X-Ray Crystal Structure and Moldesign Calculation of 1*H*-Pyrazolo [3,4-c]pyridine

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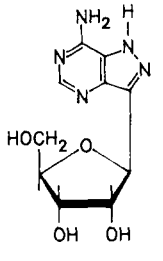
INDO calculations based on X-ray structure determination of 1*H*-pyrazolo[3,4-c]pyridine (**3**) are compared with experimental results of electrophilic substitutions and found compatible with the reactivities.

Kristallstruktur und Moldesign-Rechnungen von 1H-Pyrazolo[3,4-c] pyridin

INDO-Rechnungen basierend aud der Röntgenstrukturanalyse von 1*H*-Pyrazolo[3,4-c]pyridin (**3**) werden verglichen mit experimentellen Ergebnissen von elektrophilen Substitutionsreaktionen. In beiden Fällen wird vergleichbare Reaktivität gefunden.



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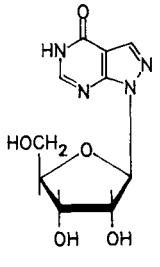

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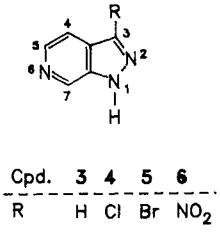

Formycin A (7-amino-3-β-D-ribofuranosyl-1*H*-pyrazolo[4,3-d]pyrimidine) (**1**)[1] and allopurinolribonucleoside (1-β-D- ribofuranosylpyrazolo[3,4-d]pyrimidin-4(5*H*)-one) (**2**)[2] are two pyrazolopyrimidine structures that have exhibited antitumor, antiviral, antibacterial, antifungal and antiparasitic properties.

In view of these observations, synthesis and evaluation of biological properties of 1*H*-pyrazolo[3,4-c]pyridine (**3**) and its derivatives is worth comtemplating since this heterocyclic structure is a deazaanalogue of formycin aglycone.

Here we report the X-ray structure determination of 1*H*-pyrazolo[3,4-c]pyridine (**3**), and the results of Moldesign calculations on this heterocycle are compared with experimental data of electrophilic substitutions.

Table 1: Heterocyclic geometry of **3** hydrochloride monohydrate
Plane equation: -0.3625x - 0.0078y + 0.9320z = 0.0178

Atoms	Distances (Å)	Atoms	Angles (degrees)	Atom	Distance to plane(Å)
N(1)-N(2)	1.354 (4)	N(1)-N(2)-C(3)	107.2 (2)	N(1)	0.002 (3)
N(1)-C(7a)	1.354 (4)	N(2)-C(3)-C(3a)	110.6 (3)	N(2)	0.001 (3)
N(2)-C(3)	1.322 (4)	C(3)-C(3a)-C(7a)	104.3 (2)	C(3)	-0.008 (3)
C(3)-C(3a)	1.412 (4)	C(3)-C(3a)-C(4)	136.2 (3)	C(3a)	0.001 (2)
C(3a)-C(4)	1.398 (4)	C(4)-C(3a)-C(7a)	119.6 (2)	C(4)	0.003 (3)
C(3a)-C(7a)	1.404 (4)	C(3a)-C(4)-C(5)	117.5 (3)	C(5)	0.003 (3)
C(4)-C(5)	1.359 (4)	C(4)-C(5)-N(6)	121.0 (3)	N(6)	-0.005 (3)
C(5)-N(6)	1.353 (4)	C(5)-N(6)-C(7)	124.5 (3)	C(7)	-0.003 (3)
N(6)-C(7)	1.334 (4)	N(6)-C(7)-C(7a)	116.3 (3)	C(7a)	0.005 (2)
C(7)-C(7a)	1.385 (4)	C(7)-C(7a)-C(3a)	121.1 (2)		
		C(7)-C(7a)-N(1)	131.7 (3)		
		N(2)-N(1)-C(7a)	110.7 (2)		
		N(1)-C(7a)-C(3a)	107.2 (2)		

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Table 2: Final atomic coordinates for **3** hydrochloride monohydrate

Atom	10^4x	10^4y	10^4z	Atom	10^3x	10^3y	10^3z
N(1)	14055 (3)	-1795 (2)	5605 (4)	H(1)	1450 (5)	-122 (2)	576 (5)
N(2)	14875 (3)	-2569 (2)	5921 (4)	H(3)	1392 (5)	-380 (2)	549 (5)
C(3)	13642 (4)	-3165 (2)	5412 (4)	H(4)	1000 (5)	-371 (3)	392 (5)
C(3a)	11955 (3)	-2784 (2)	4759 (3)	H(5)	759 (6)	-265 (2)	299 (6)
C(4)	10220 (4)	-3077 (2)	4070 (4)	H(6)	834 (5)	-119 (3)	332 (6)
C(5)	8924 (4)	-2475 (2)	3560 (4)	H(7)	1120 (5)	- 68 (3)	448 (5)
N(6)	9310 (4)	-1625 (2)	3710 (4)	H_a (11)	1248 (5)	530 (2)	282 (5)
C(7)	10932 (4)	-1303 (2)	4361 (4)	H_b (11)	1294 (6)	466 (3)	450 (7)
C(7a)	12289 (4)	-1896 (2)	4906 (4)				
Cl(10)	3277 (1)	378 (0)	2601 (1)				
O(11)	12738 (4)	4673 (2)	2953 (4)				

Table 3: Bond orders of neutral and protonated species of **3** obtained from the INDO calculation.

Bond	N(1)-N(2)	N(2)-C(3)	C(3)-C(3a)	C(3a)-C(4)	C(4)-C(5)	C(5)-N(6)	N(6)-C(7)	C(7)-C(7a)	C(7a)-N(1)	C(3a)-C(7a)
Bond order	0.419[a]	0.819	0.475	0.553	0.746	0.581	0.725	0.581	0.4535	0.572
	0.463[b]	0.802	0.507	0.539	0.765	0.530	0.646	0.631	0.4595	0.5225

[a] neutral species
[b] protonated species

Table 4: π_z-Electron densities and straight charges of neutral and protonated species of **3** obtained from the INDO calculation.

Species	N(1)	N(2)	C(3)	C(3a)	C(4)	C(5)	N(6)	C(7)	C(7a)
Neutral	1.6672[a]	1.139	1.048	1.031	1.0082	1.0128	1.065	1.014	1.012
	-0.0358[b]	-0.1257	0.0740	-0.0062	-0.0079	0.1187	-0.1889	0.0989	0.0658
Protonated	1.628[a]	1.042	1.057	0.948	0.980	0.977	1.392	0.934	1.022
	-0.0026[b]	-0.0250	0.0713	0.0461	0.0204	0.1258	0.0804	0.1461	0.0787

[a] π_z-Electron densities
[b] Straight charges

No theoretical studies have been done to explain electrophilic substitutions of 1*H*-pyrazolo[3,4-c]pyridine. In order to correlate electron densities and bond orders with the reactivity, X-ray analysis of **3** hydrochloride monohydrate was undertaken and mathematical calculations were done by Moldesign program[3] on an INDO calculation for neutral and protonated species of **3**.

The crystallographic data are presented in Tables 1-2. Bond orders, π_z-electron densities and straight charges obtained from Moldesign program are presented in Tables 3-4.

This study reveals the greatest basicity of N(6) nitrogen atom of the pyridine ring (Table 2) (as shown by the protonation on this position) and that this heterocycle is quite planar (Table 1 and Fig. 1). Inspection of bond lengths and bond orders (Tables 1 and 3) reveals the pronounced double-bond character of C(4)-C(5) and N(2)-C(3) linkages and also, for the neutral species only, of N(6)-C(7) linkage.

Comparison of π_z-electron densities clearly indicates (Table 4) that the 3-position is an electrophilic substitution target. Experimental observations (experimental section and ref.[4]) are in good agreement with these results.

Experimental Part

MPs: Kofler hot stage, uncorrected. - All reagents were purified by repeated crystallisations, distillations, or chromatography. - ^{1}H-NMR-spectra: Varian EM 360, 60 MHz spectrometer, $(CD_3)_2SO$, TMS int. stand. - MS: LKB 2091 (70 eV; source: 180°). - All compounds show parent peaks corresponding to theoretical values. - Purity was checked by TLC. - Microanalyses: Centre de Microanalyse, CNRS, Vernaison (France). Satisfactory data were obtained (C, H, N ± 0.3%)

1H-Pyrazolo[3,4-c]pyridine (**3**)

3 was prepared according to Foster[5] from 10 g ($66\cdot10^{-3}$ mole) of 3-acetamido-4- methylpyridine; m.p. 116°C (102°C[5]); yield 90%. - ^{1}H-NMR ($(CD_3)_2SO$): δ (ppm) = 7.9 (d; 1H, $J_{4,5}$ = 6 Hz, H-4), 8.38 (s; 1H, H-3), 8.4 (d; 1H: $J_{4,5}$ = 6 Hz, H-5), 9.3 (s; 1H: H-7).

3-Chloro-1H-pyrazolo[3,4-c]pyridine (**4**)

Chlorine was bubbled in a water suspension (40 ml) of lg ($8.4\cdot10^{-3}$ mole) of 1H-Pyrazolo[3,4-c]pyridine (**3**) for 1 h. Basification with conc. NH_4OH and filtration gave **4**; m.p. 197°C (212°C[4]); yield 70%. - ^{1}H-NMR ($(CD_3)_2SO$): δ (ppm) = 7.74 (dd; 1H, $J_{4,5}$ = 6 Hz, $J_{4,7}$ = 1 Hz, H-4), 8.47 (d; 1H, $J_{4,5}$ = 6 Hz, H-5), 9.25 (d; 1H, $J_{4,7}$ = 1Hz, H-7).

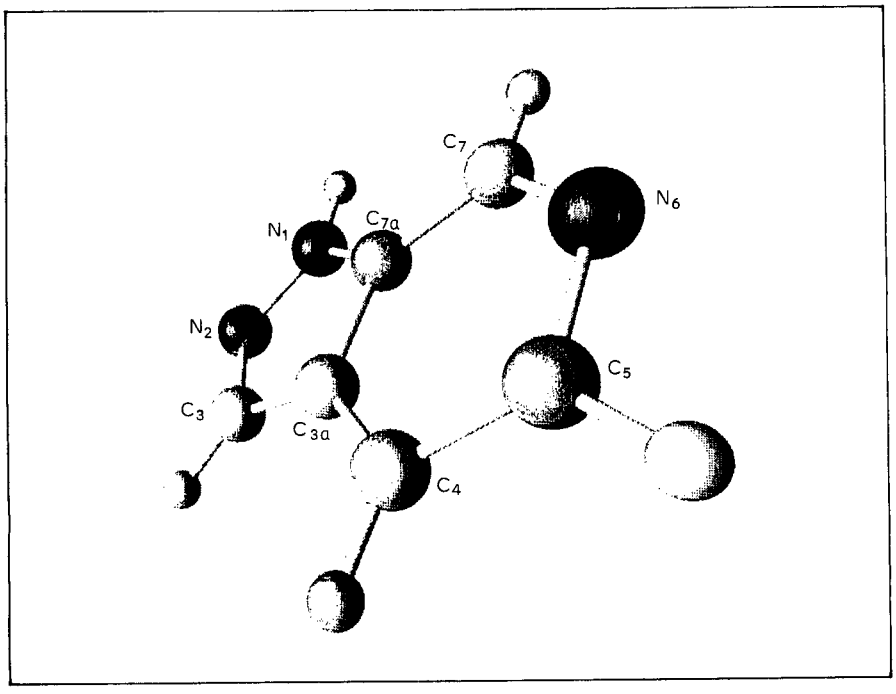

Fig. 1: Spatial representation of **3** obtained from Moldesign program.

3-Bromo-1H-pyrazolo[3,4-c]pyridine (**5**)

A suspension of lg ($8.4 \cdot 10^{-3}$ mole) of 1H-Pyrazolo[3,4-c]pyridine (**3**) in a cooled solution of NaOBr (prepared from NaOH (0.8 g) and bromine (0.5 ml) in water (20 ml)) was stirred for 1 h at 0°C. Basification with conc. NH_4OH and filtration gave **5**; m.p. 208-210°C, yield 69%; M^+ at m/z 197 and m/z = 199 (100%). - ^{1}H-NMR ($(CD_3)_2SO$): δ (ppm) = 7.65 (dd; 1H, $J_{4,5}$ = 6 Hz, $J_{4,7}$ = 1 Hz, H-4), 8.45 (d; 1H, $J_{4,5}$ = 6 Hz, H-5), 9.15 (d; 1H, $J_{4,7}$ = 1 Hz, H-7).

3-Nitro-1H-pyrazolo[3,4-c]pyridine (**6**)

6 was prepared according to Foster[5] form 1*H*-Pyrazolo[3,4-c]pyridine (**3**). Mp. = 272-274°C, yield 84%; M^+ at m/z 164 (100%). - ^{1}H-NMR ($(CD_3)_2SO$): δ (ppm) = 8.18 (d; 1H, $J_{4,5}$ = 6 Hz, H-4), 8.62 (d; 1H, $J_{4,5}$ = 6 Hz, H-5), 9.47 (s; 1H, H-7).

Crystallography

Crystal data for **3** *hydrochloride monohydrate.*

$C_6H_5N_3$; HCl; H_2O, mp. 228°C, mol. weight 173.7, monoclinic, space group $P2_1/c$, a = 7.310(3), b = 15.538(6), c = 6.946(2) Å, β = 94.31(3)°, vol. of unit cell 786.8 Å^3, Z = 4, D_c = 1.47 g·cm^{-3}, F(000) = 360, T = 293°K.

The crystal structure of **3** hydrochloride monohydrate was established by X-ray diffraction.

Intensity data up to Ø = 65° were collected on a fully-automated Enraf-Nonius CAD-4 diffractometer using graphite monochromated CuK_α radiation ($\bar{\lambda}$ = 1.54178 Å). 1296 Measurements yielded 1166 significant [$I \geq 3\sigma(I)$] diffraction maxima. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. The structure was solved by routine application of the MULTAN program[6]. The positions of the non-hydrogen atoms were refined by block-diagonal least-squares with anisotropic thermal parameters. The hydrogen atoms were derived from difference Fourier synthesis and refined with isotropic thermal parameters. The final minimum residual was R = 0.060.

List of observed and calculated structure factors and anisotropic thermal parameters are available from Fachinformationszentrum Karlsruhe, Ges. für wissentschaftl.-techn. Information mbH, D-7514 Eggenstein-Leopoldshafen under the deposit no. CSD - 53642, citing the authors and the Journal (volume, page, year).

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