mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen within 1 min was determined. This measurement was performed 0.5, 1, 2, 3, and 4 h posttreatment to determine the approximate time of peak effect. Each compound was then retested at the estimate time of peak effect by using at least four doses with 12 mice at each dose. The HS ED_{50} was calculated according to the method of Litchfield and Wilcoxon.[21]

Inhibition of MES-Induced Seizures. Groups of four mice were fasted for 90 min and were then administered a range of oral doses of each compound as a suspension in 5% acacia/water. The time to peak effect (TPE) was determined by challenging the mice with MES 0.5, 1, 2, 3, and 4 h posttreatment. Electroshock (40 mA, 0.1 s, ac) was administered through corneal electrodes, and the mice were observed for clonic, tonic-flexor, and tonic-extensor convulsions. Each compound was then retested at the estimated time of peak effect by using at least four doses with 12 mice at each dose. The MES ED_{50} for the prevention of tonic-extensor convulsions was calculated according to the method of Litchfield and Wilcoxon.[21]

Effects on Hexobarbital-Induced Sleeping Time. Groups of 10 fasted mice were treated orally with various doses of each compound in 5% acacia/water. At the previously determined time of peak effect, hexobarbital (100 mg/kg, ip) was administered to the mice. The hexobarbital was solubilized with stoichiometric quantities of sodium hydroxide, and the volume of administration for all test compounds, acacia, and hexobarbital was 10 mL/kg. Sleeping time (the time of loss of righting reflex) was determined to the nearest minute for each mouse.

Benzamide Anticonvulsant Plasma Assay. A Model 5000 liquid chromatograph (Varian Associates) equipped with a Spectraflow 783 absorbance detector (Kratos Analytical) and a Dupont Instruments autosampler was used. This instrument was fitted with a 250 mm × 4.6 mm 5-μm C18 column (Alltech Associates). The detection output signal was interfaced to an HP 1000 laboratory chromatography system.

Standard curves were prepared by adding the compounds, dissolved in 10% methanol, to drug-free plasma and serially diluting with plasma to give final concentrations of 50–2000 ng/mL. These samples were assayed, and standard curves were constructed by plotting compound concentration vs. compound/internal standard peak-height ratio. The least-squares regression lines for all standard curves gave correlation coefficients of greater than 0.999.

Plasma samples were obtained from three groups of two mice dosed orally with each compound suspended in 5% acacia. The mice were anesthetized with methoxyfluorane, and blood was collected by cardiac puncture into heparinized syringes. The blood was promptly centrifuged and the plasma separated and stored at −30 °C until analysis.

An endcapped CN solid-phase extraction column was conditioned by passing 1 column volume of methanol through the column, followed by 1 column volume of distilled, deionized water. The plasma sample (200 μL) and 50 μL of a 10 μg/mL solution of the internal standard, 4-(acetylamino)-*N*-(α-methylbenzyl)-benzamide (**8**), were placed on the column to assay compounds **2** and **4**. To assay compound **3**, we used 50 μL of a 1 μg/mL solution of 4-amino-*N*-(2-methylphenyl)benzamide (**9**) as the internal standard. The remainder of the column was filled with deionized water, the mixture was pulled through the column, and the column was washed with 2 volumes of water. Compounds were eluted with 500 μL of 0.1 M ammonium acetate/methanol/acetonitrile/acetic acid/diethylamine (50:25:25:2:0.5). A 100-μL sample was injected into the liquid chromatograph. Isocratic elution was performed by using a mobile phase of 0.1 M ammonium acetate/methanol/acetonitrile/diethylamine (470:380:150:0.6) at a flow rate of 0.7 mL/min. Approximate retention times for **2**, **3**, **4**, **5**, **6**, **8**, and **9** were 540, 650, 850, 630, 680, 670, and 500 s, respectively.

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Registry No. **2**, 787-93-9; **3**, 109306-93-6; **4**, 109306-94-7; **5**, 794-98-9; **6**, 107634-10-6; **7**, 109306-95-8; 2,6-dimethylaniline, 87-62-7; 4-nitrobenzoyl chloride, 122-04-3; 3-methyl-4-nitrobenzoyl chloride, 35675-46-8; 3,5-dimethyl-4-nitrobenzoyl chloride, 3558-73-4; 4-nitro-*N*-(2,6-dimethylphenyl)benzamide, 64594-44-1; 4-nitro-3-methyl-*N*-(2,6-dimethylphenyl)benzamide, 109306-96-9; 4-nitro-3,5-dimethyl-*N*-(2,6-dimethylphenyl)benzamide, 109306-97-0; cytochrome P-450, 9035-51-2.

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Synthesis of Potential Anticancer Agents: Imidazo[4,5-*c*]pyridines and Imidazo[4,5-*b*]pyridines

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The 1,2-dihydropyrido[3,4-*b*]pyrazines (**1**) are mitotic inhibitors with significant antitumor activity in mice. Also, the active imidazo[4,5-*b*]pyridine **3** was shown to cause the accumulation of cells at mitosis. Routes were developed for the synthesis of congeners of **3** by cyclization of 4-(substituted amino)-5,6-diaminopyridines with ethyl orthoformate. Oxidative cyclization of either 4,5- or 5,6-diaminopyridines with aryl aldehydes produced the [4,5-*c*] and [4,5-*b*] imidazopyridine ring systems, respectively. The latter reaction with 6-(substituted amino)-4,5-diaminopyridines gave imidazo[4,5-*c*]pyridine ring analogues of **1**. Biological studies indicated that the target compounds were less active than **1** and **3**.

The 1,2-dihydropyrido[3,4-*b*]pyrazines (e.g., **1**)[1,2] and 2*H*-pyrido[4,3-*b*][1,4]oxazines (e.g., **2**)[3] have shown significant antitumor activity in mice (see Scheme I). These compounds appear to interfere with cell division by binding to a cellular protein, tubulin, at a site that is different from that at which the clinically used antimitotic drug vincristine reacts.[4,5] Since the 1,2-dihydropyrido-[3,4-*b*]pyrazines are subject to air oxidation to the corresponding inactive heteroaromatic compounds,[2] metabolic

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Table I. Ethyl 5-Nitropyridin-2-ylcarbamates

compd	reaction time, h	yield, %	mp, °C	^{1}H NMR:[a] pyridine CH	formula	anal.
5a	16	88	156–157	6.93 (A)	$C_{14}H_{15}N_5O_4$	C, H, N
5b	16	89	132–133	6.87 (B)	$C_{15}H_{17}N_5O_4$	C, H, N
5c	16	82	147–148[b]	6.84 (B)	$C_{16}H_{19}N_5O_4$	C, H, N
5d	16	88	73–74[c]	6.79 (B)	$C_{18}H_{23}N_5O_4$	C, H, N
11	—[d]	84	>260 dec	—	$C_8H_{12}N_6O_4$	C, H, N

[a] Chemical shift (δ) determined in Me_2SO-d_6 (A) and $CDCl_3$ (B). [b] Prior sintering. [c] First crop; second crop (17%) and third crop (3%) were isolated in different crystalline forms, mp 83–84 °C and 103–104 °C, respectively. [d] See Experimental Section.

Table II. Ethyl 5-Aminopyridin-2-ylcarbamates

compd	reaction time, h	yield, %	mp, °C	^{1}H NMR:[a] pyridine CH	formula	anal.
6a	6	95	225–228 dec[b]	6.40	$C_{14}H_{17}N_5O_2 \cdot 2HCl$	C, H, Cl, N
6b	4	95	>178 dec	6.02	$C_{15}H_{19}N_5O_2 \cdot 1.85HCl$	C, H, Cl, N
6c	5	84	>125 dec	6.15	$C_{16}H_{21}N_5O_2 \cdot 2HCl$	C, H, Cl, N
6d	6	88	>197 dec	6.20	$C_{18}H_{25}N_5O_2 \cdot 2HCl$	C, H, Cl, N
12	—[c]	67[d]	>150 dec	6.13	$C_8H_{13}N_5O_2 \cdot 1.9HCl \cdot 0.05EtOH \cdot 0.9H_2O$[e]	C, H, Cl, N
19	—[c]	79	193	—	$C_8H_{11}ClN_4O_2$	C, H, N

[a] Chemical shift (δ) determined in Me_2SO-d_6; decomposition (**6a–d**) was indicated by the change in color of the solution and the formation of new peaks. [b] Prior sintering. [c] See Experimental Section. [d] Method A. [e] Ethanol observed in ^{1}H NMR spectrum at δ 1.05 and 3.43; H_2O and HCl at δ 6.8–8.2.

oxidation was considered to be an inactivation pathway in vivo.[6] In a continuing effort to develop more effective compounds, the synthesis of the more stable imidazo[4,5-*c*]pyridine (3-deazapurine) analogues of **1** was investigated. In addition, on the basis of the activity of an imidazo[4,5-*b*]pyridine (1-deazapurine) (**3**) reported earlier, congeners of this compound were prepared.[8]

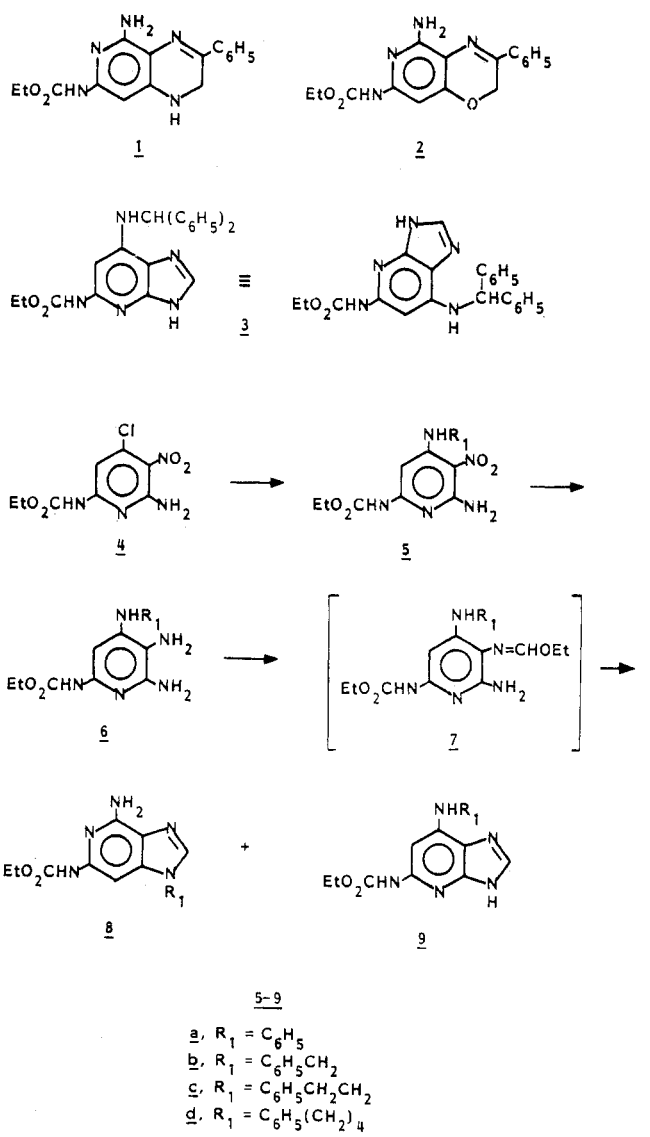
Chemistry. Previously we reported that replacement of the (diphenylmethyl)amino group of **3** with amino, dimethylamino, or [bis(4-chlorophenyl)methyl]amino groups reduced activity.[8] Orientation of the pyridine ring nitrogen of **3** to match that of **1** suggested that active compounds might result from increasing the length of the aliphatic chain connecting the amino and phenyl groups. For this study, the 1-deazapurines **9a–d** were prepared in which the amino group was substituted with phenyl, benzyl, phenethyl, and 4-phenylbutyl moieties (Scheme I).

Reaction of **4**[9] with an equimolar of freshly distilled aniline in hot ethanol containing triethylamine as the acid acceptor provided the 4-anilino-5-nitropyridine **5a** in high yield (Table I). Hydrogenation of **5a** in ethanol in the presence of Raney nickel afforded the 5-aminopyridine **6a**, which precipitated during the reaction.[10] Separation of **6a** in high yield (Table II) from the catalyst was effected by dissolution of the product with hydrochloric acid. Similar procedures were used for the synthesis of **5b–d** and **6b–d**.

Although the cyclization of **6** with ethyl orthoformate should give two isomeric deazapurines (**8** and **9**), previous work indicated that steric hindrance between the 5-(ethoxymethylene)amino and the substituted 4-amino groups in intermediate **7** favored cyclization through the 6-amino group to give the 1-deazapurine **9**.[8] Treatment of **6a** with ethyl orthoformate and concentrated hydrochloric acid gave a mixture of **8a** and **9a**, which were separated by fractional crystallization from ethanol to give **9a** (Table III) in 36% yield and **8a** (Table IV) in 15% yield.

In the cyclization of **6b**, the methylene group between the phenyl ring and nitrogen of the amino group had a

Scheme I



(6) Recent work indicated little or no metabolic oxidation in mice; see ref 7.
(7) Noker, P. E.; Hill, D. L.; Kalin, J. R.; Temple, C. G.; Montgomery, J. A. *Drug Metab. Dispos.* **1985**, *13*, 677.
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(9) Elliott, R. D.; Temple, C., Jr.; Montgomery, J. A. *J. Org. Chem.* **1966**, *31*, 1890.
(10) Compounds **6b–d** remained in solution during the hydrogenation reaction.

Table III. Ethyl 3*H*-Imidazo[4,5-*b*]pyridin-5-ylcarbamates

compd	reaction time, h	yield, %	mp, °C	^{1}H NMR[a] 6-CH	^{1}H NMR[a] 2-CH	mass spectrum, *m/e*	formula	anal.
9a[b]	216	36	>280 dec	7.55	8.60	297 $(M)^+$	$C_{15}H_{15}N_5O_2 \cdot 0.5HCl$	C, H, Cl, N
9b[c]	240	70	235[d]	6.92	8.69	311 $(M)^+$	$C_{16}H_{17}N_5O_2 \cdot HCl$	C, H, Cl, N
9c	240	47	221–222 dec[e]	6.90	8.72	325 $(M)^+$	$C_{17}H_{19}N_5O_2 \cdot HCl$	C, H, Cl, N
9d	240	72	160–161[f]	6.82	8.66	353 $(M)^+$	$C_{19}H_{23}N_5O_2 \cdot HCl$	C, H, Cl, N
13	4.5	22.5	>300	7.02[g]		297 $(M)^+$	$C_{15}H_{15}N_5O_2 \cdot 0.1H_2O$	C, H, N
15	64	39	278–280 dec	7.88		316 $(M)^+$	$C_{15}H_{13}ClN_4O_2$	C, H, N
16	2	64	>300	7.69[h]			$C_{12}H_9ClN_4 \cdot 0.5HCl \cdot 0.5H_2O$	C, H, N
25	—[i]	16	>300 dec[j]	6.78[k]		508 $(M + 1)^+$	$C_{29}H_{25}N_5O_4 \cdot 0.1CHCl_3$	C, H, N
28	17	62	>300	6.72[l]		342 $(M + 1)^+$	$C_{16}H_{15}N_5O_4 \cdot 2.5HCl \cdot 0.5Et_2O$	C, H, N

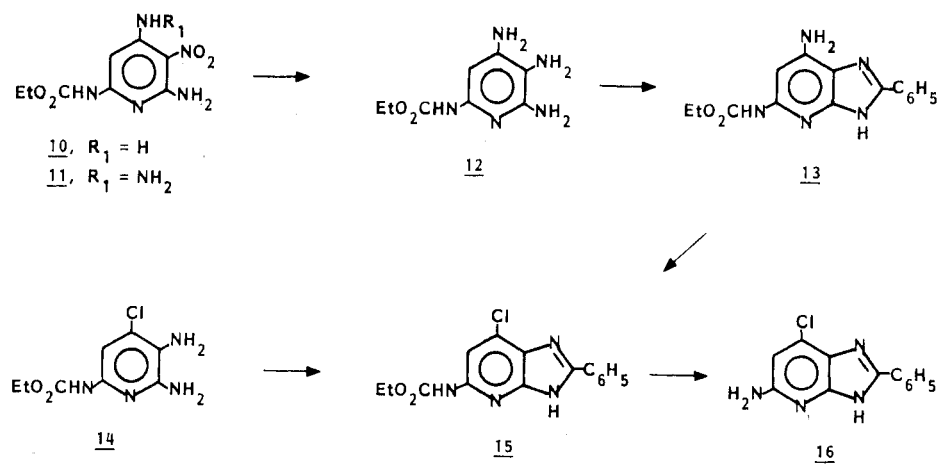
[a] Chemical shift (δ) determined in Me_2SO-d_6. [b] The isomeric imidazolo[4,5-*c*]pyridine **8a** was isolated (see Experimental Section). [c] Isomeric imidazolo[4,5-*c*]pyridine detected but not purified. [d] Gradual softening. [e] Softening from 202 °C. [f] Prior sintering. [g] H_2O observed in integral, δ 3.3. [h] H_2O and HCl observed in integral, δ 4–10. [i] See Experimental Section. [j] Glass formation at 150 °C. [k] CH of diphenylmethyl moiety. [l] Et_2O observed at δ 1.09, 3.38.

Table IV. 1*H*-Imidazo[4,5-*c*]pyridin-6-ylcarbamates

compd	reaction time, h	yield, %	mp, °C	^{1}H NMR:[a] 7-CH	mass spectrum, *m/e*	formula	anal.
8a	216	15	150–152 dec	6.94[b]	297 $(M)^+$	$C_{15}H_{15}N_5O_2 \cdot HCl \cdot H_2O$	C, H, Cl, N
21	—[c]	30	155–160	8.00	316 $(M)^+$	$C_{15}H_{13}ClN_4O_2 \cdot H_2O$	C, H, N
22	174	56	187–189	7.02	482 $(M)^+$	$C_{28}H_{23}ClN_4O_2$	C, H, N
24a	168	58	191[d]	6.86 d[e,f]	464 $(M + 1)^+$	$C_{28}H_{25}N_5O_2 \cdot 0.4EtOH \cdot 1.4H_2O$	C, H, N
24b	168	67	255–260 dec	6.83 d[e]	494 $(M + 1)^+$	$C_{29}H_{27}N_5O_3$	C, H, N
24c	—[c]	48	>300 dec[g]	6.85 d[e,f]	508 $(M + 1)^+$	$C_{29}H_{25}N_5O_4 \cdot 0.3H_2O$	C, H, N
24d	—[h]	50	>300 dec	7.05 d[i]	480 $(M + 1)^+$	$C_{28}H_{25}N_5O_3 \cdot 0.3HCl$	C, H, N
26	—[c]	24	285–290 dec	—[j]	343 $(M + 1)^+$	$C_{15}H_{14}N_6O_4 \cdot 0.1MeOH \cdot 0.3H_2O$	C, H, N
27a	144	78	290–295 dec	6.91	298 $(M + 1)^+$	$C_{15}H_{15}N_5O_2 \cdot 2.1HCl$	C, H, N
27b	164	40.5	>300 dec	6.87[k]	328 $(M + 1)^+$	$C_{16}H_{17}N_5O_3 \cdot 2HCl \cdot 0.1PrOH \cdot H_2O$	C, H, N
27c	48	75	>300 dec	6.81[l]	342 $(M + 1)^+$	$C_{16}H_{15}N_5O_4 \cdot 3HCl \cdot 0.3Et_2O$	C, H, N
27d	165	82	>300 dec	6.87[m]	314 $(M + 1)^+$	$C_{15}H_{15}N_5O_3 \cdot 2HCl \cdot 1.4H_2O$	C, H, N[n]

[a] Chemical shift (δ) determined in Me_2SO-d_6; 7-CH unless otherwise noted. [b] 2-CH, δ 8.68. [c] See Experimental Section. [d] Glass formation at 115 °C. [e] CH of diphenylmethyl moiety. [f] H_2O observed at δ 3.3–3.4. [g] Glass formation at 140 °C. [h] See Experimental Section, preparation of **24c**. [i] NH of (diphenylmethyl)amino moiety. [j] MeOH observed at δ 3.17 d. [k] PrOH observed at δ 0.82, 1.41, 3.33. [l] Et_2O observed at δ 1.04, 3.43. [m] H_2O and HCl observed at δ 5.5–7.5. [n] N: calcd, 17.02; found, 16.55.

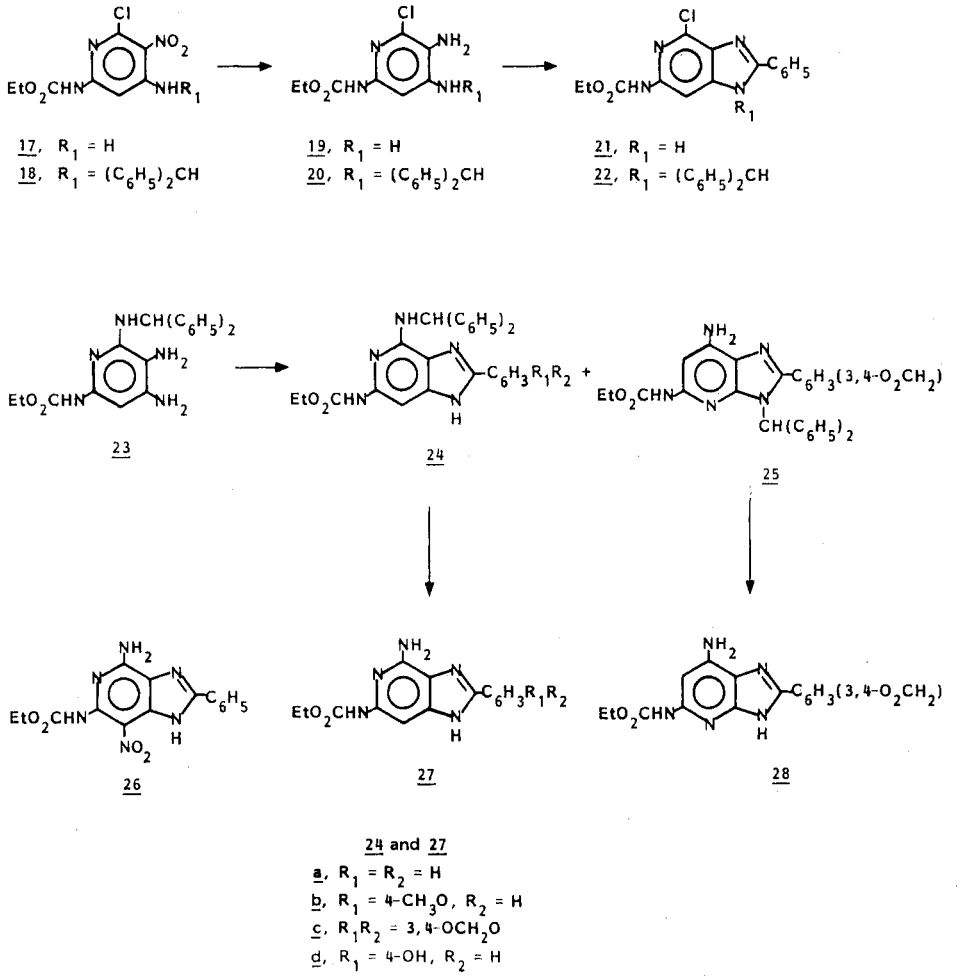
Scheme II



pronounced effect on the yield of **9b**. The latter was isolated in 70% yield, whereas **8b**, contaminated with **9b**, was isolated in only 7.7% yield. Cyclization of **6c**, with ethylene as a spacer group, appeared to give only one isomer, **9c**, in 47% yield. An additional amount of **9c** (<33%) was isolated as a mixture with a formyl derivative of **6c**, presumably formed by hydrolysis of the (ethoxymethylene)amino intermediate **7c**. With the butylene spacer group, **6d** gave a 72% yield of **9d** and about a 16% yield of impure **8d**. Although the relative nucleophilicities of the 4- and 6-amino groups of **7** under acidic conditions are probably important in determining the direction of cyclization, our results indicate that the length of the aliphatic spacer chain in **7** determines the amount of **8** formed. The structures of these products are based on spectral data. The ^{1}H NMR spectrum of **9b** showed spin–spin coupling between the CH_2 (δ 4.60, d) and NH (δ 9.05, t) of the benzylamino group. Both **9c** and **9d** showed broad multiplets for the corresponding CH_2 and NH for which the assignments were verified by spin decoupling. The structures of **8a** and **9a** were confirmed by UV spectra. In the 270–305-nm range, **9a–d** gave single peaks of 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH. The peak in base, relative to that in a neutral medium, was shifted 6–7 nm to a higher wavelength, which is attributed to ionization of the acidic imidazole NH of **9a–d**. For the same range, **8a** gave two peaks in 0.1 N HCl and superimposable curves in pH 7 buffer and 0.1 N NaOH.

In the approach to 8-phenyl-3-deazapurines, the oxidative cyclization of the 4,5,6-triaminopyridine **12** with aryl

Scheme III



aldehydes was considered although we realized that both 1- and 3-deazapurines might be formed (Scheme II). Previously, the nitropyridine **10** was prepared by treatment of **4** with ethanolic ammonia.[9] On a large scale, mass spectral data indicated that this reaction generated impurities resulting from the cleavage of the urethane groups of both **4** and **10**. Removal of these impurities could be effected by recrystallization from ethanol or acetic acid with the resulting loss in yield of **10**. In addition, one experiment suggested that complete conversion of **10** to **12** by hydrogenation over Raney nickel would be difficult.[11] These problems were circumvented by reaction of **4** with hydrazine to give **11**[12] followed by hydrogenation to effect simultaneous reduction of the nitro group and cleavage of the hydrazino group to give **12** in 67% yield. During this time the hydrogenation of **10** in the presence of benzaldehyde was carried out. This reaction gave a complex mixture, but a major component was separated by chromatography and identified as the 1-deazapurine **13**. Because of this result, the procedure developed for the preparation of **12** was not fully utilized in this work.

To confirm the structure of **13**, the amino group was diazotized in hydrochloric acid and the resulting diazo group was replaced by a chloro group. The product **15** was prepared by an unambiguous route involving the oxidative cyclization of the 4-chloropyridine **14** with benzaldehyde.[13] Cleavage of the urethane group of **15** to give **16** was effected with ethanolic KOH.

The oxidative cyclization of 4,5-diaminopyridines with aryl aldehydes was demonstrated with **19** and **20** (Scheme III). The former was prepared from **17**[14] and the latter from **18**.[9] Reaction of **19** and **20** with benzaldehyde provided acceptable yields of **21** and **22**, respectively. These results suggested that a bulky substituent on the 6-amino group of **12** would direct cyclization to the 3-deazapurine ring system.

The reaction of the 6-[(diphenylmethyl)amino]pyridine **23**[15] with the sodium bisulfite addition product of benzaldehyde and 4-methoxybenzaldehyde gave good yields of **24a,b**. Apparently, this type of reaction involves the formation of a dihydro intermediate and bisulfite in which the latter acts as an oxidizing agent in the generation of product.[16] However, the reaction of **23** with 4-hydroxybenzaldehyde at reflux in methanol to give **24d** indicated that good yields could be obtained in the absence of bisulfite. Unexpectedly, reaction of **23** with 3,4-(methylenedioxy)benzaldehyde in methanol either at room temperature or at reflux gave a 48% yield of **24c** and a 16% yield of the 1-deazapurine **25**. This result suggested that strong electron-donating groups in the aryl ring increased the rate of air oxidation of the dihydro precursor leading to **25** relative to that leading to **24c**. The structures of

(11) Elliott et al. reported the in situ preparation of **12**: Elliott, R. D.; Temple, C., Jr.; Montgomery, J. A. *J. Org. Chem.* **1968**, *33*, 2393.
(12) Wood, N. F., originally prepared **11** in our laboratories.
(13) Temple, C., Jr.; Smith, B. H., Jr.; Montgomery, J. A. *J. Org. Chem.* **1973**, *38*, 613.
(14) Elliott, R. D.; Temple, C., Jr.; Frye, J. L.; Montgomery, J. A. *J. Org. Chem.* **1971**, *36*, 2818.
(15) Temple, C., Jr.; Smith, B. H., Jr.; Montgomery, J. A. *J. Org. Chem.* **1973**, *38*, 1095.
(16) Ridley, H. F.; Spickett, R. G. W.; Timmis, G. M. *J. Heterocycl. Chem.* **1965**, *2*, 453.

24a–d were confirmed by the ^1H NMR spectra in which spin–spin coupling was observed between the NH and CH of the (diphenylmethyl)amino moiety.

No difficulties were encountered in removal of the diphenylmethyl blocking group of **24a–d** and **25** with concentrated HCl at room temperature to give **27a–d** and **28**, respectively. As expected, treatment of **27a** with nitric acid resulted in electrophilic substitution in the pyridine rather than the phenyl ring to give **26**.

Biological Evaluation. The 1-deazapurine **3** was reported to give a 59% increase in life span at a dose of 40 mg/kg on a single dose schedule against L1210 leukemia.[8] At that time the identification of the site of action was unsuccessful. Comparison of the structure of **3** with the more recently prepared mitotic inhibitor **1**[1,2] suggested that **3** could be considered a ring-open analogue of **1**. On reevaluation,[5] **3** inhibited the proliferation of cultured L1210 cells (IC_{50} = 0.37 μM) and caused the accumulation of mitotic cells ($MI_{0.5}$ = 1.15 μM) at a similar concentration.

The 1-deazapurines **9a–d** were evaluated for cytotoxicity in the KB cell culture screen.[17] Only **9a** (ED_{50} = 9.5 μM) was active at less than 10 μM, and none showed activity against L1210 leukemia in mice on a day 1 schedule. The remaining 1-deazapurines **13**, **15**, **16**, **25**, and **28** were inactive in cultured L1210 cells, and **16** gave no increase in life span against P388 leukemia in mice on a single dose schedule. Similarly, the precursors to the 1-deazapurines (**5a–d**, **6a–d**, **10**, **11**, **12**, and **14**) showed no significant cytotoxicity in cell culture.

In the 3-deazapurine series, **27a** inhibited the proliferation of cultured L1210 cells (IC_{50} = 1.7 μM) and showed antimitotic activity ($MI_{0.5}$ = 7 μM). Although the presence of electron-donating groups in the phenyl ring was expected to increase activity, **27b–d** were less cytotoxic than **27a**. In addition, **27a,b** gave no increase in life span against P388 in mice on a chronic schedule. Similarly, the 3-deazapurines **8a**, **21**, **22**, **24a–d** and **26** as well as the precursors **19** and **23** were inactive in cell culture. In conclusion, deazapurines containing a number of structural variations were prepared and shown to be less active than the model compounds **1**, **2**, and **3**. The ring NH and aryl substituent in **1** are necessary for activity and thus probably contribute to the binding of **1** to tubulin.[2,5] The disappointing activity of **27a–d**, relative to **1**, might be attributed to the conformation of the aryl ring and the decreased basicity of the imidazole ring nitrogen.

Experimental Section

Melting and decomposition temperatures were determined in capillary tubes in a Mel-Temp apparatus. The ^1H NMR spectra were determined either with a Varian XL-100-15 or Nicolet NT 300NB spectrometer with tetramethylsilane as internal standard; d = doublet, m = multiplet. Mass spectra were taken with a Varian Mat 311A spectrometer operating in either the electron-impact or fast-atom-bombardment mode to provide the M^+ and $(M + 1)^+$ molecular ions, respectively. The progress of reactions was followed by thin-layer chromatography (TLC) on plates of silica gel, which were usually developed with mixtures of $CHCl_3$ and MeOH. Raney nickel no. 2800 was obtained from Davison Specialty Chemical Company. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

General Procedure (5a–d). Ethyl 6-Amino-5-nitro-4-[(phenylmethyl)amino]pyridin-2-ylcarbamate (5b). A mixture of **4** (4.00 g, 15.3 mmol),[9] benzylamine (1.97 g, 18.4 mmol), and triethylamine (1.57 g, 15.5 mmol) in ethanol (100 mL) was refluxed with stirring under a N_2 atmosphere for 16 h. The reaction mixture was evaporated to dryness in vacuo, and the residue was washed by stirring with water. The resulting dried solid was recrystallized from ethanol (230 mL) to give fluorescent yellow needles, which were collected by filtration and dried in vacuo over P_2O_5 at 65 °C; yield, 3.97 g.

Evaporation of the recrystallization filtrate to 50 mL followed by recrystallization (EtOH) of the collected precipitate gave a second crop: yield, 0.56 g.

General Procedure (6a–d). Ethyl 5,6-Diamino-4-(phenylamino)pyridin-2-ylcarbamate Dihydrochloride (6a). A suspension of **5a** (4.00 g, 12.6 mmol) and Raney nickel (~5 g, wet, washed with H_2O and EtOH) in ethanol (200 mL) was stirred rapidly under hydrogen at atmospheric pressure and room temperature. The white solid that precipitated during the hydrogenation was dissolved by the addition of concentrated HCl (1 mL) (no precipitation was observed during the formation of **6b–d**). The catalyst was removed by filtration through Celite into a flask containing concentrated HCl (1.5 mL), and the clear filtrate was evaporated to dryness in vacuo. A solution of the residue in ethanol (75 mL) under N_2 was diluted slowly with ether (800 mL) to deposit a dense white crystalline solid: yield, 4.31 g.

General Procedure (9a–d). Ethyl 7-(Phenylamino)-3*H*-imidazo[4,5-*b*]pyridin-5-ylcarbamate (9a) and Ethyl 1-Phenyl-1*H*-imidazo[4,5-*c*]pyridin-6-ylcarbamate (8a). A suspension of **6a**·2HCl (3.82 g, 10.6 mmol) in triethyl orthoformate (80 mL) containing concentrated HCl (0.88 mL, ~11 mmol) was stirred at room temperature under N_2 for 216 h. The progress of the reaction was followed by TLC. The white solid was collected by filtration under N_2 pressure and washed liberally with Et_2O to give a mixture of **8a** and **9a**: yield, 3.40 g. The isomers were separated by fractional crystallization from ethanol (100 mL). Crops of each isomer, as determined by TLC, were combined and again recrystallized from ethanol: yield, 1.19 g (**9a**) and 0.58 g (**8a**).

In the purification of **9b** by fractional recrystallization from ethanol, the final filtrate provided a residue, which was recrystallized from ethanol–ether to give impure **8b**: yield, 236 mg. The filtrate from **9c** gave a mixture of **9c** and noncyclized pyridine intermediates (TLC, ^1H NMR, MS): yield, 1.04 g. In the purification of **9d**, the final filtrate was diluted with ether to give a mixture of **8d** contaminated with **9d** (TLC, ^1H NMR, MS): yield, 0.63 g.

Ethyl 6-Amino-4-hydrazino-5-nitropyridin-2-ylcarbamate (11).[12] A hot solution of **4** (2.34 g, 9.00 mmol) and anhydrous hydrazine (4.00 mL, ~119 mmol) in ethanol (60 mL) was refluxed with mechanical stirring for 1 h. After cooling of the reaction mixture, the product was collected by filtration, washed with H_2O, and dried in vacuo over P_2O_5: yield, 1.93 g; mass spectrum, m/e 256 (M^+).

Ethyl 4,5,6-Triaminopyridin-2-ylcarbamate (12).[11] **Method A.** A suspension of **11** (500 mg, 1.95 mmol) in 1:1 ethanol–water (100 mL) was hydrogenated in the presence of Raney nickel (1.5 g, wet, washed with water) at room temperature and atmospheric pressure. The theoretical volume of H_2 (4 molar equiv) was absorbed in 3.5 h. After removal of the catalyst by filtration through Celite, the pale pink filtrate was evaporated to give a light amber glass, which was treated with 1.02 N ethanolic HCl (3.8 mL). The light beige solid was collected by filtration and dried in vacuo over P_2O_5: yield, 392 mg; mass spectrum, m/e 212 $(M + 1)^+$.

Method B. A suspension of **10** (150 mg, 0.620 mmol)[9] in ethanol (15 mL) containing Raney nickel (0.3 g, wet, washed with water, then ethanol) was hydrogenated as described in method A. The H_2 uptake was 98% of the calculated amount in about 3 h. The product was isolated as its hydrochloride (182 mg, 89%); however, the ^1H NMR spectrum showed the presence of about 10% of **10**.

Ethyl 7-Amino-2-phenyl-3*H*-imidazo[4,5-*b*]pyridin-5-ylcarbamate (13). A suspension of **10** (501 mg, 2.08 mmol)[9] and benzaldehyde (220 mg, 2.07 mmol) in ethanol (65 mL) was hydrogenated over Raney nickel (0.5 g, washed with H_2O and EtOH) at atmospheric pressure and room temperature. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to dryness in vacuo to give a complex mixture (TLC). A major component (**13**) was isolated by silica gel chromatography

(17) Geran, R. I.; Greenberg, N. H.; Macdonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(2).

(95:5 $CHCl_3$–MeOH): yield, 140 mg.

Ethyl 7-Chloro-2-phenyl-3*H*-imidazo[4,5-*b*]pyridin-5-ylcarbamate (15). A. A mixture of **14**·HCl (1.00 g, 4.32 mmol),[13] benzaldehyde (0.460 g, 4.34 mmol), and KOAc (0.423 g, 4.32 mmol) in ethanol (75 mL) was stirred at room temperature for 64 h. After evaporation of the mixture to dryness in vacuo, the residue was washed with H_2O, and the resulting dried solid was fractionally recrystallized from ethanol: yield, 0.530 g.

B. A solution of **13** (40 mg, 0.13 mmol) in concentrated HCl (5 mL) was treated with a solution of $NaNO_2$ (11 mg, 0.16 mmol) in H_2O (1 mL). After the mixture was stirred at room temperature for 64 h, the insoluble material was removed by filtration and the filtrate was concentrated to deposit crude **15**. Purification of this material was effected by silica gel chromatography (95:5 $CHCl_3$–MeOH): yield, 9 mg. The ^1H NMR spectrum of a mixture of this material and that prepared in A showed that both preparations gave **15**.

5-Amino-7-chloro-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (16). A solution of **15** (236 mg, 0.746 mmol) and KOH (472 mg, 8.43 mmol) in propanol (10 mL), protected with a $CaCl_2$–NaOH drying tube, was refluxed for 2 h and evaporated to dryness in vacuo. The residue was dissolved in H_2O (10 mL) and adjusted to pH 1 (paper) with concentrated HCl. After the mixture was stirred at room temperature for 2 h, the product was collected by filtration and dried in vacuo over P_2O_5: yield, 130 mg.

Ethyl 4,5-Diamino-6-chloropyridin-2-ylcarbamate (19). A solution of **17** (5.00 g, 19.2 mmol)[9,14] in ethanol (250 mL) containing Raney nickel (5 g, wet, washed with H_2O and EtOH) was hydrogenated under atmospheric pressure at room temperature for 200 min. The catalyst was removed by filtration through Celite and washed with hot ethanol (40 mL). The filtrate was evaporated to dryness in vacuo, and the residue was washed with ethanol (25 mL) and then ether (10 mL) and dried in vacuo over P_2O_5: yield, 3.51 g; mass spectrum, m/e 230 (M^+).

Ethyl 4-Chloro-2-phenyl-1*H*-imidazo[4,5-*c*]pyridin-6-ylcarbamate (21). A solution of **19**·HCl (516 mg, 1.93 mmol), benzaldehyde (206 mg, 1.94 mmol), and KOAc (190 mg, 1.94 mmol) in ethanol (30 mL) was refluxed with stirring for 9 h each day until TLC indicated the absence of **19**. After 9 days the reaction mixture was evaporated to dryness, and the residue was washed with H_2O containing 1 N NaOH (2 drops) and then with 1:1 hexane–tetrahydrofuran: yield, 195 mg.

Ethyl 4-Chloro-2-phenyl-1-(diphenylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-6-ylcarbamate (22). A solution of **18** (500 mg, 1.17 mmol)[9] in ethanol (60 mL) containing Raney nickel (0.5 g, wet, washed with H_2O and EtOH) was hydrogenated under atmospheric pressure at room temperature for 11 h. The uptake of H_2 was 133% of the theoretical value. On the basis of mass spectral data, overreduction was attributed in part to dehydrochlorination of **18**. The catalyst was removed by filtration and washed with hot ethanol (50 mL). The filtrate containing **20**[15] was concentrated to one-half volume followed by the addition of benzaldehyde (137 mg, 1.29 mmol). After being stirred at room temperature for 174 h, the reaction mixture was evaporated to dryness, and the resulting residue was extracted with ether. A solution in $CHCl_3$ of the residue from evaporation of the ether extract was eluted from a silica gel column (25 g) with $CHCl_3$. The product-containing fractions were evaporated, and the resulting residue was recrystallized from ether at −78 °C: yield, 320 mg.

General Procedure (24a,b). Ethyl 2-(4-Methoxyphenyl)-4-[(diphenylmethyl)amino]-1*H*-imidazo[4,5-*c*]pyridin-6-ylcarbamate (24b). The sodium bisulfite addition product of 4-methoxybenzaldehyde (2.17 g, 9.03 mmol) was added with stirring to a suspension of **23**·2HCl (3.66 g, 8.13 mmol)[15] in deoxygenated (N_2) ethanol (360 mL) containing sodium ethoxide (1 g). After 168 h at room temperature, the precipitate was collected by filtration, washed with ethanol (50 mL) and then water (100 mL), and recrystallized from propanol (275 mL): yield, 2.70 g. On TLC this material showed a single spot, but the ^1H NMR spectrum indicated the presence of less than 10% of a second component. The peaks coalesced on the addition of a drop of deuteriated trifluoroacetic acid, which indicated the presence of NH tautomers in the original spectrum.

Ethyl 2-[3,4-(Methylenedioxy)phenyl]-4-[(diphenylmethyl)amino]-1*H*-imidazo[4,5-*c*]pyridin-6-ylcarbamate (24c) and Ethyl 7-Amino-2-[3,4-(methylenedioxy)phenyl]-3-(diphenylmethyl)-3*H*-imidazo[4,5-*b*]pyridin-5-ylcarbamate (25). To a stirred solution of **23**·HCl (102 mg, 0.226 mmol)[15] in methanol (10 mL) was added anhydrous sodium acetate (37 mg, 0.45 mmol), followed by 3,4-(methylenedioxy)benzaldehyde (340 mg, 0.226 mmol). The clear solution was stirred at reflux for 3.5 h and then at 25 °C for 20 h, and the resulting amber solution was evaporated to dryness in vacuo. After evaporation of several portions of benzene from the dark semisolid, the resulting residue was purified by column chromatography (20 g, $CHCl_3$) to give **24c** as a beige glass: yield, 56 mg.

Further development of the column afforded **25** as a beige solid: yield, 18 mg.

This reaction was repeated at room temperature for 20 h to provide similar amounts of **24c** and **25**.

Ethyl 4-Amino-7-nitro-2-phenyl-1*H*-imidazo[4,5-*c*]-pyridin-6-ylcarbamate (26). A solution of **27a** (104 mg, 0.280 mmol) in concentrated H_2SO_4 (2 mL) at 0 °C was treated with 70% HNO_3 (17 μL, 0.27 mmol), and the resulting yellow solution was stirred at 25 °C for 22 h. The reaction mixture was added dropwise to ice (15 g), and the yellow solid was collected by filtration, washed with water (2 × 5 mL), and recrystallized from methanol (30 mL) to afford yellow needles: yield, 23.5 mg.

General Procedure for Removal of Diphenylmethyl Groups. Ethyl 4-Amino-2-(4-methoxyphenyl)-1*H*-imidazo-[4,5-*c*]pyridin-6-ylcarbamate (27b). A suspension of **24b** (2.20 g, 4.46 mmol) in concentrated HCl (100 mL) was stirred vigorously at 25 °C for 164 h, and the insoluble material was collected by filtration. The white solid was dried in vacuo over NaOH, washed with Et_2O (2 × 30 mL), and recrystallized from propanol (450 mL): yield, 0.77 g.

A second crop (0.91 g) containing 15–20% of **24b** was obtained by evaporation of the propanol filtrate.

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Registry No. **4**, 6506-86-1; **5a**, 109182-31-2; **5b**, 109182-32-3; **5c**, 109182-33-4; **5d**, 109182-34-5; **6a**·2HCl, 109182-35-6; **6b**·2HCl, 109182-36-7; **6c**·2HCl, 109182-37-8; **6d**·2HCl, 109182-38-9; **8a**, 109182-67-4; **8a**·HCl, 109182-59-4; **8b**, 109182-63-0; **8d**, 109182-64-1; **9a**, 109217-56-3; **9a**·$^1/_2$HCl, 109182-60-7; **9b**, 109182-68-5; **9b**·HCl, 109217-54-1; **9c**, 109182-70-9; **9c**·HCl, 109182-61-8; **9d**, 109182-71-0; **9d**·HCl, 109182-62-9; **10**, 6502-02-9; **10**·HCl, 109182-39-0; **11**, 109182-40-3; **12**·2HCl, 109182-41-4; **13**, 109182-42-5; **14**·HCl, 37436-93-4; **15**, 109182-43-6; **16**, 109217-55-2; **16**·$^1/_2$HCl, 109182-44-7; **17**, 6502-04-1; **18**, 6497-85-4; **19**, 109182-45-8; **19**·HCl, 109182-51-6; **20**, 109182-46-9; **21**, 109182-47-0; **22**, 109182-48-1; **23**·2HCl, 38359-80-7; **24a**, 109182-53-8; **24b**, 109182-54-9; **24c**, 109182-55-0; **24d**, 109182-56-1; **25**, 109182-49-2; **26**, 109182-50-5; **27a**, 109182-69-6; **27a**·2HCl, 109182-57-2; **27b**, 109217-57-4; **27b**·2HCl, 109182-58-3; **27c**, 109182-72-1; **27c**·3HCl, 109182-65-2; **27d**, 109182-73-2; **27d**·2HCl, 109182-66-3; **28**, 109182-74-3; **28**·$^5/_2$HCl, 109182-52-7; 4-$MeOC_6H_4CH(OH)SO_3Na$, 33402-67-4; $PhCH(OH)SO_3Na$, 4657-12-9; 3,4-(methylenedioxy)benzaldehyde, 120-57-0.