SYNTHESIS, REACTIVITY AND ^{13}C-NMR OF 1*H*-PYRAZOLO[3,4-*c*]-PYRIDINE DERIVATIVES

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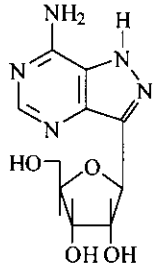
Abstract- The synthesis of various 1*H*-pyrazolo[3,4-*c*]pyridines was reported. 3-Cyano derivatives were obtained from the corresponding nitro compounds by Sandmeyer Reaction using $Na_3[Cu(CN)_4]$ at pH 1. The ^{13}C-NMR data of this serie were also described.

Formycin A (7-amino-3-β-D-ribofuranosyl-1*H*-pyrazolo[4,3-*d*]pyrimidine) **(I)** is a *C*-nucleoside that exhibited antitumor, antiviral, antibacterial and antifungal properties.[1]



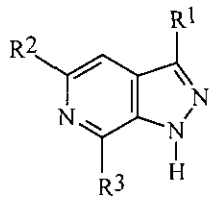
(I)

The heterocyclic base; pyrazolo[4,3-*d*]pyrimidines have been extensively studied,[2] while the 4-deaza analogs: pyrazolo[3,4-*c*]pyridines have been poorly studied. From the synthetic procedure rewieved,[3] the method by Hurst *et al.*, using thermal rearrangment of *N*-nitrosoacetamide, appeared as one of the most convenient.[4,5]

As a part of our program on nitrogen heterocycles,[6] we were interested in synthesis, reactivity and ^{13}C-NMR spectroscopy of 1*H*-pyrazolo[3,4-*c*]pyridine derivatives.

Thus, parent compound **(1a)** and 5- and 7-chloro derivatives **(1b,c)** were synthesized according to the described procedure by Hurst.[4,5] It has been demonstrated experimentally[5] and theoretically[7] that electrophilic substitution (*e.g.* chlorination, bromination and nitration) on **1a,c** occured at the 3-position. When these reactions were carried out on **1b**, the same results were obtained to give **2b**, **3b** and **4b** respectivelly (Table 1).

Table 1



Cpd	(1a)	(1b)	(1c)	(2a)	(2b)	(3a)	(3b)	(4a)	(4b)
R^1	H	H	H	Cl	Cl	Br	Br	NO_2	NO_2
R^2	H	Cl	H	H	Cl	H	Cl	H	Cl
R^3	H	H	Cl	H	H	H	H	H	H

No ^{13}C-NMR study of this series of compounds has been reported so far. While the different attributions were made by incremental calculation from indazole.[8] Further confirmation was made using XHCOR on **1c**. The chemical shift values in ppm obtained in DMSO-d_6 are reported in Table 2.

Table 2

	C-3	C-3a	C-4	C-5	C-7	C-7a
(1a)	133.1	[126.3]	114.6	138.3	135.2	[137.1]
(2a)	[137.9]	[123.2]	112.4	139.2	135.9	[132.2]
(4a)	[148.9]	[120.3]	113.7	140.9	138.0	[141.7]
(1b)	[132.8]	[129.5]	114.2	[139.3]	134.7	[136.5]
(2b)	[137.4]	[126.1]	112.2	[140.2]	135.0	[131.7]
(4b)	[144.0]	[122.1]	113.3	[ND]	137.1	[137.8]
(1c)	133.4	[128.3]	114.9	137.6	[134.7*]	[135.3*]

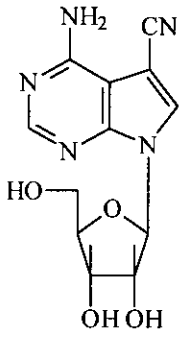
[ ] quaternary carbons

Table 2

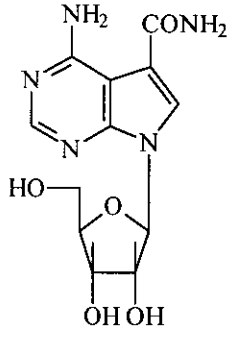
	J_{C3H3}	J_{C4H4}	J_{C4H5}	J_{C4H7}	J_{C5H5}	J_{C5H7}	J_{C5H4}	J_{C7H7}	J_{C7H5}	J_{C7H4}
(1a)	190	166	8	-	179	11	3	184	11	-
(2a)	-	160	8	2	182	12	2	187	11	2
(4a)	-	171	8	-	181	10	3	185	11	-
(1b)	195	174	-	2	-	-	-	185	-	-
(2b)	-	174	-	2	-	13	2	190	-	-
(4b)	-	179	-	2	-	-	-	193	-	-
(1c)	187	168	8	-	185	-	3	-	-	-

ND: not detected ; * may be inverted

In order to prepare toyocamycin **(II)** and sangivamycin **(III)** analogs, we were then interested in the preparation of 3-cyano derivatives.



Toyocamycin **(II)**

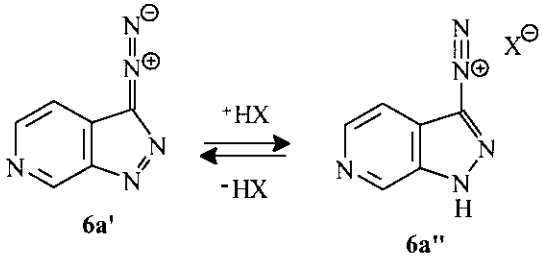


Sangivamycin **(III)**

In this way, substitution of the halogen in compounds **(2a,b and 3b)** with sodium or potassium cyanide failed under different conditions. These results are in good agreement with the works of Hurst who showed that nucleophilic displacement of halogen occured only with the 7-chloro derivative **(2c)** using aniline or piperidine.[5] Next we turned our attention to the Sandmeyer reaction. Thus, amines (**5a,b**) (obtained by reduction of **4a,b** using stannous chloride in hydrochloric acid), were treated with sodium nitrite in sulfuric acid, then action of ammonia gave the diazo compounds **(6a,b).** The reaction with CuCN in alkaline media led to no desired derivatives, but **2a,b** were obtained. Explanation of this result was found in UV spectroscopy by studying influence of pH on the structure of the diazo compounds.

The UV spectra (2.10^{-5} M) of **6a** at pH 7 showed four maxima at 199, 238, 260 and 336 nm. When the pH was varied from pH 1 to pH 11, hypsochrom and bathochrom effects were observed for the

maximum at 260 and 336 nm respectively (Table 3). The same effect could be found in azomethine maximum variation from the pH.[9] This study showed that the suitable form (**6a"**) for nucleophilic substitution exists only in acidic media.

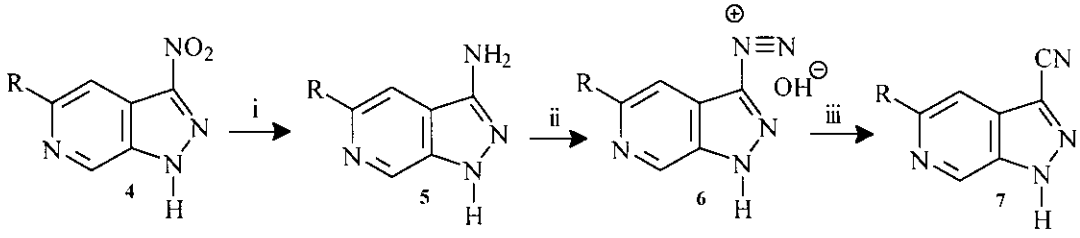


6a' **6a"**

Table 3

pH	λ_{max1} (ε)	λ_{max2} (ε)	λ_{max3} (ε)	λ_{max4} (ε)
1	205 (14500)	241 (31500)	300 (10000)	317 (10250)
2	200 (15000)	241 (31500)	300 (10000)	320 (10250)
5	199 (23000)	239 (24000)	260 (9600)	338 (10500)
7	199 (21500)	238 (22600)	260 (9600)	336 (10000)
8	201 (19250)	238 (23250)	250 (10000)	336 (10250)
11	ND (-)	238 (22250)	263 (7800)	335 (9600)

This hypothesis was confirmed by reaction of **6a,b** with $Na_3[Cu(CN)_4]$ at pH 1 to give the cyano derivatives (**7a,b**) in 35 and 30% yield respectively.



a: R=H; b: R=Cl

Reagents and conditions : i: $SnCl_2$, HBr ; ii : $NaNO_2$, H_2SO_4, H_2O; iii : $Na_3[Cu(CN)_4]$, pH = 1

EXPERIMENTAL

General

Mp were determined on a Kofler hot stage and are uncorrected. All reagents were purified by repeated crystallisations, distillations, or chromatography. UV spectra were obtained on a Varian Superscan

spectrophotometer. IR spectra were recorded on a Beckman AcuLab II spectrophotometer. MS spectra were recorded with a LKB 2091 spectrometer at 70 eV (θ_{source}: 180°C). ^{1}H-NMR spectra were obtained on a Varian EM 360 instrument. The ^{13}C-NMR were recorded on a Brüker WP 80 spectrometer operating at 20.115 MHz. Saturated solutions of samples in DMSO-d_6, with TMS as internal standard, were used for these experiments at room temperature. XHCOR was made in $CDCl_3$ on the Brüker WM 360 spectrometer. Compounds **(1a-c, 2-6a)** were obtained according to the known procedures.[3-5]

3,5-Dichloro-1H-pyrazolo[3,4-c]pyridine **(2b)** : A solution of **1b** (1.5 g, 9.8 mmol) in 32% aqueous sodium hypochloride (50 mL, 214 mmol) was stirred for 1 h at rt. The media was made neutral with glacial acetic acid and extracted with ether. After drying over magnesium sulfate and evaporation *in vacuo*, the residue was purified on silica gel eluted with ether-methanol (100/0 to 90/10 v/v) to give **2b** (0.55 g, 30%) as pale yellow plates; mp: 203-205°C (CH_2Cl_2:MeOH); IR (KBr) cm^{-1} : 3150 (NH) ; MS, *m/z* (%) : 191 (M+4, 8), 189 (M+2, 71), 187 (M,100), 154 (12), 152 (43), 127 (17), 125 (40), 117 (20), 64 (33) ; ^{1}H-NMR 7.90 (d, 1H, $J_{4,7}$= 1 Hz, H-4), 9.10 (d, 1H, $J_{4,7}$= 1 Hz, H-7); Anal. Calcd for $C_6H_3N_3Cl$: C, 38.30; H, 1.59 ; N, 22.34. Found: C, 38.51 ; H, 1.44 ; N, 22.17.

3-Bromo-5-chloro-1H-pyrazolo[3,4-c]pyridine **(3b)** : A mixture of **1b** (1.53 g, 10 mmol), bromine (3.2 g, 20 mmol) in water (50 mL) was stirred at rt for 1 h and made basic with 30% ammonia. The formed precipitate was collected and purified by chromatography on silica gel eluted with dichloromethane to give **3b** (2.0 g, 88%) as pale yellow plates; mp : 221-223°C (CH_2Cl_2:MeOH); IR (KBr) cm^{-1} : 3100 (NH) ; MS, *m/z* (%): 235 (M+4,26), 233 (M+2,100), 231 (M,81), 154 (22), 152 (63), 127 (15.5), 125 (42), 117 (14) ; ^{1}H-NMR 7.56 (s, 1H, H-4), 8.87 (s, 1H, H-7) ; Anal. Calcd for $C_6H_3N_3BrCl$: C, 30.97 ; H, 1.29 ; N, 18.06. Found : C, 31.12 ; H, 1.22 ; N, 17.89.

5-Chloro-3-nitro-1H-pyrazolo[3,4-c]pyridine **(4b)** : To a cooled solution (5°C) of **1b** (3.9 g, 12 mmol) in concentrated sulfuric acid (d=1.84, 30 mL) was slowly added a mixture of nitric acid (d=1.38, 8 mL) and sulfuric acid (d=1.84, 8 mL). The solution was heated to 95°C for 1 h then poured onto ice. The media was made basic with concentrated ammonia (d=0.88), the precipitate was collected, washed with water and dried in an oven. Chromatography on silica gel eluted with dichloromethane-methanol (100/0 to 93/7 v/v) gave pure **4b** (4.4 g, 87%) as yellow plates; mp : 195-197°C (CH_2Cl_2:MeOH); IR (KBr) cm^{-1}: 3250 (NH), 1550, 1370 (NO_2); MS, *m/z* (%) : 200 (M+2, 36), 198 (M,100), 170 (9), 168 (25), 127 (12), 125 (33), ^{1}H-NMR 8.10 (d, 1H, $J_{4,7}$= 1 Hz, H-4), 9.16 (d, 1H, $J_{4,7}$= 1 Hz, H-7) ; Anal. Calcd for $C_6H_3N_3O_2Cl$: C, 36.27 ; H, 1.51; N, 28.21. Found : C, 36.39 ; H, 1.35 ; N, 28.07.

3-Amino-5-chloro-1H-pyrazolo[3,4-c]pyridine **(5b) :** A solution of **4b** (1.99 g, 10 mmol) in 37% hydrochloric acid (10 mL) was poured into a solution of stannous chloride (6.46 g, 34 mmol) in hydrochloric acid (10 mL). The reaction mixture was refluxed for 3 h. After cooling, the pH was adjusted to 12 with sodium hydroxide (20%) and the resulting solution was extracted continuously with dichloromethane for 2 days. The organic layers were collected, dried over calcium chloride and evaporated to dryness. The residue was chromatographed on silica gel eluted with dichloromethane-methanol (100/0 to 90/10 v/v) to give **5b** (1.2 g, 70%) as pale brown plates; mp: 223-225°C (CH_2Cl_2:MeOH); IR (KBr) cm^{-1}: 3400, 3150 (NH_2, NH) ; MS, *m/z* (%) : 170 (M+2, 38), 168 (M,100), 155 (6), 153 (14), 76 (36) ; ^{1}H-NMR 7.75 (d, 1H, $J_{4,7}$ = 1 Hz, H-4), 8.60 (d, 1H, $J_{4,7}$= 1 Hz, H-7) ; Anal. Calcd for $C_6H_5N_4Cl$: C, 42.73 ; H, 2.97 ; N, 33.23. Found : C, 42.89 ; H, 2.82 ; N, 33.12.

5-Chloro-3-diazo-3H-pyrazolo[3,4-c]pyridine **(6b) :** A solution of sodium nitrite (0.625 g, 9 mmol) in cold water (10 mL) was slowly added to **5b** (0.84 g, 5 mmol) in 20% sulfuric acid (25 mL) cooled to 0°C. The resulting mixture was stirred at 0°C for 30 min, then made neutral with ammonia (d=0.88). The precipitated diazo derivative (0.99 g, 68%) was collected by filtration and used without purification due to its unstability; IR (KBr) cm^{-1}: 2200 (diazo)

3-Cyano-1H-pyrazolo[3,4-c]pyridine **(7a)** and *5-chloro 3-cyano-1H-pyrazolo[3,4-c]pyridine* **(7b) :**
Cuprous cyanide (450 mg, 5 mmol) and sodium cyanide (750 mg, 15.3 mmol) were dissolved in water (10 mL) and buffer pH 1 (KCl 1M, HCl 1N, water : 25/67/8/ v/v : 10 mL) was added. To the resulting mixture was slowly added **6a** (580 mg, 4 mmol) in buffer pH 1 (20 mL). The solution was stirred overnight, the precipitate which was formed was filtered off. The filtrate was made basic with sodium carbonate, and extracted with dichloromethane. After drying over calcium chloride, the extracts were evaporated. The residue was subjected to chromatography on neutral alumina (CH_2Cl_2/MeOH 95/5 v/v).

3-Cyano-1H-pyrazolo[3,4-c]pyridine **(7a)** was obtained as white plates (400 mg, 70%) ; mp 170-172°C (CH_2Cl_2, MeOH); IR (KBr) cm^{-1}: 2200 (CN) ; MS, *m/z* (%): 144 (100), 117 (40), 64 (11) ; ^{1}H-NMR 8.10 (d, 1H, $J_{4,5}$= 6 Hz, H-4), 8.60 (d, 1H, $J_{4,5}$= 6 Hz, H-5), 9.43 (s, 1H, H-7); Anal. Calcd for $C_7H_4N_4$: C, 58.33 ; H, 2.78; N, 38.89. Found : C, 58.42; H, 2.87; N, 38.71.

5-Chloro-3-cyano-1H-pyrazolo[3,4-c]pyridine **(7b)** was obtained as above from **6b** (730 mg, 4 mmol) as white plates (470 mg, 65%) ; mp 224-226°C (CH_2Cl_2:MeOH); IR (KBr) cm^{-1}: 2240 (CN) ; MS, *m/z* (%) : 180 (M+2, 31), 178 (M,100), 143 (29), 64 (21) ; ^{1}H-NMR 8.20 (d, 1H, $J_{4,7}$= 1 Hz, H-4), 9.28

(d, 1H, $J_{4,7}$= 1 Hz, H-7); Anal. Calcd for $C_7H_3N_4Cl$: C, 47.06; H, 1.68 ; N, 31.37. Found : C, 46.89; H, 1.65 ; N, 31.54.

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