 4.33; N, 15.16. Found: C, 73.67; H, 4.35; N, 15.20.

8-Methyl-2-(4-chlorophenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2l**).

This compound had mp 187-189°; <sup>1</sup>H nmr (deuteriochloroform, 400 MHz): δ 2.73 (s, CH<sub>3</sub>), 7.27 (d, J<sub>6,7</sub> = 8.0 Hz, H-7), 7.40 (d, J<sub>2,3'</sub> = 8.7 Hz, H-3',5'), 7.41 (d, J<sub>4,5</sub> = 9.3 Hz, H-5), 7.52 (d, H-4), 7.95 (d, H-2',6') 7.96 (d, H-6), 8.70 (s, H-1); ms: (EI) 295 (M<sup>+</sup> + 2, 33), 293 (M<sup>+</sup>, 100), 258 (11), 143 (18), 129 (11), 116 (9).

*Anal.* Calcd. for C<sub>17</sub>H<sub>12</sub>ClN<sub>3</sub>: C, 69.51; H, 4.09; N, 14.31. Found: C, 69.59; H, 4.08; N, 14.36.

8-Methyl-2-(4-methoxyphenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2m**).

This compound had mp 144-146°; <sup>1</sup>H nmr (deuteriochloroform, 400 MHz): δ 2.72 (s, CH<sub>3</sub>), 3.86 (s, OCH<sub>3</sub>), 6.99 (d, J<sub>2,3'</sub> =

8.9 Hz, H-3',5'), 7.23 (d, J<sub>6,7</sub> = 8.0 Hz, H-7), 7.37 (d, J<sub>4,5</sub> = 9.3 Hz, H-5), 7.53 (d, H-4), 7.93 (d, H-6), 7.96 (d, H-2',6'), 8.62 (s, H-1).

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O: C, 74.74; H, 5.19; N, 14.53. Found: C, 74.86; H, 5.17; N, 14.48.

2-Benzoyl-6-methyl-8-phenylimidazo[1,2-*a*][1,8]naphthyridine (**2n**).

This compound had mp 216-218°; <sup>1</sup>H nmr (deuteriochloroform, 400 MHz): δ 2.78 (s, CH<sub>3</sub>), 7.55 (m, 5H), 7.62 (m, 2H), 7.75 (d, J = 7 Hz, 1H), 7.80 (s, 1H), 8.20 (m, 2H), 8.35 (m, 2H), 9.23 (s, 1H).

*Anal.* Calcd. for C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>O: C, 79.34; H, 4.68; N, 11.57. Found: C, 79.20; H, 4.66; N, 11.61.

2-Benzoyl-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**2o**).

This compound had mp 190-192°; <sup>1</sup>H nmr (deuteriochloroform, 400 MHz): δ 2.67 (s, CH<sub>3</sub>), 2.69 (s, CH<sub>3</sub>), 7.20 (s, H-7), 7.55 (m, 2H), 7.60 (m, 2H), 7.71 (d, 1H), 8.29 (m, 2H), 9.07 (s, H-1).

*Anal.* Calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O: C, 75.75; H, 4.98; N, 13.95. Found: C, 75.89; H, 4.96; N, 13.99.

Ethyl 1,4-Dibromo-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**3b**), Ethyl 1-Bromo-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**3a**) and Bis-3,6-dibromo-2,4-dimethyl-7-azo[1,8]naphthyridine (**3c**).

To 269 mg (1 mmole) of **2c** dissolved in glacial acetic acid (10 ml) was added 0.1 ml (2.06 mmoles) of bromine. The mixture was stirred at room temperature for 15 minutes. The suspension was made basic with sodium carbonate and extracted with methylene chloride. The organic layers were dried over calcium chloride, concentrated *in vacuo* and chromatographed on neutral alumina. Elution with methylene chloride led to ethyl 1,4-dibromo-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**3b**) (35 mg, 8%) as yellow plates, mp 136-138°; <sup>1</sup>H nmr (deuteriochloroform, 300 MHz): δ 1.48 (t, CH<sub>3</sub>), 2.65 (s, CH<sub>3</sub>), 2.70 (s, CH<sub>3</sub>), 4.53 (q, CH<sub>2</sub>), 7.23 (s, H-7), 8.03 (s, H-5); <sup>13</sup>C nmr (deuteriochloroform, 75 MHz): δ 14.5 (CH<sub>3</sub>), 19.2 (CH<sub>3</sub>-6), 24.4 (CH<sub>3</sub>-8), 61.6 (CH<sub>2</sub>), 104.2 (C-1), 110.8 (C-4), 116.6 (C-5a), 123.7 (C-7), 125.6 (C-5), 135.2 (C-2), 143.5 (C-3a\*), 144.7 (C-9a\*), 145.4 (C-6\*), 157.5 (C-8), 162.4 (C=O).

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: C, 42.15; H, 3.04; N, 9.84. Found: C, 41.99; H, 3.06; N, 9.87.

Further elution gave ethyl 1-bromo-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxylate (**3a**) as white plates (20 mg, 6%), mp 141-143°; <sup>1</sup>H nmr (deuteriochloroform, 300 MHz): δ 1.50 (t, CH<sub>3</sub>), 2.55 (s, CH<sub>3</sub>), 2.62 (s, CH<sub>3</sub>), 4.55 (q, CH<sub>2</sub>), 7.15 (s, H-7), 7.48 (d, J<sub>4,5</sub> = 10 Hz, H-4 or 5), 7.61 (d, H-5 or 4); <sup>13</sup>C nmr (deuteriochloroform, 75 MHz): δ 14.5 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>-6), 24.3 (CH<sub>3</sub>-8), 61.3 (CH<sub>2</sub>), 102.6 (C-1), 115.9 (C-5a), 117.0 (C-4), 123.2 (C-5 or C-7), 123.3 (C-7 or C-5), 134.0 (C-2), 145.0 (C-3a or C-9a), 145.2 (C-9a or C-3a), 146.0 (C-6), 157.1 (C-8), 162.4 (C=O).

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>2</sub>: C, 51.72; H, 4.02; N, 12.07. Found: C, 51.89; H, 4.04; N, 12.11.

Further elution with a mixture dichloromethane-methanol (98-2 v/v) gave 50 mg (30% yield) of bis-3,6-dibromo-2,4-dimethyl-7-azo[1,8]naphthyridine (**3c**), mp 172-174°; <sup>1</sup>H nmr (deuteriochloroform, 60 MHz): δ 2.67 (s, CH<sub>3</sub>), 2.83 (s, CH<sub>3</sub>), 8.38 (s, H-4); ms: (EI) 331 (M<sup>+</sup> + 4/2, 52), 329 (M<sup>+</sup> + 2/2,

100), 327 ( $M^{+}/2$ , 53), 251 ( $M^{+} - Br/2$ , 32), 249 ( $M^{+} - Br/2$ , 32), 170 ( $M^{+} - 2Br/2$ , 32), 77 (12).

1-Bromo-2-(4-fluorophenyl)-8-methylimidazo[1,2-*a*][1,8]naphthyridine (**4a**) and 1,7-Dibromo-2-(4-fluorophenyl)-8-methylimidazo[1,2-*a*][1,8]naphthyridine (**4b**).

One g (3.61 mmoles) of **2k** in acetic acid (25 ml) was treated with bromine (0.3 ml, 0.94 g) with stirring. The suspension was stirred for 1 hour at 20°. The precipitate which was formed was filtered, dissolved in water, basified with sodium carbonate and extracted with methylene chloride. The organic layers were dried over calcium chloride, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel. Elution with methylene chloride gave 350 mg of **4b** (22%), mp 197-199°; <sup>1</sup>H nmr (deuteriochloroform, 60 MHz): δ 2.75 (s, CH<sub>3</sub>), 6.83 (s, 1H), 7.13 (d, 1H), 7.30 (m, 2Ph), 8.13 (m, 2Ph), 8.43 (d, 1H).

*Anal.* Calcd. for C<sub>17</sub>H<sub>10</sub>Br<sub>2</sub>FN<sub>3</sub>: C, 46.90; H, 2.30; N, 9.66. Found: C, 47.07; H, 2.31; N, 9.62.

Further elution gave **4a** (500 mg, 39%), mp 195-197°; <sup>1</sup>H nmr (deuteriochloroform, 60 MHz): δ 2.75 (s, CH<sub>3</sub>), 7.13 (d, 1H), 7.33 (m, 2H), 7.50 (s, 2H), 8.02 (d, 1H), 8.17 (m, 2H).

*Anal.* Calcd. for C<sub>17</sub>H<sub>11</sub>BrFN<sub>3</sub>: C, 57.30; H, 3.09; N, 11.80. Found: C, 57.12; H, 3.10; N, 11.83.

1-Bromo-6,8-dimethyl-2-(4-fluorophenyl)imidazo[1,2-*a*][1,8]naphthyridine (**5**).

One g of **2e** (3.43 mmoles) dissolved in acetic acid (10 ml) was treated with 0.2 ml of bromine (0.63 g, 3.94 mmoles) with stirring. The stirring was continued for 30 minutes at room temperature then the suspension was filtered. The precipitate was suspended in water, basified with sodium carbonate then extracted with methylene chloride. After drying, the organic layers were concentrated *in vacuo* and the residue chromatographed on neutral alumina. Elution with dichloromethane gave 350 mg of **5** (28%) as white plates, mp 218-220°; <sup>1</sup>H nmr (deuteriochloroform, 300 MHz): δ 2.64 (s, CH<sub>3</sub>-6), 2.69 (s, CH<sub>3</sub>-8) 7.16 (s, H-7), 7.18 (t, J<sub>2,3</sub> = 8.5 Hz, H-3',5'), 7.57 (d, J<sub>4,5</sub> = 9.5 Hz, H-4 or 5), 7.66 (d, H-5 or 4), 8.09 (d, H-2',6'); <sup>13</sup>C nmr (deuteriochloroform, 75 MHz): δ 19.2 (CH<sub>3</sub>-6), 24.5 (CH<sub>3</sub>-8), 93.7 (C-1), 115.3 (J<sub>CF</sub> = 21.6 Hz, 2C-Ph), 115.8 (C-5a), 116.3 (C-4), 122.1 (C-5), 122.7 (C-7), 129.2 (C-2), 130.6 (J<sub>CF</sub> = 7.65 Hz, 2C-Ph), 142.6 (C-9a), 144.9 (C-3a), 145.3 (C-Ph or C-6), 145.9 (C-6 or C-Ph), 156.9 (C-8), 162.8 (J<sub>CF</sub> = 248 Hz, C-Ph).

*Anal.* Calcd. for C<sub>18</sub>H<sub>13</sub>BrFN<sub>3</sub>: C, 58.38; H, 3.51; N, 11.35. Found: C, 58.26; H, 3.53; N, 11.39.

1-Bromo-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**6**).

One g of **2b** (5.07 mmoles) dissolved in acetic acid (10 ml) was treated with 0.3 ml of bromine (954 mg, 5.96 mmoles). The mixture, with workup as for **4**, gave 0.5 g of **6** (36%) as white plates, mp 197-199°; <sup>1</sup>H nmr (deuteriochloroform, 300 MHz): δ 2.52 (s, CH<sub>3</sub>-6), 2.62 (s, CH<sub>3</sub>-8), 7.02 (s, H-7), 7.38 (d, J<sub>4,5</sub> = 10 Hz, H-4 or 5), 7.45 (d, H-5 or 4), 7.51 (s, H-2); <sup>13</sup>C nmr (deuteriochloroform, 75 MHz): δ 18.8 (CH<sub>3</sub>-6), 24.3 (CH<sub>3</sub>-8), 96.6 (C-1), 115.3 (C-5a), 116.5 (C-4), 121.0 (C-5), 122.4 (C-7), 135.1 (C-2), 144.5, 145.6, 145.9 (C-3a, C-9a or C-6), 156.6 (C-8).

*Anal.* Calcd. for C<sub>12</sub>H<sub>10</sub>BrN<sub>3</sub>: C, 52.17; H, 3.62; N, 15.22. Found: C, 51.99; H, 3.63; N, 15.26.

6,8-Dimethyl-1-nitroimidazo[1,2-*a*][1,8]naphthyridine (**7**).

One g of **2b** (5.07 mmoles) was dissolved in concentrated sulfuric acid (10 ml) cooled to -10° while not allowing the tempera-

ture to rise above 0°. When the solution was again at -10°, 1.6 ml of nitric acid (d = 1.38) was added until the temperature rose to 0°. The mixture was stirred for 2 hours at 0° and then allowed to stand 2 hours at room temperature. The solution was poured onto ice, basified with sodium carbonate and extracted with methylene chloride. The organic layers were dried over calcium chloride, concentrated *in vacuo* and chromatographed on neutral alumina. Elution with methylene chloride gave 300 mg of **7** (24%), mp 247-249°, <sup>1</sup>H nmr (deuteriochloroform, 300 MHz): δ 2.65 (s, CH<sub>3</sub>), 2.70 (s, CH<sub>3</sub>), 7.25 (s, H-7), 7.61 (d, J<sub>4,5</sub> = 9 Hz, H-4), 7.94 (d, H-5), 8.23 (s, H-2); <sup>13</sup>C nmr (deuteriochloroform, 75 MHz): δ<sub>CH</sub> 18.9 (CH<sub>3</sub>-6), 24.7 (CH<sub>3</sub>-8), 116.1 (C-4), 123.9 (C-7), 126.2 (C-5), 135.0 (C-2).

*Anal.* Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>: C, 59.50; H, 4.13; N, 23.14. Found: C, 59.72; H, 4.15; N, 23.22.

Nitration of 6,8-Dimethyl-2-(4-fluorophenyl)imidazo[1,2-*a*][1,8]naphthyridine (**2e**).

One g of **2e** (3.43 mmoles) was treated as above. At 18° the temperature rose spontaneously to 60° and the mixture was poured onto ice. The formed precipitate was filtered, taken up in water and basified with sodium carbonate. The solution was extracted with dichloromethane. The organic layers were dried over calcium chloride and evaporated *in vacuo*. The residue was chromatographed on neutral alumina. Elution with dichloromethane gave 860 mg of mixture of two dinitro derivatives which could not be separated.

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