The Synthesis of 5-Azaindoles by Substitution-Rearrangement of 7-Azaindoles upon Treatment with Certain Primary Amines

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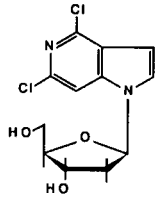
Received August 1, 1988

Certain 4-substituted 1*H*-pyrrolo[2,3-*b*]pyridines (7-azaindoles) undergo a nucleophilic substitution-rearrangement upon treatment with various primary amines at elevated temperatures to yield *N*-1-substituted 4-amino-1*H*-pyrrolo[3,2-*c*]pyridines (5-azaindoles). Treatment of the same 7-azaindoles with secondary amines under the same reaction conditions led to simple nucleophilic substitution products.

J. Heterocyclic Chem., **26**, 317 (1989).

Recent reports [1,2] from our laboratory have described the preparation of two new azaindole nucleosides, 1-(2-deoxy-β-D-*erythro*pentofuranosyl)-4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (**1**) and 6-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (**2**), (as well as the arabinofuranosyl derivative of **2** *via* the sodium salt glycosylation procedure.



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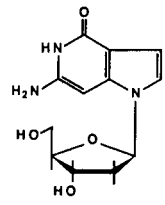


2

Our continuing efforts to extend these synthetic methods to other azaindole systems, namely the 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) system, have led to studies involving nucleophilic substitution-rearrangement reactions of 4-substituted 7-azaindoles, which is the subject of the present report.

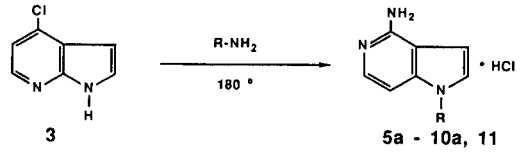
When 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**3**) [3] was treated with aniline at 180° for 3 hours the product obtained was not the expected 4-anilino-1*H*-pyrrolo[2,3-*b*]pyridine formed by simple nucleophilic substitution, but instead was found to be the hydrochloride salt of 4-amino-1-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine (**5a**, Scheme I, Method A). No other product was detected in this reaction. Similarly, when 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (**4**) [4] was treated with a mixture of aniline, phosphorus pentoxide and triethylamine hydrochloride at 200° for 3 hours (Method B) according to the procedures of Girgis *et al.* [5], the same substitution-rearrangement reaction occurred and **5b**, the free base form of **5a**, was isolated in 67% yield. The structures of **5a** and **5b** were determined by single-crystal X-ray diffraction studies (Figures 1 and 2).

While similar rearrangements in the pyrrolopyridines have been reported [6,7], they involve the rearrangment of

Scheme I

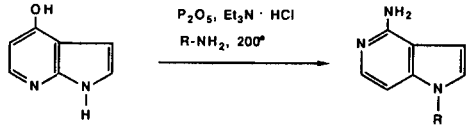
Substitution-Rearrangement of 7-aza to 5-azaindoles

Method A

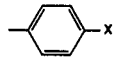


3 — 5a - 10a, 11

Method B



4 — 5b - 10b

5 - 10, R = 

11, R = CH_3

N-1-substituted pyrrolo[3,2-*c*]pyridines to *N*-1-substituted pyrrolo[2,3-*b*]pyridines after nucleophilic displacement of a 4-chloro group by primary alkylamines. In our own studies, *N*-1-unsubstituted 4-chloro- (or activated 4-hydroxy-) pyrrolo[2,3-*b*]pyridines were treated with a variety of amines, always resulting in nucleophilic displacement and, in some cases, rearrangement to the *N*-1-substituted pyrrolo[3,2-*c*]pyridines. No mixtures of the two ring systems were detected as products in any reaction studied.

In order to investigate the possible influence of resonance or field effects of various substituted anilines with respect to rearrangement *versus* nucleophilic displacement products, ease of reaction and product yield, we

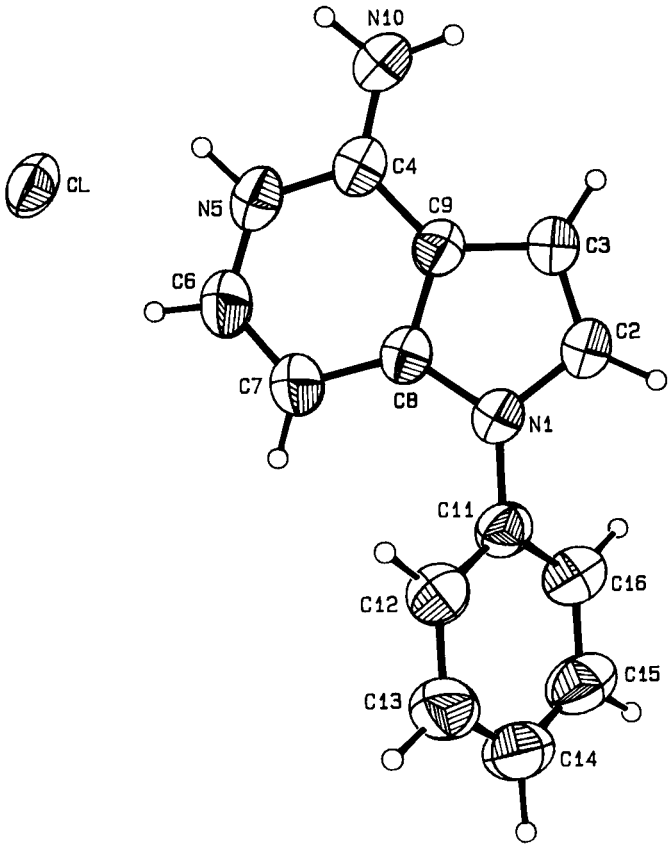


Figure 1. Perspective drawing of **5a**.

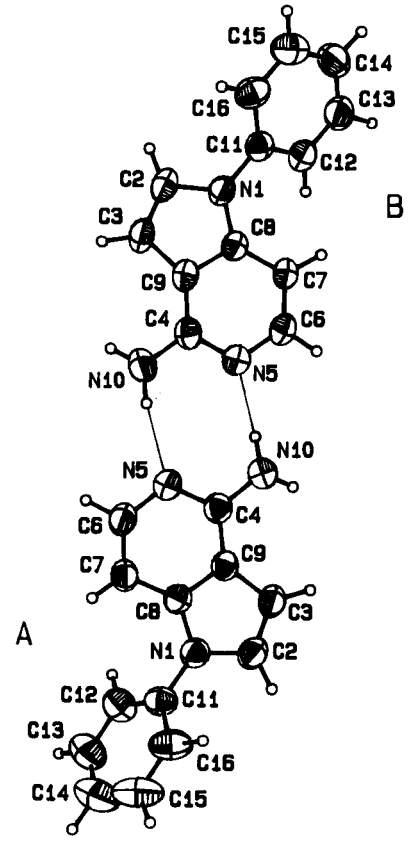


Figure 2. Perspective drawing of the **5b** dimer.

chose several *para*-substituted anilines having electron-withdrawing (F, Cl, NO_2) and electron-donating substituents (CH_3, OCH_3) compared to hydrogen. The results summarized in Table 1 indicate that reaction of these anilines by either Method A or B always led exclusively to displacement-rearrangement products and there was little or no difference in isolated product yields *vis-à-vis* the presence of donating *versus* withdrawing substituents in the aniline reactants. However, there appeared to be a difference in the rate of reaction between the two general groups. Those reactions involving anilines bearing donating groups were complete in less than half the time required for those involving anilines substituted with electron withdrawing functional groups under the same reaction conditions. One might expect an increased rate of reaction using anilines bearing electron donating groups due to the increased nucleophilicity and basicity of the amine function by resonance (for the OCH_3 group) or field (for the CH_3 group) effects. This increased nucleophilicity of the amino group would likely facilitate both the initial displacement step as well as the subsequent attack on the pyrrole ring resulting in ring-opening and rearrangement (see Scheme II and discussion of mechanism below).

Studies involving the use of a few primary and secondary alkylamines (Table 2) showed that treatment of **3** or **4** with simple primary alkylamines led to substitution-rearrangement products while treatment with secondary

Table 1

Reaction of *para*-Substituted Anilines with **3** or **4**

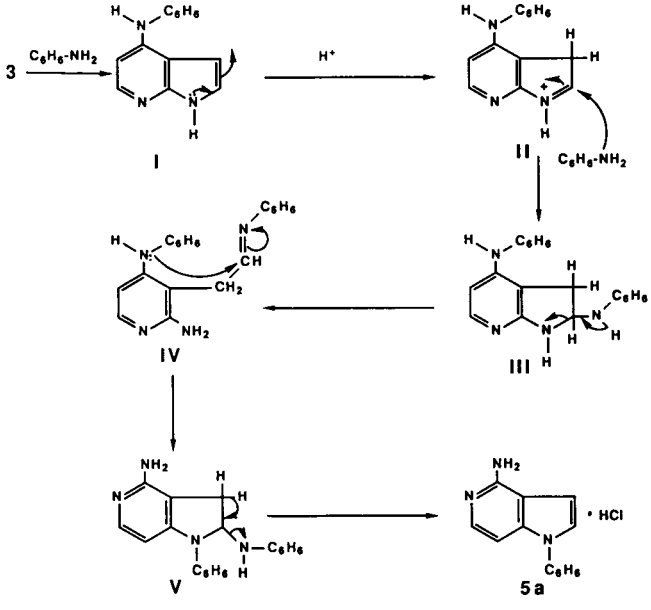
para-substituent, X	Method [a]	Reaction Time, hours [b]	Product	% Yield [c]
H	A	3	**5a**	84
	B	3	**5b**	67
F	A	2	**6a**	69
	B	3	**6b**	72
Cl	A	3	**7a**	70
	B	3	**7b**	84
NO_2	A	5	**8a**	55
	B	5	**8b**	63
CH_3	A	1	**9a**	62
	B	1.5	**9b**	78
OCH_3	A	1	**10a**	83
	B	1.5	**10b**	75

[a] Methods outlined in Scheme I. [b] Time required for completion of reaction as monitored by tlc. [c] Isolated yields.

amines led to substitution products without rearrangement. Thus, reaction of **3** with methylamine hydrochloride according to method A gave the hydrochloride salt of 4-amino-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**11**), the rearranged product, while treatment with dimethylamine hydrochloride under the same conditions afforded 4-(dimethylamino)-1*H*-pyrrolo[2,3-*b*]pyridine (**12**), the substituted product. Likewise, treatment of **3** with *N*-methylaniline under conditions of method A provided only the substituted product, 4-(*N*-methylanilino)-1*H*-pyrrolo[2,3-*b*]pyridine (**13**) as the hydrochloride salt. The ^{1}H nmr of **13** revealed an interesting phenomenon. The chemical shift for H-3 was observed at 4.95 ppm as a singlet rather than the usual doublet around 6.80 ppm. Upon deuteration the usual doublet pattern was observed but the chemical shift remained unusually far upfield. The upfield chemical shift may be due to anisotropic shielding provided by the phenyl ring current of the anilino group in close proximity to H-3 of the pyrrole ring. Dramatic upfield chemical shift changes have been observed in other systems where an aromatic ring is found in close proximity to the protons in question [9,10]. Indeed, preliminary X-ray diffraction studies of **13** have supported this possible explanation, albeit in the solid state as opposed to the nmr solution studies [11].

Scheme II

Proposed Mechanism of Rearrangement of **3** → **5a**

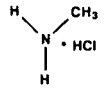
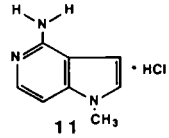
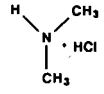
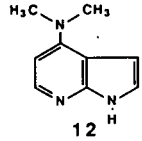
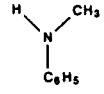
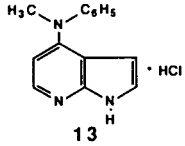
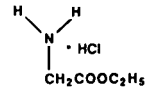
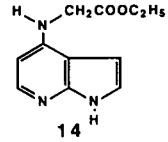


A proposed mechanism for the conversion of **3** to **5a** is depicted in Scheme II. The mechanism involves the generation of a Schiff base intermediate **IV** similar to that proposed for the rearrangement of the 5-azaindole to the 7-azaindole system [6]. While no Schiff base intermediates were ever isolated during the course of these studies, the formation of such intermediates is supported by the observation that reaction with primary amines generally gave the rearrangement products whereas reaction with secondary amines gave simple substitution products. Secondary amines do not normally form Schiff bases without dealkylation occurring [8] and one could assume that under these reaction conditions no dealkylation occurs and thus only substitution takes place. An exception to the general observation of rearrangements occurring with the use of primary amines was noted when **3** was reacted with glycine ethylester hydrochloride under conditions of Method A. In this case only the substitution product **14** was obtained.

It should be noted that these same reaction products **5-14** are obtained if one uses 4-methoxy-1*H*-pyrrolo[2,3-*b*]-pyridine (**15**, prepared by treatment of **3** with methanolic sodium hydroxide) as starting material in Method A instead of **3**; however, the time required for completion of reaction was considerably longer using **15**. In addition, the substitution-rearrangement reactions in any of the procedures could be carried out with similar results, using amines in the free base or hydrochloride salt forms.

Table 2

Reaction of Aliphatic Amines with **3** or **4**

Substrate	Amine	Method [a]	Product	% Yield [b]
3		A	 **11**	45
3		A	 **12**	68
4		B		62
3		A	 **13**	63
3		A	 **14**	46

[a] Methods outlined in Scheme I.
[b] Isolated yield.

Table 3

Positional and Equivalent Isotropic Thermal Parameters for Non-hydrogen Atoms in **5a** and **5b**

Atom	x/a	y/b	z/c	U_{eq} [a]	Atom	x/a	y/b	z/c	U_{eq} [a]
				5a					
N1	.50777(10)	.36194(13)	.85296(8)	.0519(4)	C2	.42566(13)	.3034(2)	.88232(10)	.0570(6)
C3	.37848(13)	.3967(2)	.92361(10)	.0540(5)	C4	.42076(12)	.6513(2)	.95294(9)	.0491(5)
N5	.49032(11)	.7450(2)	.94029(8)	.0578(5)	C6	.5709(2)	.7189(2)	.89920(12)	.0649(6)
C7	.58557(14)	.5968(2)	.86606(11)	.0614(6)	C8	.51405(12)	.4958(2)	.87706(9)	.0489(5)
C9	.43347(12)	.5200(2)	.92116(9)	.0473(5)	N10	.34587(13)	.6851(2)	.99405(9)	.0599(5)
C11	.57399(12)	.2925(2)	.80596(9)	.0524(5)	C12	.60706(15)	.3568(2)	.74354(11)	.0622(6)
C13	.6717(2)	.2878(3)	.69846(12)	.0739(8)	C14	.6998(2)	.1555(3)	.71429(14)	.0774(8)
C15	.6646(2)	.0908(3)	.77562(14)	.0758(8)	C16	.60170(15)	.1590(2)	.82234(11)	.0627(6)
CL	.64244(3)	.98858(4)	1.00638(3)	.0665(2)					
				5b					
				Molecule A					
N1A	.1093(2)	.01148(4)	.64148(10)	.0528(5)	C2A	−.0448(3)	.02967(5)	.67127(13)	.0590(7)
C3A	−.0015(3)	.06206(5)	.67380(13)	.0569(7)	C4A	.3091(3)	.09215(5)	.63006(12)	.0513(6)
N5A	.4803(2)	.08803(4)	.59462(11)	.0574(5)	C6A	.5342(3)	.05672(5)	.57400(13)	.0591(7)
C7A	.4318(3)	.02871(5)	.58735(13)	.0553(6)	C8A	.2523(2)	.03352(4)	.62335(12)	.0478(6)
C9A	.1874(2)	.06520(4)	.64370(11)	.0471(5)	N10A	.2557(3)	.12376(5)	.65020(14)	.0664(7)
C11A	.1133(3)	−.02354(5)	.63099(12)	.0558(6)	C12A	.2587(4)	−.04190(5)	.6672(2)	.0681(8)
C13A	.2595(4)	−.07607(6)	.6580(2)	.0849(10)	C14A	.1154(5)	−.09152(7)	.6137(2)	.0942(12)
C15A	−.0278(5)	−.07340(7)	.5780(2)	.0916(11)	C16A	−.0296(4)	−.03927(6)	.58600(14)	.0720(8)
				Molecule B					
N1B	.8988(2)	.25472(4)	.61299(9)	.0494(5)	C2B	1.0542(3)	.23911(6)	.57489(13)	.0592(7)
C3B	1.0248(3)	.20624(5)	.57085(13)	.0594(7)	C4B	.7339(3)	.17138(5)	.62100(12)	.0516(6)
N5B	.5620(2)	.17324(4)	.65655(10)	.0536(5)	C6B	.4928(3)	.20360(5)	.67662(12)	.0517(6)
C7B	.5848(2)	.23287(5)	.66671(12)	.0486(6)	C8B	.7673(2)	.23065(4)	.63228(11)	.0445(5)
C9B	.8430(3)	.20003(5)	.60659(12)	.0493(6)	N10B	.7964(3)	.14053(5)	.5991(2)	.0714(7)
C11B	.8801(2)	.28931(5)	.62783(12)	.0486(6)	C12B	.7966(3)	.30091(5)	.70431(13)	.0558(7)
C13B	.7749(3)	.33463(6)	.7171(2)	.0683(8)	C14B	.8380(3)	.35658(6)	.6541(2)	.0735(9)
C15B	.9247(3)	.34497(6)	.5781(2)	.0704(9)	C16B	.9453(3)	.31137(6)	.56504(13)	.0596(7)

[a] $U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* A_{ij}$, where A_{ij} is the dot product of the i^{th} and j^{th} direct-space unit-cell vectors.

X-Ray Diffraction Studies of **5a** and **5b**.

Atomic coordinates for **5a** and **5b** are listed in Table 3. Bond lengths and bond angles are given in Tables 4 and 5, respectively. The atom labeling and conformations of the structures are illustrated in Figures 1 and 2 in which non-hydrogen atoms are represented by thermal ellipsoids drawn at the 50% probability level and hydrogen atoms are drawn with arbitrary radii.

Compound **5b** crystallizes with two independent molecules (designated A and B) in an asymmetric unit of the unit cell. The bond lengths and bond angles indicate that they are essentially identical (rms deviations of 0.003 Å for bond lengths in the heterocycle, 0.006 Å for all bonds and 0.36° for all angles). The C15A-C14A bond is significantly shorter than the average phenyl C-C bond of 1.38 Å for the three structures. Atoms of all phenyl rings have above average thermal parameters (Table 3, Figures 1 and

Table 4

Bond Lengths (Å) in **5a** and **5b**

		5a	5b	
			A	B
C2	N1	1.383(2)	1.395(3)	1.398(2)
C8	N1	1.373(2)	1.380(2)	1.381(2)
C11	N1	1.429(2)	1.425(2)	1.422(2)
C3	C2	1.349(3)	1.346(3)	1.347(3)
C9	C3	1.419(2)	1.425(3)	1.425(3)
N5	C4	1.346(2)	1.342(2)	1.339(2)
C9	C4	1.410(2)	1.407(3)	1.412(3)
N10	C4	1.326(2)	1.367(3)	1.365(3)
C6	N5	1.372(3)	1.359(3)	1.357(2)
C7	C6	1.346(3)	1.362(3)	1.361(3)
C8	C7	1.410(3)	1.402(3)	1.402(2)
C9	C8	1.400(2)	1.396(3)	1.405(2)
C12	C11	1.381(3)	1.387(3)	1.383(3)
C16	C11	1.382(3)	1.379(3)	1.383(3)
C13	C12	1.391(3)	1.388(3)	1.385(3)
C14	C13	1.372(4)	1.375(4)	1.378(4)
C15	C14	1.376(4)	1.366(5)	1.385(4)
C16	C15	1.390(3)	1.385(4)	1.380(3)

Table 5

Bond Angles (°) in **5a** and **5b**

			5a	5b	
				A	B
C2	N1	C8	108.34(14)	107.7(2)	107.78(15)
C2	N1	C11	124.92(14)	125.1(2)	125.6(2)
C8	N1	C11	126.74(14)	127.2(2)	126.57(14)
C3	C2	N1	110.1(2)	110.0(2)	109.9(2)
C9	C3	C2	106.6(2)	107.1(2)	107.3(2)
N5	C4	C9	116.6(2)	121.4(2)	121.3(2)
N5	C4	N10	119.6(2)	117.2(2)	116.6(2)
C9	C4	N10	123.8(2)	121.3(2)	122.2(2)
C6	N5	C4	123.8(2)	117.6(2)	118.2(2)
C7	C6	N5	122.2(2)	126.1(2)	125.9(2)
C8	C7	C6	116.1(2)	115.5(2)	115.6(2)
C9	C8	N1	107.06(14)	107.71(15)	107.60(15)
C9	C8	C7	122.0(2)	121.0(2)	121.0(2)
N1	C8	C7	130.9(2)	131.3(2)	131.4(2)
C3	C9	C4	132.8(2)	134.2(2)	134.7(2)
C3	C9	C8	107.89(14)	107.5(2)	107.3(2)
C4	C9	C8	119.32(14)	118.3(2)	118.0(2)
C12	C11	C16	120.6(2)	119.9(2)	120.0(2)
C12	C11	N1	120.0(2)	120.2(2)	120.4(2)
C16	C11	N1	119.3(2)	119.9(2)	119.6(2)
C13	C12	C11	119.3(2)	119.7(2)	119.9(2)
C14	C13	C12	120.5(2)	119.9(3)	120.0(2)
C15	C14	C13	119.8(2)	120.4(3)	120.1(2)
C16	C15	C14	120.6(2)	120.4(3)	120.0(2)
C11	C16	C15	119.1(2)	119.7(2)	120.0(2)

2). The hydrochloride **5a** is similar to **5b** with the following significant differences resulting from the protonation of N5. The amino nitrogen (N10) is much more strongly conjugated with the heterocycle [1.326(2) Å bond length for **5a** *versus* an average of 1.366(1) Å for **5b**]. Bonds involving N5 are longer and C4–N5–C6 bond angle is about 6.0° larger in **5a** than in **5b** while the C6–C7 bond is shorter. All other bonds are essentially unaffected by the protonation. In the structure of 1-deaza-isotubercidin [12], a 5-azaindole, the ribose is attached to N5 resulting in similar but more pronounced changes in these geometrical features in which the N5 heterocyclic bonds are 1.367 (C4) and 1.394 Å (C6) and the adjacent bonds C4–N10 and C6–C7 are significantly shorter (1.313 and 1.312 Å, respectively).

The three 5-azaindole moieties are less planar than the 1-deazatubercidin analog (rms deviations of atoms from the plane are 0.0181(6) Å for **5a**, 0.0263(7) Å for **5b-A**, 0.0163(6) Å for **5b-B** compared to 0.0059 Å). The pyrrole

Table 6

Hydrogen Bonding in **5a** and **5b**

D	–	H	...	A	Symmetry of A relative to D	d(D···A) (Å)	d(H···A) (Å)	∠(D-H··A) (°)
					5a			
N10		H10A		CL	1.0-x, 2.0-y, 2.0-z	3.167(2)	2.30(3)	161.(2)
N10		H10B		CL	x-0.5, 1.5-y, 2.0-z	3.290(2)	2.34(2)	173.(2)
N5		H5		CL	1.0-x, 1.0-y, 1.0-z	3.321(2)	2.55(2)	139.4(15)
					5b			
N10A		H10A2		N5B	x, y, z	2.961(2)	1.98(3)	168.(2)
N10B		H10B2		N5A	x, y, z	3.094(3)	2.11(3)	171.(2)

Table 7

Crystal and Experimental Data [a,b] for Compounds **5a** and **5b**

	5a	**5b**
Empirical formula	$C_{13}H_{11}N_3 \cdot HCl$	$C_{13}H_{11}N_3$
Formula weight	245.71	209.25
Crystal system	orthorhombic	orthorhombic
Space group	Pbca	Pbca
a (Å)	13.8941(13)	7.1179(5)
b (Å)	9.6924(9)	40.424(6)
c (Å)	18.315(2)	15.1274(16)
V (Å^3)	2466.4(4)	4352.6(8)
Z	8	16
ρ_{calcd} (g cm^{-3})	1.323	1.277
F(000) (electrons)	1024	1760
Radiation, λ (Å)	CuKα, 1.54178	CuKα, 1.54178
Crystal dimensions (mm)	0.36 x 0.36 x 0.215	0.39 x 0.15 x 0.15 x 0.13
Crystal volume (mm^3)	0.0147	0.00935
μ (cm^{-1})	26.042	5.879
Max 2θ (°)	152	152
Total refls, measd, unique	2565, 2565	4506, 4506
Observed refls ($F \geq 4\sigma_F$)	2011	2903
No. of variables	203	378
S (goodness of fit)	1.680	1.516
R, wR [c]	0.0339, 0.0515	0.0426, 0.0518
Extinction parameter	5.6 (7) x 10^{-7}	2.03 (8) x 10^{-7}
Max Δ/σ	0.002	0.021
Max, min in $\Delta\rho$ map (e/Å^3)	0.19, −0.18	0.15, −0.18

[a] Unit-cell parameters were obtained by least-squares refinement of the setting angles of 25 reflections in the ranges: for **5a**, $54.9 < 2\theta < 57.7°$; for **5b**, $45.6 < 2\theta < 55.0°$. [b] Intensity measurements were made on an Enraf-Nonius CAD4 automatic diffractometer equipped with a graphite monochromator using an $\omega - 2\theta$ scan procedure and variable scan speeds. Data reduction was accomplished with the SDP-Plus program package and included Lorentz, polarization, decay and absorption corrections [53]. [c] Function minimized was $\Sigma w(|F_o| - |F_c|)^2$, where $w = (\sigma_F^2 + 0.0004F^2)^{-1}$ for both structures: $\sigma_F = F\sigma_I/2I$ and $\sigma_I = (N_{pk} + N_{bg1} + N_{bg2})^{1/2}$.

Table 8

Analytical Data

Compound	mp, °C	Formula	Analysis, % Calcd./Found					uv λ max (ε)		
			C	H	N	Cl	F	*p*H 1	*p*H 7	*p*H 11
4	238-239 [a]	$C_7H_6N_2O$	62.68 62.43	4.51 4.27	20.88 20.39			271 (6500) 293s (4000)	267 (6500) 290 (8500)	267 (6500) 290 (8500)
5a	268-269	$C_{13}H_{11}N_3 \cdot HCl$	63.55 63.43	4.92 4.82	17.10 16.98	14.43 14.22		239 (25000) 272 (10500)	same same	same same
5b	158	$C_{13}H_{11}N_3$	74.62 74.64	5.30 5.28	20.08 20.17			[c]		
6a	320-321	$C_{13}H_{10}FN_3 \cdot HCl$	59.21 59.46	4.20 4.14	15.93 15.86	13.44 13.45	7.20 7.07	237 (33500) 272 (13600)	same same	same same
6b	303-304	$C_{13}H_{10}FN_3$	68.71 68.82	4.44 4.30	18.49 18.24		8.38 8.22			
7a	268-269	$C_{13}H_{10}ClN_3 \cdot HCl$	55.73 55.63	3.96 3.76	15.00 14.80	25.31 25.22		245 (31000) 272 (13000)	245(31000) 272 (13000)	244 (19600) 273 (11000)

7b	200-201	$C_{13}H_{10}ClN_3$	64.07	4.14	17.24	14.55			
			64.15	4.02	16.99	14.25			
8a	>300	$C_{13}H_{10}N_4O_2 \cdot HCl$	53.71	3.81	19.27		222(26000)	223 (18100)	
			54.21	3.70	19.40		279 (19800)	277 (14600)	273 (4000)
8b	>300	$C_{13}H_{10}N_4O_2$	61.41	3.96	22.04				
			61.73	3.80	21.66				
9a	279-280	$C_{14}H_{13}N_3 \cdot HCl$	64.73	5.43	16.18		241 (25800)	241 (25200)	240 (19000)
			64.89	5.28	16.30		271 (10500)	269 (10400)	275 (10600)
9b	191-192	$C_{14}H_{13}N_3$	75.31	5.87	18.82				
			75.16	5.81	19.09				
10a	279	$C_{14}H_{13}N_3O \cdot HCl$	60.98	5.12	15.24	12.86	243 (22200)	243 (22200)	242 (11700)
			60.68	4.96	15.10	13.01	271s (12900)	271s (12900)	276 (7700)
10b	247	$C_{14}H_{13}N_3O$	70.28	5.48	17.56				
			69.99	5.32	17.25				
11	249-251 [b]	$C_8H_9N_3 \cdot HCl$	52.32	5.49	22.88	19.31	225 (25000)	225 (25000)	
			52.43	5.23	22.60	19.05	277 (10000)	277 (20000)	276 (10900)
12	136-137	$C_9H_{11}N_3$	67.06	6.88	26.07		229 (20000)	229 (20000)	229 (18200)
			67.24	6.75	26.03		270 (3900)	270 (3900)	275 (2700)
							312 (12000)	312 (12000)	301 (10600)
13	307-308	$C_{14}H_{13}N_3 \cdot HCl$	64.74	5.43	16.18	13.65	226 (28300)	same	
			64.48	5.33	15.96	13.49	270 (6000)	same	
							317 (18100)	same	
14	180-182	$C_{11}H_{13}N_3O_2$	60.26	5.98	19.17		224 (19000)	224 (19000)	227 (12500)
			60.33	5.63	18.98		272 (5600)	272 (5600)	272s (2600)
							303 (9000)	303 (9000)	294 (7100)
15	180-182	$C_9H_8N_2O$	64.85	5.44	18.91		274 (8000)	same	
			64.97	5.62	18.73		295s (5000)	same	

[a] Lit [4] 238-239°. [b] Lit [7] 251°. [c] The uv spectra of all **b** series compounds are identical to their respective **a** series compounds.

rings in each case are planar within experimental error whereas the pyridine rings are slightly nonplanar. The dihedral angles between the pyrrole and pyridine planes are 1.98(7)° for **5a**, 3.15(9)° for **5b-A** and 1.62(7)° for **5b-B**. The isotubercidin analog exhibits a dihedral angle of only 0.48°. The phenyl rings are not coplanar with the heterocycle in any of the structures of this study. The dihedral angles between the phenyl rings and the heterocycles are 45.56(6)° for **5a**, 51.80(7)° for **5b-A** and 40.45(6)° for **5b-B**. The H7-H12 intramolecular contacts resulting from these phenyl ring orientations are 2.40(3), 2.54(3) and 2.33(3) Å for **5a**, **5b-A** and **B**, respectively, which correspond to van der Waals contact, suggesting a propensity toward phenyl-ring coplanarity with the heterocycle.

EXPERIMENTAL

X-Ray Crystallography.

Compound **5a** crystallized from ethanol as triangular plates; compound **5b** crystallized from ethanol as hexagonal needles. Crystal and experimental data for **5a** and **5b** are summarized in Table 7. Initial positions of all non-hydrogen atoms for both structures were obtained by direct methods (MULTAN82 [13]). Positions of hydrogen atoms were obtained from electron density difference maps (for **5a**, peaks were 0.32-0.56 e Å^{-3} and R = 0.069, for **5b**, peaks were 0.27-0.48 e Å^{-3} and R = 0.084). Both structures were refined by full-matrix least-squares (SHELX76 [14]) by which all atomic positions, anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms were varied. Atomic scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from the "International Tables for X-ray Crystallography" [15]. Scattering factors for hydrogen atoms were taken from Stewart, Davidson and Simpson [16]. Figures were drawn with ORTEPII [17]. Least-squares planes were calculated with the program PLANES [18].

General Procedures.

Melting points (Table 8) were taken on a Haake-Buchler capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H nmr, Table 9) spectra were determined at 300.1 MHz with an IBM NR300AF spectrophotometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Ultraviolet spectra (uv: s = shoulder; Table 8) were recorded on a Beckman DU-50 spectrophotometer. Elemental analyses (Table 8) were performed by Robertson Laboratories, Madison N.J. Evaporations were carried out under reduced pressure with the bath temperature below 40°. Thin layer chromatography (tlc) was run on silica gel 60 F-254 plates (EM Reagents). E. Merck silica gel (230-400 mesh) was used for flash column chromatography.

Method A.

A mixture of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**3**, 3.0 g, 20 mmoles) and the appropriate amine (100 mmoles) was heated in an oil bath at 180° for 1-5 hours. After cooling, the dark brown reaction mixture was worked up by adding ethanol (or methanol in the case of **6a** and **10a**), filtering the crude product and crystallizing from ethanol. In a few cases,

Table 9

^{1}H nmr Data in DMSO-d_6

δ, multiplicity / (J constant in Hz)

Compound	H-1	Phenyl	H-2	H-3	NH_2	CH_3	H-5	H-6	H-7	Other
4	11.38 s		7.17 d (3.30)	6.45 d (3.30)			6.38 d (5.10)	7.88 d (5.10)		10.60 s OH
5a		7.35-7.65 m [a]	7.77 d (3.30)	7.36 d (3.30)	8.63 s			7.65 [a]	6.94 d (7.20)	13.42 s HCl salt
5b		7.37-7.60 m	7.46 d (3.30)	6.88 d (3.30)	6.37 s			7.62 d (6.06)	6.72 d (6.06)	
6a		7.48-7.68 m [a]	7.74 d (3.30)	7.33 d (3.30)	8.59 s			7.68 [a]	6.91 d (6.57)	13.40 s HCl salt
6b		7.35-7.58 m [a]	7.58 [a]	6.87 d (3.24)	6.30 s			7.62 d (6.00)	6.60 d (6.00)	
7a		7.49-7.65 m [a]	7.77 d (3.30)	7.37 d (3.30)	8.63 s			7.65 [a]	6.94 d (7.17)	13.41 s HCl salt
7b		6.55-7.64 m [a]	7.43 d (3.20)	6.87 d (3.20)	6.30 s			7.64 [a]	6.71 d (6.00)	
8a		7.91 & 8.43 2d	7.86 d (3.40)	7.32 d (3.40)	8.27 s			7.70 d (7.05)	7.08 d (7.05)	
8b		7.85 & 8.39 2d	7.61 d (3.21)	6.97 d (3.21)	6.39 s			7.69 d (5.97)	6.87 d (5.97)	
9a		7.44 m	7.72 d (3.30)	7.30 d (3.30)	8.55 s	2.38 s		7.61 d (7.05)	6.92 d (7.05)	13.30 s HCl salt
9b		7.39 m [a]	7.39 [a]	6.84 d (3.33)	6.25 s	2.37 s		7.60 d (6.00)	6.67 d (6.00)	
10a		7.14 & 7.50 2d	7.68 d (3.10)	7.29 d (3.10)	8.54 s	3.83 s		7.60 d (7.10)	6.55 d (7.10)	13.20 s HCl salt
10b		7.11 & 7.45 2d	7.34 d (3.24)	6.81 d (3.24)	6.22 s	3.82 s		7.58 d (7.58)	6.61 d (7.58)	
11			7.43 d (3.00)	7.08 [a]	8.38 s	3.81 s		7.60 d (7.08)	7.09 [a]	
12	11.36 s		7.13 d (3.60)	6.60 d (3.60)		3.17 s $2CH_3$	6.16 d (5.70)	7.83 d (5.70)		
13	12.56 s	7.41-7.58 m	7.07 s 6.98 d [b] (3.35)	4.95 s 4.85 d [b] (3.35)		3.58 s	6.70 d (7.20)	8.08 d (7.20)		14.72 s HCl salt
14	11.23 s		7.10 d (3.30)	6.53 d (3.30)	6.98 t NH	4.11 m [a] NCH_2	5.99d (5.25)	7.80 d (5.25)		1.20 t & 4.11 m [a] OCH_2CH_3
15	11.55 s		7.28 d (3.60)	6.62 d (3.60)		4.05 s	6.59 d (5.70)	8.27 d (5.70)		

[a] Resonance signals overlap. [b] After deuteration with deuterium oxide.

7a, **8a**, **11**, **12** and **14**, flash silica gel column chromatography was required using 10-20% methanol in dichloromethane after dissolving the reaction mixture in ethanol or methanol and pre-adsorbing on silica gel. The products were generally isolated as the hydrochloride salts.

Method B.

The amine reagent was prepared by mixing phosphorous pentoxide (120 mmoles), triethylamine hydrochloride (120 mmoles) and the appropriate amine (120 mmoles) in a three-necked flask fitted with a reflux condenser, mechanical stirrer and drying tube. The mixture was heated at 200° in an oil bath until a homogeneous, transparent mixture was obtained. To this reagent was added 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (**4**, 4.3 g, 30 mmoles) [4] and heating and stirring were continued at 200° for 3 hours. The reaction mixture was allowed to cool to about 100° and a solution of 2 *N* sodium hydroxide was added with stirring, the *p*H being adjusted to about 10. The alkaline solution was then extracted with ethyl acetate (3 x 200 ml), the organic layer washed with water (1 x 250 ml) and dried (sodium sulfate). Evaporation of the solvent afforded a dark syrup which was adsorbed onto silica gel and flash chromatographed using methanol in dichloromethane (10-20%). The product obtained was crystallized from ethanol or methanol, or was allowed to crystallize from the eluent solvent mixture.

1*H*-Pyrrolo[2,3-*b*]pyridin-4-ol (**4**).

A suspension of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**3**, 1.52 g, 10 mmoles) [3] in aqueous sodium hydroxide solution (30 ml, 1 *N*) was heated in a steel bomb at 180° for 12 hours. After cooling, the reaction mixture was filtered and the filtrate neutralized with glacial acetic acid. The resulting solution was evaporated to dryness and the residue was extracted with hot ethanol (100 ml). The extract was concentrated to about one-third the original volume and the product allowed to crystallize to yield 1.2 g (85%) of **4** as a colorless solid.

4-Methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (**15**).

A suspension of **3** (4.57 g, 30 mmoles) in a 90% methanolic sodium hydroxide solution (4.0 g, 100 mmoles in 75 ml) was heated in a steel bomb at 150° for 12 hours. After cooling, the reaction mixture was poured into crushed ice (about 500 g). The solid which precipitated was collected by filtration and purified by silica gel flash column chromatography using dichloromethane - acetone (4:1, v/v) to give 3.1 g (70%) of **15**.

Acknowledgement.

The excellent technical assistance of Dr. Fangchen Lee in preparing the computer-generated structures is gratefully acknowledged.

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