A general synthesis of 5,7-diaminoimidazo[4,5-*b*]pyridine ribosides ("2-amino-1-deazaadenosines") from 5-amino-4-imidazolecarboxamide riboside (AICA riboside)

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This paper is dedicated to Professor Zdenek (Denny) Valenta on the occasion of his 65th birthday

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A short general synthesis of 5-substituted 5,7-diaminoimidazo[4,5-*b*]pyridines from 5-amino-4-imidazolecarboxamide riboside (AICA riboside) was designed to prepare isosteres of substituted 2-aminoadenosines that are selective adenosine A_2 receptor agonists. AICA riboside was converted to a hydroxyl-protected 5-amino-4-imidazolecarbonitrile riboside and reacted with an *N*,*N*-disubstituted acetamide in the presence of phosphoryl chloride. Sodium hydride treatment completed the ring closure and introduced the 7-amino group. The hydroxyl protecting groups were removed under standard conditions. *N*-Substitution of the acetamide by one benzyl moiety led to a 5-*N*-substituted derivative through hydrogenolysis whereas *N*,*N*-dibenzylacetamide led to the 5,7-diamino compound. A 6-methyl analog was obtained from an *N*,*N*-disubstituted propionamide. This synthesis may be adapted to other heterocyclic systems, as illustrated by the preparation of an example of the imidazo[4,5-*b*]pyrrolo[3,2-*e*]pyridine ring system.

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Dans le but de préparer des isostères des 2-aminoadénosines substituées qui sont des agonistes sélectifs du récepteur A_2 de l'adénosine, on a développé une courte méthode générale de synthèse des 5,7-diamino-imidazo[4,5-*b*]pyridines substituées en position 5 utilisant le riboside du 5-amino-4-imidazolecarboxamide (riboside du AICA) somme produit de départ. On a transformé le riboside du AICA en un riboside du 5-amino-4-imidazolecarbonitrile dont l'hydroxyle était protégé et on a fait réagir ce dernier avec un acétamide *N*,*N*-disubstitué, en présence de chlorure de phosphoryle. Un traitement avec de l'hydrure de sodium a permis de compléter la fermeture du cycle et l'introduction du groupe 7-amino. Utilisant des conditions standard, on a alors enlevé les groups protégeant les hydroxyles. La *N*-substitution de l'acétamide par une portion benzylique a conduit par hydrogénolyse à la formation d'un dérivé 5,*N*-substitué; dans les mêmes conditions, un *N*,*N*-dibenzylacétamide conduit au composé 5,7-diamino. À partir d'une propanamide *N*,*N*-disubstituée, on a obtenu un analogue portant un groupement méthyle en position 6. On peut adapter cette synthèse à d'autres systèmes hétérocycliques et on l'a illustré avec la préparation d'un exemple du système cyclique imidazo[4,5-*b*]pyrrolo[3,2-*e*]-pyridine.

[Traduit par la rédaction]

Adenosine (**1***a*), an endogenous purine nucleoside, was reported by Drury and Szent-Gyorgyi to have potent hypotensive and bradycardic activity in 1929 (*1*). In 1963, Berne (2) spurred additional interest when he proposed that adenosine plays an important role as the mediator of metabolically regulated coronary flow. Based on subsequent investigations (3), the role of adenosine as a local regulator of blood flow in other tissues was postulated. Although this short-acting compound seems an excellent lead structure for the design of novel cardiovascular drugs through molecular modification, research has not yet produced such a drug, except for the natural product itself, which was recently marketed[2] for the intravenous treatment of supraventricular tachycardia (4).

A recent rebirth of interest in modification of the adenosine structure (5) followed the recognition and characterization of purinergic receptors in peripheral cell membranes (6), particularly the A_1 and A_2 receptors (7, 8). The negative dromo-, chrono-, and inotropic effects of adenosine are thought to be A_1 mediated (9) whereas the vasodilatory effects are A_2 mediated (10).

Our interest in vasodilators led to a search for selective A_2 receptor agonists. A lead compound was the moderately A_2 selective agonist 2-anilinoadenosine (**1***b*) (11), which had been characterized as a coronary dilator in anaesthetized dogs (12) at the time we began our research. Subsequent modification of **1***b* led us to a series of 2-substituted aminoadenosines which were highly selective A_2 receptor agonists that lowered blood pressure effectively in spontaneously hypertensive rats (13).

Since 7-amino-3-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyridine (1-deazaadenosine, **2***a*) showed adenosine-like activity (14), it seemed worthwhile to prepare 1-deaza analogs structurally related to **1***b* and our active 2-aminoadenosines, i.e., 5,7-diaminoimidazo[4,5-*b*]pyridine ribosides of the general structure **2***b*. Ethyl *N*-(7-chloro-3*H*-imidazo[4,5-*b*]pyridin-5-yl)carbamate (**3**), prepared in nine steps from chelidamic acid (**4**) (15), was converted in nine further steps to structures of type **2***b* in which the R′ group is hydrogen and the *R*″ group is hydrogen, alkyl, or substituted alkyl (16).

Herein we report a much shorter and more general synthesis starting from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside, **5**), accessible chemically from inosine (17) or by fermentation (18). This had been used as a building block for **1***b* and many related 2-aminoadenosines (19) and contains all of the chiral centres and most of the atoms present in the compounds we planned to synthesize.

A route similar to the preparation of 2-alkylaminoadenosines from 2-chloroadenosine (**1***c*) (13) was not feasible in the 7-aminoimidazo[4,5-*b*]pyridine series because a halide at position 5 is not easily displaced. The report of a convenient synthesis of 2,4-diaminoquinoline derivatives (20) from anthranilonitriles suggested a viable route to our target compounds. We studied some variations of the published

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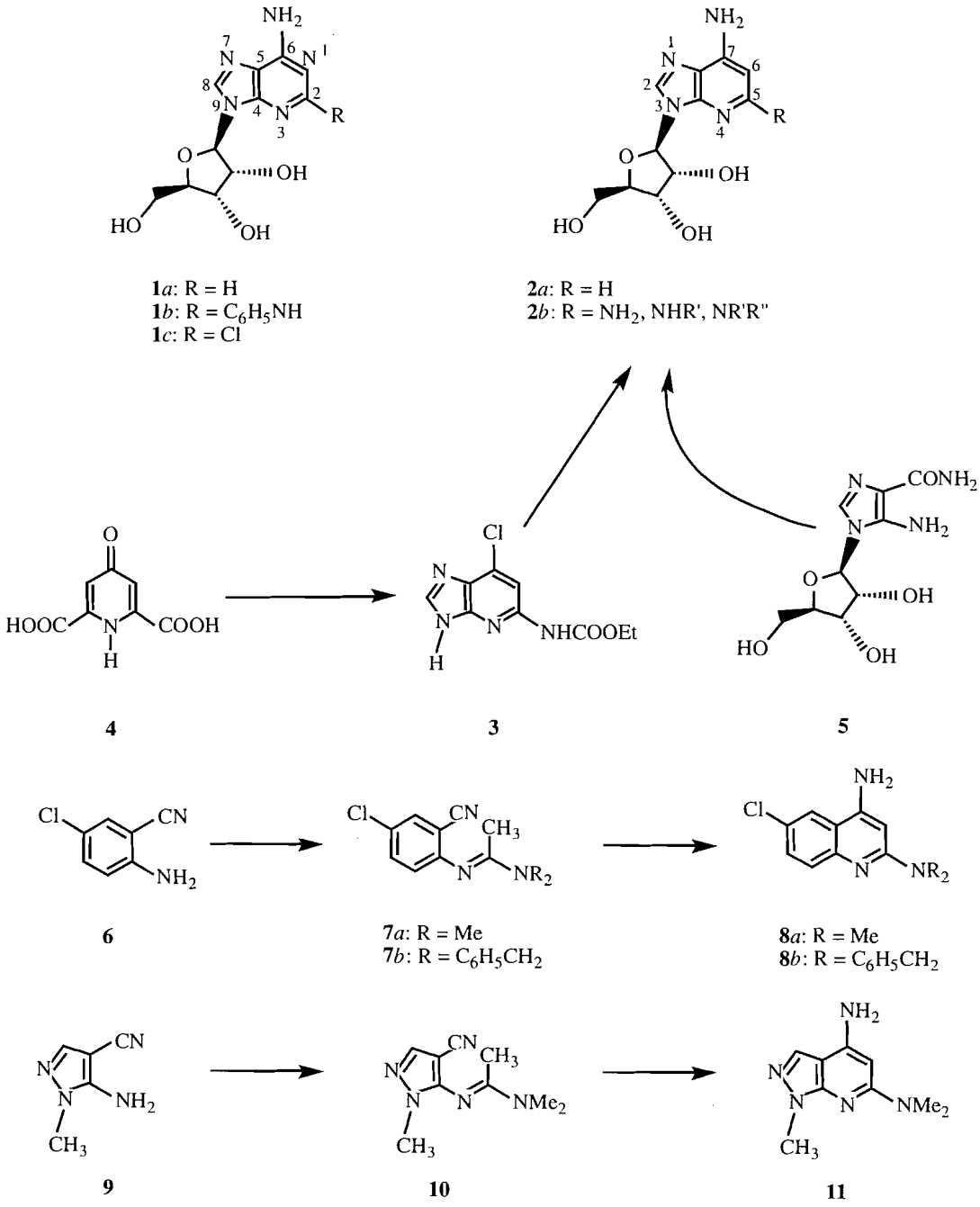
methodology through model reactions. We found that 5-chloroanthranilonitrile (**6**) reacted with dimethylacetamide dimethyl acetal in refluxing cyclohexane to form the intermediate **7***a* in 79% yield and this could be converted conveniently with sodium hydride in refluxing dioxane to **8***a* in 80% yield. Similarly, the aminocyanopyrazole **9** was converted via intermediate **10** (in this case prepared in refluxing acetonitrile) to the pyrazolo[3,4-*b*]pyridine **11** in 50% overall yield.

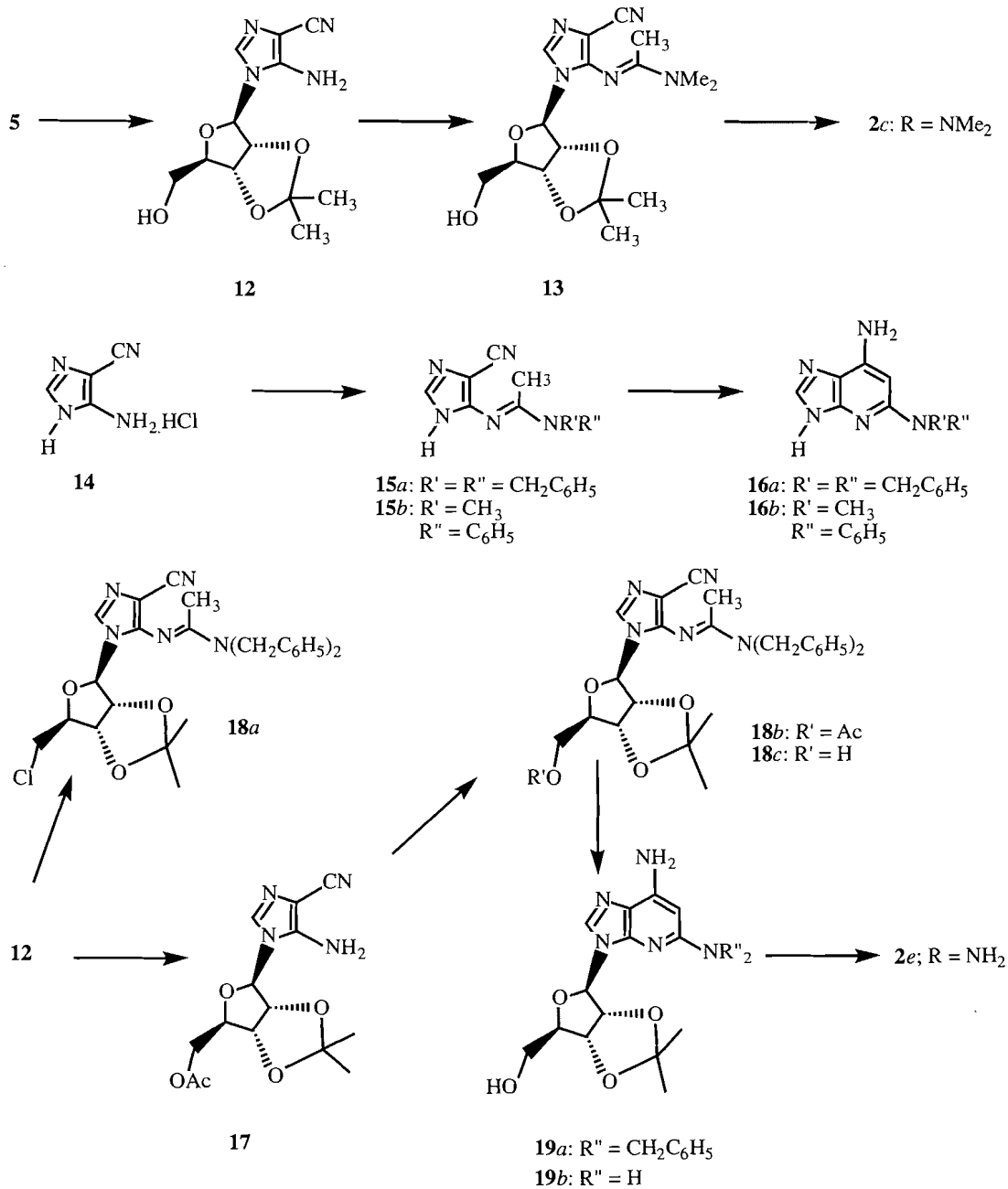


AICA riboside (**5**) was converted to the 2′,3′-protected aminonitrile **12** by a six-step literature route (21) in 25% yield. Reaction of this intermediate with commercial dimethylacetamide dimethyl acetal gave the expected product **13** under the mild conditions of overnight treatment at room temperature. The same result was obtained by the use of dimethylacetamide treated with dimethyl sulphate and neutralized with sodium methoxide. Cyclization with sodium hydride/dioxane at 110°C over 1 h followed by deprotection with 90% trifluoroacetic acid at 0°C in 0.5 h gave **2***c* (R = NMe_2) in 83% yield. Attempted removal of the isopropylidene protecting group with dilute hydrochloric acid, 80% acetic acid, or 50% formic acid resulted in some loss of the ribosyl moiety.

The paucity of commercially available orthoamides limits the general utility of this approach. Since condensation of an orthoester with the aminonitrile followed by displacement of the alkoxide group by a secondary amine was shown

to involve temperatures of 150°C in each step (20), we did not pursue this alternate two-step approach. Replacement of dimethylacetamide with other tertiary amides revealed a further disadvantage of the orthoamide approach. Reaction of **12** with *N*-methylacetanilide/dimethyl sulphate/sodium methoxide gave none of the desired compound **2***d* (R = $N(Me)C_6H_5$). *N*-Methylaniline was detected as a product of the reaction, indicative of preferential C—N bond cleavage rather than C—O cleavage with alkoxide elimination. The result is not surprising since the ready displacement of *N*-methylaniline anion rather than alkoxide from an amide acetal at basic pH has been observed previously (22).

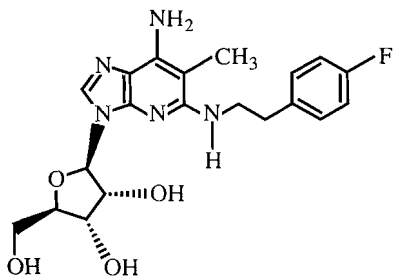
We turned to the method of activating the tertiary amide through conversion to its imidinium chloride. Treatment of *N*,*N*-dibenzylacetamide with phosphoryl chloride in acetonitrile at room temperature followed by addition of **6** gave the desired intermediate **7***b* in 67% yield, which was converted to **8***b* with sodium hydride. By the same route, 5-amino-(1*H*)imidazole-4-carbonitrile (**14**) was converted to **15***a* and cyclized to **16***a*, a potential building block for a wide variety of 5,7-diaminoimidazo[4,5-*b*]pyridines. Substitution of *N*-methylacetanilide as the tertiary amide led to **15***b* and **16***b*. The synthesis of **10** from **9** with dimethylacetamide and phosphoryl chloride was achieved in 97% yield.



The remaining target compounds were then prepared in the following manner. Intermediate **12** was protected at the 5′-position as the acetate (**17**) before condensation with an imidinium chloride. Omission of this step in the reaction with dibenzylacetamide led to a significant amount of the 5′-chloro derivative **18***a*. Condensation of **17** with *N*,*N*-dibenzylacet-

amide/phosphoryl chloride in acetonitrile at room temperature over 16 h gave the desired intermediate **18***b* as an oil that was hydrolysed with methanolic ammonia to afford **18***c* in 90% overall yield. Cyclization with sodium hydride in dioxane produced crude **19***a* as a foam. Removal of both benzyl groups was achieved with hydrogen over palladium hydroxide in ethanol at 50°C and 45 psi (1 psi = 6.89 kPa) to afford **19***b* in nearly quantitative yield. Removal of the remaining protecting group with 90% trifluoroacetic acid gave **2***e* (R = NH_2), characterized as both the trifluoroacetate and dihydrochloride. When *N*-benzylacetanilide was substituted for *N*,*N*-dibenzylacetamide in the sequence, the target compound **2***f* (R = NHC_6H_5) was obtained. Targets **2***g* (R = $NHCH_2CH_2C_6H_4$-*p*-$CH_2CH_2C_6H_5$) and **2***h* (R = $NHCH_2CH_2$-C_6H_4-*p*-CH_2CH_2COOH) were also prepared. For **2***h*, the *p*-substituent was introduced conveniently by Heck reaction conditions (23) from the N^5-*p*-bromophenethyl intermediate with the 2′ and 3′ hydroxyls protected.

Substitution in the 6-position by methyl was achieved through the use of an *N*-substituted *N*-benzylpropionamide, as illustrated by the synthesis of **20**. Finally, annelation of the imidazopyridine ring system at the 5- and 6-positions was accomplished through the use of an *N*-benzylated lactam. Specifically, *N*-benzylbutyrolactam was converted through the usual steps to the tricyclic compound **21**, an example of the previously unreported imidazo[4,5-*b*]pyrrolo[3,2-*e*]pyridine ring system.



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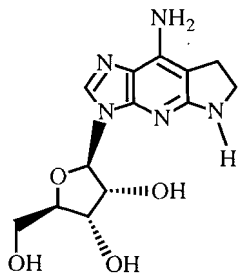

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Some biochemical and pharmacological results on this series will be reported separately. Since these 1-deazaadenosine derivatives cannot be metabolized to intermediates that can form Watson–Crick base pairs (24), we hope that these compounds will show fewer side effects than their purine riboside isosteres.

Experimental

All reactions were carried out under nitrogen. Melting points (uncorrected) were determined on a Thomas–Hoover capillary apparatus. Proton NMR were determined on a Varian XL-300, Varian XL-400, Bruker AC-300, or Bruker AC-250 instrument with tetramethylsilane as internal standard in deuterated dimethyl sulphoxide unless otherwise stated. Spectral shifts are reported as δ (ppm) values. Solvents used were spectral or HPLC grade. Chromatography was done under nitrogen pressure with silica gel 60 (230–400 mesh) from E. Merck. Where noted, compounds analysed for C, H, and N within ±0.4 units unless otherwise stated. IR spectra, taken in Nujol mulls, were recorded on a Perkin–Elmer model 457 spectrometer and peaks are expressed in reciprocal centimeters. Mass spectra were taken with a Hewlett–Packard 5985B mass spectrometer in the Cl mode. Silica gel 60 TLC plates were obtained from EM Science.

*5-Chloro-2-[1-dimethylamino)ethylideneamino]benzonitrile (7*a*)*

A mixture of 5-chloroanthranilonitrile (9.5 g, 62 mM), dimethylacetamide dimethylacetal (ca. 90%, containing methanol, 9.7 mL), and cyclohexane (70 mL) was heated in a Dean–Stark apparatus at reflux until 40 mL of liquid were collected (ca. 4.5 h). The red solution was concentrated to dryness at 70°C under water pump vacuum, taken up in hot cyclohexane (100 mL), and filtered. The filtrate was treated with hexane (50 mL) as it cooled and crystals began to form. The mixture was refrigerated overnight and the off-white needles were collected and air dried to afford 10.47 g (79%), mp 84–87°C. A sample was sublimed for analysis at 60°/0.1 Torr (1 Torr = 133.3 Pa) to a pure white solid, mp 85–87°C; IR: 2222, 1602, 1586, 1300, 1191, 841; ^{1}HMR: 1.9 (s, 2 CH_3), 3.0 (s, CH_3), 6.8 (d, H at 3), 7.5 (dd, H at 4), 7.73 (d, H at 6); MS: 222 (M + 1). Anal. $C_{11}H_{12}ClN_3$: C, H, N.

*4-Amino-6-chloro-2-dimethylaminoquinoline (8*a*)*

A mixture of **7***a* (1.11 g, 5 nM), 50% sodium hydride in oil (0.5 g), and dioxane (15 mL) was heated under reflux for 5.5 h during which time a yellow solid began to form. The mixture was cooled and the product was collected, washed with a little dioxane, and suspended in ether (30 mL) in a separatory funnel to which water (20 mL) was cautiously added. The clear ether layer was collected and the aqueous layer extracted twice with ether (2 × 10 mL). The ether extract was dried (Mg_2SO_4) and concentrated to dryness at reduced pressure. The residue was triturated with hexane and collected as an off-white solid, pure by TLC (R_f = 0.1 with 3:1 toluene – ethyl acetate vs. starting material, R_f = 0.7) (0.89 g, 80%, mp 155–160°C). Recrystallization from toluene gave pure white crystals, mp 165–167°C; IR: 3341, 3188, 1643, 1591, 1503, 825; ^{1}HMR: 3.05 (s, 2 CH_3), 6.1 (s, H at 3), 6.4 (s, NH_2, exchangeable with D_2O), 7.35 (m, H, s at 3 and 4), 8.0 (s, H at 6). Anal. $C_{11}H_{12}ClN_3$: C, H, N.

*5-[1-(Dimethylamino)ethylideneamino]-1-methylpyrazole-4-carbonitrile (**10**)*

A mixture of 5-amino-1-methylpyrazole-4-carbonitrile (**9**) prepared by the literature method (25) (0.61 g, 5 nM), dimethylacetamide dimethyl acetal (1 mL), and acetonitrile (21 mL) was stirred at 90°C for 4 h. It was concentrated to dryness at 70°C under water vacuum to a dark oil and triturated with hexane to yellow-orange solid **10** (0.74 g, 77%, mp 45–50°C), pure by TLC (R_f = 0.5, 4:1 CH_2Cl_2–EtOAc vs. starting material, R_f = 0.33), and used directly to prepare **11**.

A mixture of **9** (0.8 g, 6.5 mM), dimethylacetamide (2.35 g), and acetonitrile (10 mL) was treated dropwise at room temperature with phosphoryl chloride. After 5 min, TLC (1:1 CH_2Cl_2–EtOAc) indicated complete reaction. The mixture was poured into ice-cold ammonium hydroxide and extracted with ethyl acetate (2 × 40 mL). The organic extract was washed with brine, dried (Na_2SO_4), and concentrated to dryness at reduced pressure. Treatment of the oily residue with hexane with seed crystals yielded **10** as a yellow solid (1.12 g, 90%, mp 59–61°C); IR: 2215, 1597, 1511, 1029; ^{1}HMR: 2.0 (s, N-CH_3), 3.1 (d, 2 CH_3), 3.5 (s, C-CH_3), 7.7 (s, H at 3). Anal. calcd. for $C_9H_{13}N_5$: C 56.53, H, N; found: C 57.08.

*4,6-Diamino-1,N^6,N^6-trimethylpyrazolo[3,4-b]pyridine (**11**)*

A mixture of **10** (0.74 g, 3.9 mM), 50% sodium hydride in oil (0.39 g), and dioxane (10 mL) was stirred at reflux for 1.5 h. It was cooled and filtered free of white solid (**caution ! nasal irritant !**) and concentrated at reduced pressure to a semisolid. This was triturated with ether, and water was then added to form a yellow solid, insoluble in both solvents. The material was collected, washed with water (3 × 10 mL), then with hexane (2 × 10 mL), and vacuum oven dried at 80°C/10 Torr) to afford **11** (0.47 g, 64%), mp 174–177°C. It was recrystallized from toluene to form the pure product as yellow crystals, mp 178–181°C; IR: 3352, 3210, 1606, 1592, 1165, 985; ^{1}HMR: 3.0 (s, 2 CH_3), 3.75 (s, N-CH_3), 5.55 (s, H at 5), 6.3 (s, NH_2, exchangeable with D_2O), 7.75 (H at 3); MS: 192 (M + 1). Anal. $C_9H_{13}N_5$: C, H, N.

*5-[1-(Dimethylamino)ethylideneamino]-1-[2′,3′-O-(1-methylethylidene)-β-D-ribofuranosyl]-1H-imidazole-4-carbonitrile (**13**)*

To a suspension of 5-amino-1-[2′,3′-*O*-)1-methylethyidene)-β-D-ribofuranosyl)]imidazole-4-carbonitrile (**12**), prepared as described in the literature (21), (0.56 g, 2 mM) in acetonitrile (10 mL) was added dimethylacetamide dimethylacetal (1.0 mL) and the mixture stirred at room temperature overnight. It was concentrated under high vacuum (0.1 Torr) and the residue was redissolved in ether–acetonitrile (1:1), treated with charcoal, filtered, and the filtrate was concentrated to dryness at reduced pressure and triturated with ether to afford **13** (0.45 g, 64%), mp 122–125°C. It was recrystallized from ethyl acetate to give the pure material, mp 127–129°C; IR: 2210, 1609; ^{1}HMR ($CDCl_3$): 1.35 (s, CH_3), 1.58 (s, CH_3), 2.13 (s, CH_3), 3.1 (s, 2 CH_3), 3.85 (m, 5′-CH_2), 4.1 (br s, OH), 4.33 (m, 4′-H), 4.95 (m, 3′ + 2′-H), 5.75 (d, H at 1′), 7.8 (s, H at 8); MS: 350 (M + 1). Anal. $C_{16}H_{23}N_5O_4$: C, H, N.

*5,7-Diamino-3-[β-D-ribofuranosyl]-N^5,N^5-dimethyl-3H-imidazo[4,5-b]pyridine(**2**c)*

Sodium hydride (60% in oil, 1.2 g) was prewashed with hexane, suspended in dioxane (60 mL), then treated with **13** (2.6 g, 7.4 mM), and the mixture was stirred at 110°C for 1 h. It was poured into ice-water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with brine, dried (Na_2SO_4), decolorized with charcoal, filtered, and evaporated at reduced pressure to a semisolid. This was triturated with ether and collected as a white solid (1.95 g, 75%), which was pure *5,7-diamino-3-[2′,3′-O-(1-methylethylidene)-β-D-ribofuranosyl]-N^5,N^5-dimethyl-3H-imidazo[4,5-b]pyridine*, mp 176–178°C; $[\alpha]_D^{25}$ −8.15 (*c* = 1.36, DMSO); IR: 3437, 3361, 3248, 3098, 1637, 1598, 1510; ^{1}HMR ($CDCl_3$): 1.4 (s, CH_3), 1.65 (s, CH_3), 3.1 (s, 2 CH_3), 3.85 (m, 5′-CH_2), 4.4 (m, 4′-H), 4.9 (br s, NH_2), 5.15 (m, 3′-H), 5.6 (m, 2′-H), 5.75 (s, H at 6), 5.9 (d, 1′-H), 7.8 (s, H at 2); MS: 350 (M + 1), 178 (aglycone). Anal. $C_{16}H_{23}N_5O_4$: C, H, N. This intermediate (0.70 g, 2 mM) was stirred in an ice-cold 9:1 mixture of trifluoroacetic acid and water (5 mL) at 0–5°C for 1 h. Ether (75 mL) was added and after 10 min the trifluoroacetic acid salt of **2***c* was collected as a while solid (0.81 g, 95%). It was added to 8% aqueous sodium bicarbonate solution and, after several minutes, the free base crystallized. This was washed with water and dried under vacuum to afford white crystals (0.52 g, 85%, mp 219–222°C); $[\alpha]_D^{25}$ −36.87 (*c* = 1.55, DMSO); IR: 3408, 3312, 3218, 3125, 1634, 1602, 1522, 1078, 1032; ^{1}HMR: 2.9 (s, 2 CH_3), 3.6 (m, 5′-CH_2), 3.75 (m, 4′-H), 4.15 (dd, 3′-H), 4.65 (dd, 2′-H), 4.85 (br s, OH), 5.1 (br s, OH), 5.3 (br s, OH), 5.7 (s, H at 6), 5.8 (d, 1′-H), 5.95 (s, NH_2), 7.9 (s, H at 2); MS: 310 (M + 1), 178 (aglycone). Anal. $C_{13}H_{19}N_5O_4$: C, H, N.

*2-[1-(Dibenzylamino)ethylideneamino]-5-chlorobenzonitrile (**7**b)*

A stirring mixture of 5-chloroanthranilonitrile (1.52 g, 10 mM) and *N,N*-dibenzylacetamide (9.56 g, 40 mM) in acetonitrile (25 mL) was treated dropwise with phosphoryl chloride (3.06 g, 20 mM) and stirred 3 h at room temperature. The mixture was poured into ice-cold ammonium hydroxide and extracted with ethyl acetate (2 × 100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to dryness at reduced pressure to a red oil. The oil was triturated several times with hexane and the hexane wash discarded. The residue was triturated with isopropanol and the product obtained as a white solid after vacuum oven drying (2.48 g, 67%), mp 101–110°C; IR: 2220, 1592, 698; ^{1}HMR: 2.0 (s, CH_3), 4.7 (s, 2 CH_2), 6.9 (d, 3-H), 7.3 (m, 10 aromatic H), 7.57 (dd, 4-H), 7.8 (d, 6-H). Anal. $C_{23}H_{20}ClN_3$: C, H, N. By the same procedure, 5-aminoimidazole-4-carbonitrile hydrochloride (**14**) (26) was converted to **15***a*, a foam, mp 144–148°C, in 42% yield. Anal. $C_{20}H_{19}N_5$: C, H, N. Similarly, **17**, prepared as described by Suzuki and Kumashiro (27), was converted to **18***b*, an oil, in 88% yield; MS: 544 (M + 1). *N*-Methylacetanilide, combined with **14** and phosphoryl chloride by the same procedure, led to **15***b*, mp 222–225°C, in 67% yield. Anal. $C_{13}H_{13}N_5 \cdot 0.25H_2O$: C, H, N.

*2,4-Diamino-N^2,N^2-dibenzyl-6-chloroquinoline (**8**b)*

A mixture of **7***b* (0.37 g, 1 mM) and sodium hydride (60% in oil, 0.16 g) in dioxane (5 mL) was heated 3 h at reflux. It was poured into ice-water, extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), treated with charcoal, filtered, and concentrated to dryness at reduced pressure to a reddish-brown solid (0.28 g, 76%). This residue was triturated with hexane–ether to afford the pure material (0.21 g), mp 217–220°C; IR: 3490, 3305, 3175, 1638, 1592, 1497, 1215, 736; ^{1}HMR: 4.8 (2 CH_2), 6.1 (H at 3), 6.4 (NH_2, exchangeable with D_2O), 7.2–7.4 (m, 12 H), 8.0 (s, H at 5). Anal. $C_{23}H_{20}ClN_3$: C, H, N. By the same procedure, **15***a* was converted to **16***a*, mp 196–198°C, in 69% yield. Anal. $C_{20}H_{19}N_5$: C, H, N. Similarly, **15***b* was converted to **16***b*, mp 214–216°C, in 71% yield. Anal. $C_{13}H_{13}N_5$: C, H, N.

*5,7-Diamino-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (**2**e)*

A mixture of **18***b* (7.0 g, 13 mM) and methanol saturated with ammonia (250 mL) was stirred overnight at room temperature. The mixture was concentrated to dryness at room temperature and the residue was taken up in ethyl acetate (300 mL), washed with water (3 × 100 mL), then with brine (100 mL), dried (Na_2SO_4), and concentrated to dryness at reduced pressure to afford crude **18***c* as a foam. This was chromatographed on a 220 × 50 mm column with 2:1 methylene chloride – ethyl acetate as eluent (4 × 600 mL fractions) followed by ethyl acetate alone (30 mL) fractions. The product was collected in ethyl acetate fractions 19–60 and concentrated at reduced pressure to afford chromatographically pure **18***c* as a foam (5.9 g, 91%). The foam (5.8 g, 11.5 mM) was added in dioxane (50 mL) to sodium hydride (60% in oil, 1.85 g, prewashed with hexane) in dioxane (100 mL) and the mixture was heated at 100°C for 1 h. The reaction mixture was poured into ice-water, extracted with ethyl acetate (3 × 100 mL), and the extract washed with brine (50 mL), dried (Na_2SO_4), and concentrated to dryness to afford **19***a* as a foam (5.7 g, 98%). The cyclized intermediate **19***a* (5.6 g) was hydrogenated in the presence of palladium hydroxide (5.6 g) in 95% ethanol (200 mL) in a Parr apparatus at 45 psi and 50°C for 4.5 h. The mixture was filtered and the filtrate concentrated to dryness at reduced pressure to give **19***b*, the 2′,3′-*O*-(1-methylethylidene) derivative of **2***e*, as a colorless foam (3.3 g, 94%). This acetonide (2.65 g, 8.2 mM) was stirred in an ice-cold solution of 90% aqueous trifluoroacetic acid until TLC (9:1 CH_2Cl_2–NH_3-saturated methanol) showed complete loss of starting material, R_f = 0.5, with product R_f = 0.0. The solution was diluted with ether (375 mL), stirred 15 min, and the precipitated crude trifluoroacetate salt of **2***e* collected and air dried (3.2 g, 100%), mp 124–127°C. A portion (0.5 g) was dissolved in acetonitrile (50 mL), filtered, and the filtrate saturated with dry HCl under ice cooling. A turbid mixture formed that during 18 h at room temperture became a white solid. The product (0.35 g), mp 105°C (dec.), was the dihydrochloride of **2***e*; $[\alpha]_D^{25}$ −67.4 (*c* = 1, H_2O); ^{1}HMR (CD_3OD): 3.9 (m, 5′-CH_2), 4.3 (m, 4′-H + 3′-H), 4.45 (dd, 2′-H), 5.9 (s, H at 6), 5.95 (d, 1′-H), 8.55 (s, H at 2); MS: 150 (aglycone, M + 1). Anal. calcd. for $C_{11}H_{17}Cl_2N_5O_4$: C, H, N, Cl 20.01; found: Cl 19.57.

*7-Amino-5-anilino-3-(β-D-ribofuranosyl)imidazo[4,5-b]pyridine (**2**f)*

N-Benzylacetanilide, bp 135–150°C at 3 Torr, prepared by reacting *N*-benzylaniline with a 50% excess of triethylamine and a 40% excess of acetyl chloride at room temperature over 42 h (6.4 g, 28.8 mM), and **17** (2.3 g, 7.2 mM) in acetonitrile (25 mL) were treated dropwise under stirring with phosphoryl chloride (2.2 g, 14.4 mM). After 48 h, the mixture was quenched in ice-cold sodium bicarbonate solution, extracted with ethyl acetate, and the extract washed several times with dilute bicarbonate, then with water and brine, dried (Na_2SO_4), and concentrated to dryness at reduced pressure to an oily residue (3.8 g). The oil was flash

chromatographed with methylene chloride – ethyl acetate (5:1) and 60 35-mL fractions were collected. A 1:1 solvent mixture was used for the next 20 35-mL fractions. Combined fractions 41–80, one spot by TLC, were concentrated to dryness to afford the pure material (1.1 g, 29%) as an oil. This intermediate was stirred overnight in ammonia-saturated methanol (50 mL) and concentrated to dryness at reduced pressure. The residue was taken up in ethyl acetate (25 mL), washed with water (4 × 10 mL), then with brine, dried (Na_2SO_4), and concentrated to dryness to an off-white foam. This was combined with material from a similar run and flash chromatographed with 1:1 methylene chloride ethyl acetate (100 mL × 12 fractions) followed by ethyl acetate alone (100 mL × 4 fractions). Fractions 4–14 were combined and concentrated to a white foam, mp 68–78°C (1.85 g, 94%). This 5′-alcohol (1.8 g, 3.7 mM) in dioxane (15 mL) was added dropwise to a suspension of sodium hydride (60% in oil, 0.6 g, 14.8 mM, washed 3 times with hexane) in dioxane (30 mL) and heated at reflux for 1.5 h. The mixture was quenched in ice-water and extracted with ethyl acetate (3 × 70 mL). The extract was washed with water, then with brine, dried (Na_2SO_4), and concentrated at reduced pressure to a foam (1.8 g), which contained a trace of impurity (TLC). It was flash chromatographed with 3:1 methylene chloride – ethyl acetate, followed by a 1:1 mixture, then by ethyl acetate alone. The pure product was found in the ethyl acetate eluent. Evaporation of the combined fractions yielded the 2′,3′-*O*-(1-methylethylidene) derivative of N^5-benzyl **2***f* as a foam, mp 93–99°C (1.63 g, 90%). Anal. $C_{27}H_{29}N_5O_4$: C, H, N. The *N*-benzyl compound (1.5 g) was hydrogenolized in 95% ethanol (150 mL) with palladium hydroxide (1.5 g) at 50°C and 50 psi for 6 h, then with fresh catalyst for another 6 h. The mixture was filtered and the solvent removed at reduced pressure to afford the crude 2′,3′-*O*-(1-methylethylidene) derivative of **2***f* (1.0 g, 83%). Recrystallization from ethyl acetate gave pure material, mp 225–228°C; $[\alpha]_D^{25}$ 9.68 (c = 0.91, DMSO); ^{1}HMR: (CD_3OD): 1.4 (s, CH_3), 1.6 (s, CH_3), 3.65 (m, 5′-CH_2), 4.3 (m, 4′-H), 4.95 (dd, 3′-H), 5.45 (dd, 2′-H), 6.0 (s, H at 6), 6.1 (d, 1′-H), 6.9 (dd, *p*-H), 7.25 (dd, 2 *m*-H), 7.5 (d, 2 *o*-H), 8.0 (s, H at 2); MS: 398 (M + 1). Anal. $C_{20}H_{23}N_5O_4$: C, H, N. The acetonide (0.6 g) was stirred at 0–5°C in 90% aqueous trifluoroacetic acid (4 mL) for 1 h. It was diluted with ether (20 mL) and, after 20 min, the trifluoroacetate salt (320 mg) was collected, suspended in dilute sodium bicarbonate solution, extracted with ethyl acetate, and the organic extract washed with brine, dried (Na_2SO_4), and concentrated to dryness to an off-white solid (220 mg) containing trace impurities. The material was chromatographed with mixtures of methylene chloride and ammonia-saturated methanol, 15:1 for the first 44 × 25-mL fractions, followed by 5:1 for the next 8 × 25-mL fractions. Fractions 21–48 were combined and concentrated to pure **2***f* obtained as a foamy solid (160 mg, 30%). The analytical sample was recrystallized from water, mp 192–195°C; $[\alpha]_D^{25}$ −19.33 (c = 1.29, DMSO); ^{1}HMR: 3.8 (m, 5′-CH_2), 4.1 (dt, 4′-CH_2), 4.3 (dd, 3′-H), 4.75 (dd, 2′-H), 5.95 (d, 1′-H), 6.1 (s, H at 6), 6.9 (m, *p*-H), 7.25 (m, 2 *m*-H), 7.4 (m, 2 *o*-H), 8.05 (s, H at 2); MS: 358 (M + 1). Anal. $C_{17}H_{19}N_5O_4 \cdot 0.25H_2O$: C, H, N.

5,7-Diamino-N^5*-[2-[4-(2-phenylethyl)phenyl]ethyl]-3-(*β-D-*ribofuranosyl)imidazo[4,5-*b*]pyridine (***2***g)*

A mixture of 2-(4-bromophenyl)ethylamine (Aldrich, 50 g, 0.25 M), and benzaldehyde (26.5 g, 0.25 M) in petroleum ether (700 mL) and acetic acid (200 mL) was treated dropwise under stirring at room temperature with borane–pyridine complex (Fluka, 23 g, 0.25 M) and, after 2 h, 5 N hydrochloric acid (150 mL) was added slowly to give a white precipitate. The precipitated salt was collected and the filtrate was extracted with ether and the ether layer discarded. The solid was added to the aqueous acidic layer, made basic with ice-cold sodium hydroxide solution, and extracted with ether. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure to an oil (63.7 g), which was chromatographed with 5:1 methylene chloride – ethyl acetate. Fractions containing the desired product were combined and concentrated to afford N-*benzyl-2-(4-bromophenyl)ethylamine* as an oil (42.7 g, 59%; ^{1}HMR ($CDCl_3$): 1.65 (NH), 2.8 (m, 2 CH_2), 3.8 (s, CH_2), 7.05–7.45 (m, 9 aryl H)) used directly in the next step. A mixture of the amine (42.6 g, 147 mM) and triethylamine (22.3 g, 220 mM) in cold methylene chloride (400 mL) was treated dropwise under stirring with an ice-cold solution of acetyl chloride (12.6 g, 162 mM) and stirred for 18 h at ambient temperature. The solution was extracted with 1 N hydrochloric acid (4 × 100 mL), water (100 mL), dilute aqueous sodium bicarbonate (2 × 100 mL), and water (100 mL), then dried (Na_2SO_4) and concentrated to dryness at reduced pressure. The oily product (48.3 g) was distilled to give 42.5 g (87%) of N-*acetyl*-N-*benzyl-2-(4-bromophenyl)ethylamine*, bp 216–218°C at 0.5 Torr; IR (neat): 3028, 1646, 1489, 1419, 1011. Anal. $C_{17}H_{18}BrNO$: C, H, N. A mixture of this amide (20 g, 60 mM), styrene (8.1 g, 78 mM), palladium acetate (0.14 g, 0.6 mM), tri-*o*-tolylphosphine (0.73 g, 2.4 mM), and triethylamine (39.4 g, 0.39 M) was heated at reflux for 18 h. The residue was treated with ice-cold 2 N hydrochloric acid (300 mL) and extracted with methylene chloride (3 × 400 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to dryness at reduced pressure. The residue was recrystallized from ethanol to afford pure N-*acetyl*-N-*benzyl-2-[4-(2-phenylethenyl)phenyl]ethylamine* (14.3 g, 67%), mp 136–138°C: Anal. $C_{25}H_{25}NO$: C, H. N. This material (14.2 g, 40 mM) was reacted with **17** (3.22 g, 10 mM) and phosphoryl chloride (3.06 g, 20 mM) and worked up as described in **2***f* to afford the desired adduct as a foam (4.1 g, 62%). This was saponified with methanolic ammonia as described and obtained as one-spot material by TLC in quantitative yield. Cyclization with sodium hydride in dioxane (reflux, 2 h) and subsequent work-up gave *5,7-diamino-*N^5*-benzyl-*N^5*-[2-[4-(2-phenylethenyl)phenyl]ethyl]-3-[2′,3′-*O*-(1-methylethylidene)-*β-D-*ribofuranosyl]imidazo[4,5-b]pyridine*, mp 174–177°C; MS: 618 (M + 1). Anal. $C_{37}H_{39}N_5O_4$: C, H, N. This intermediate (2.6 g, 4.2 mM) was hydrogenated in 95% ethanol (200 mL) containing 1 N hydrochloric acid (10 mL) in the presence of palladium hydroxide (5.2 g) at 50 psi at room temperature over 6 h. The mixture was filtered and the filtrate was stirred with propylene oxide (10 mL) for 30 min. Removal of the solvent gave a crystalline mass, which was triturated with ether to afford the 2′,3′-*O*-(1-methylethylidene) derivative of **2***g* (1.7 g, 77%) as a foam; IR: 3327, 3221, 3135, 1655, 1625, 1605, 1514; MS: 530 (M + 1). The acetonide (1.6 g, 3 mM) was stirred in 90% trifluoroacetic acid (10 mL) at 0–5°C for 1 h. Ether (15 mL) was added and after 15 min the salt was collected (1.6 g). It was dissolved in methanol (75 mL), filtered, and the filtrate treated with 6.5 N HCl in methanol (0.5 mL). The dihydrochloride salt of **2***g* crystallized as a white solid (1.1 g, 65%), mp 150–156°C; $[\alpha]_D^{25}$ −14.9 (c = 1.01, DMSO); IR: 3455, 3403, 3321, 3294, 3234, 2720 (br), 1678, 1659, 1574, 1513, 1093; ^{1}HMR: 2.8 (m, 3 CH_2), 3.4 (dd, CH_2-N), 3.65 (m, 5′-CH_2), 4.05 (dt, 4′-H), 4.15 (dd, 3′-H), 4.4 (dd, 2′-CH_2), 5.75 (s, H at 6), 5.9 (d, 1′-H), 7.2-7.3 (m, 9 aryl H), 8.7 (br s, H at 2); MS: 490 (M + 1 of base, weak), 358 (M + 1, aglycone). Anal. $C_{27}H_{31}N_5O_4 \cdot 2HCl$: C, H, N.

5,7-Diamino-N^5*-[2-[4-(2-carboxyethyl)phenyl]ethyl]-3-(*β-D-*ribofuranosyl)imidazo[4,5-*b*]pyridine (***2***h)*

N-Acetyl-*N*-benzyl-2-(4-bromophenyl)ethylamine (25.6 g, 80 mM) was reacted with **17** (6.44 g, 20 mM) and phosphoryl chloride (6.12 g, 40 mM) in acetonitrile and worked up as described for **2***f* to afford the crude adduct containing residual amide. This material was saponified with methanolic ammonia as described previously and chromatographed with 2:1 methylene chloride – ethyl acetate followed by ethyl acetate to afford 8.8 g (75%) of foamy solid. This material was reacted with a fourfold excess of sodium hydride as described for **2***f* to afford *5,7-diamino-*N^5*-benzyl-*N^5*-[2-(4-bromophenyl)ethyl]-3-[2′,3′-*O*-(1-methylethylidene)-*β-D-*ribofuranosyl]imidazo[4,5-b]pyridine* in 80% yield; MS: 594/596 (M + 1); Anal. $C_{29}H_{32}BrN_5O_4 \cdot H_2O$: C, H, N. This interme-

diate (1.78 g, 3 mM) was mixed with benzyl acrylate (0.64 g, 3.9 mM), palladium acetate (7 mg, 0.03 mM), tri-*o*-tolylphosphine (36 mg, 12 mM), and triethylamine (1.97 g, 19.5 mM) and the whole refluxed over 18 h. The mixture was treated with dilute sodium bicarbonate solution, extracted with methylene chloride, and the organic extract dried (Na_2SO_4) and concentrated to dryness under vacuum (0.1 Torr). The crude product (1.7 g, 85%) was chromatographed with 20:1 methylene chloride – methanol and the product collected as a foam. It was triturated with methanol to produce crystals (0.57 g, 28%), mp 152–155°C; MS: 676 (M + 1). Anal. $C_{39}H_{41}N_5O_6 \cdot 0.5H_2O$: C, H, N. This product (0.54 g, 0.8 mM) was hydrogenated in 95% ethanol (100 mL) with palladium hydroxide (1.0 g) at 60°C and 45 psi for 5 h. The mixture was filtered and filtrate concentrated to an oil (0.35 g). The product crystallized on addition of a little methanol (0.32 g, 80%), mp 107–117°C. This intermediate (0.30 g, 0.6 mM) was treated with 90% trifluoroacetic acid over 1 h. Ether was added and HCl gas was bubbled through the mixture for ca. 5 min to afford **2***h* as a dihydrochloride dihydrate (210 mg, 62%), mp 63–78°C (dec.); $[\alpha]_D^{25}$ −38.36 (*c* = 2, MeOH); IR: 3400–3200 (br), 2760–2670 (br), 1742, 1679, 1081, 1019; MS: 458 (M + 1, free base, weak), 326 (M + 1, aglycone). Anal. $C_{22}H_{27}N_5O_6 \cdot 2HCl \cdot 2H_2O$: C, H, N.

*5,7-Diamino-*N^5*-[2-(4-fluorophenyl)ethyl]-6-methyl-3-(*β-D-*ribofuranosyl)imidazo[4,5-*b*]pyridine (**20**)*

Benzaldehyde was condensed with 2-(4-fluorophenyl)ethylamine in the presence of borane – pyridine as described previously to afford *N*-benzyl-2-(4-fluorophenyl)ethylamine in 44% yield as an oil; ^{1}HMR ($CDCl_3$): 1.35 (s, NH), 2.8 (m, 2 CH_2), 3.8 (s, CH_2), 6.9–7.4 (m, 9 aryl H). An ice-cold mixture of this amine (10.5 g, 46 mM) and triethylamine (7.0 g, 69 mM) in methylene chloride (150 mL) was treated dropwise with propionyl chloride (4.7 g, 51 mM) in methylene chloride (50 mL) and stirred overnight at ambient temperature. The mixture was worked up as described for previous amides and the crude material was distilled to afford pure N-*benzyl*-N-*propionyl-2-(4-fluorophenyl)ethylamine* (10.9 g, 83%), bp 162–163°C at 0.9 Torr; IR (neat): 1648, 1510, 1221, 1158, 827, 733. Anal. $C_{18}H_{20}FNO$: C, H, N. The amide was reacted with **17** and phosphoryl chloride as described previously and the amidine isolated after chromatography with 5:1 methylene chloride – ethyl acetate as an oil in 41% yield. Saponification of the 5′-ester with methanolic ammonia gave the 5′-alcohol as an oil in 85% crude yield. Cyclization of the amidine alcohol with sodium hydride in dioxane was achieved after 2 h reflux to afford crude product as an oil. Trituration with ether gave *5,7-diamino-*N^5*-benzyl-*N^5*-[2-[4- fluorophenyl]ethyl]- 6-methyl- 3-[2′,3′-*O*-(1-methylethylidene)-*β-D-*ribofuranosyl]imidazo[4,5-*b*]pyridine* as a white solid (0.7 g, 42%), mp 146–147°C; IR: 3470, 3377, 3127, 1626, 1603, 1227, 1066; ^{1}HMR: (CD_3OD): 1.35 (s, CH_3), 1.6 (s, CH_3), 2.15 (s, CH_3), 2.75 (m, CH_2), 3.3 (m, CH_2 + MeOH), 3.65 (m, 5′-CH_2), 4.25 (m, CH_2 + 4′-H), 5.05 (m, 3′-H), 5.45 (m, 2′-H), 6.1 (d, 1′-H), 6.85–7.1 (m, 9 aryl H), 8.1 (s, H at 2). Anal. $C_{30}H_{34}FN_5O_4$: C, H, N. Additional material from the mother liquor was combined in the following step. The intermediate (1.65 g, 3 mM) was hydrogenated in 95% ethanol (200 mL) containing 1 N hydrochloric acid (5 mL) with palladium hydroxide (3.3 g) at 50 psi for 6 h at room temperature. The catalyst was filtered off and the filtrate treated with propylene oxide (5 mL) for 30 min. Evaporation of the solvent and trituration with ether gave the 2′,3′-*O*-(1-methylethylidene) derivative of **20** as a solid (0.83 g, 56%), mp 199–205°C (dec); MS: 458 (M + 1). Anal. $C_{23}H_{28}FN_5O_4 \cdot 1.5\ H_2O$: C, H, N. This acetonide (0.8 g, 1.8 mM) was stirred in ice-cold 90% trifluoroacetic acid for 1 h. TLC indicated a single new product. Addition of ether formed a hygroscopic solid. This material was dissolved in a little isopropanol and treated with HCl in ethanol but no crystals formed. Propylene oxide was added and, after 30 min, the mixture was concentrated to dryness at reduced pressure. The residue was dissolved in ethyl acetate and washed with bicarbonate solution, then with brine, dried (Na_2SO_4), and concentrated to dryness to a foam. TLC indicated two products. The material was flash chromatographed with 15:1 methylene chloride – methanol followed by a 10:1 mixture. The first product isolated (foam, 110 mg) was shown to be the aglycone of **20**; ^{1}HMR (CD_3OD): 1.9 (s, CH_3), 2.9 (t, CH_2), 3.6 (t, CH_2), 7.0 (m, 2 aryl H), 7.2 (m, 2 aryl H), 7.7 (H at 2). The second product (foam, 270 mg, 36%) was **20**. This second product was triturated with ether to form a white solid (240 mg), mp 157–160°C; $[\alpha]_D^{25}$ +7.2 (*c* = 1, EtOH); ^{1}HMR: (CD_3OD): 1.9 (s, CH_3), 2.9 (t, CH_2), 3.55–3.85 (m, CH_2 + 5′-CH_2 + 4′-H), 4.1 (dd, 3′-H), 4.4 (dd, 2′-H), 5.95 (d, 1′-H), 7.0 (m, 2 aryl H), 7.25 (m, 2 aryl H), 7.95 (s, H at 2); MS: 418 (M + 1), 286 (aglycone). Anal. $C_{20}H_{24}FN_5O_4$: C, H, N.

*8-Amino-6,7-dihydro-3-(*β-D-*ribofuranosyl)imidazo[4,5-b]pyrrolo[2,3-*e*]pyridine (**21**)*

A solution of *N*-benzyl-2-pyrrolidinone (Aldrich, 4.9 g, 28 mM), **17** (2.25 g, 7 mM), and acetonitrile (30 mL) was treated dropwise with phosphoryl chloride (2.14 g, 14 mM) and stirred at room temperature overnight. After the usual work-up, the oily product was chromatographed with 1:1 methylene chloride – ethyl acetate to give the desired intermediate as an oil (2.75 g, 82%); IR (neat): 2885, 2217, 1746, 1616, 1299; MS 480 (M + 1). Saponification of 2.7 g (5.6 mM) with methanolic ammonia gave the 5′-alcohol as a foam in 95% yield; IR (KBr): 3280 (br), 2936, 2215, 1618, 1081; MS: 438 (M + 1), 266 (aglycone). Reaction of 2.2 g (5 mM) of this product with sodium hydride in dioxane (reflux, 2 h) followed by the standard work-up gave the cyclized product as a solid in 95% yield. It was recrystallized from methanol to afford pure *8-amino-5-benzyl-3-[2′,3′-*O*-(1-methylethylidene)-*β-D-*ribofuranosyl]imidazo[4,5-b]pyrrolo[2,3-*e*]pyridine* (1.2 g, 55%), mp 184–185°C; ^{1}HMR: 1.25 (s, CH_3), 1.5 (s, CH_3), 2.75 (dd, CH_2), 3.3 (dd, CH_2), 3.5 (m, 5′-CH_2), 4.1 (ddd, 4′-H), 4.45 (q, CH_2), 4.9 (dd, 3′-H), 5.05 (t, OH), 5.35 (dd, 2′-H), 5.9 (s, NH_2), 6.05 (d, 1′-H) 7.25 (m, 5 aryl H), 7.85 (H at 2); MS: 438 (M + 1), 266 (aglycone). Anal. $C_{23}H_{27}N_5O_4$: C, H, N. This material (2.0 g, 4.5 mM) was dissolved in 95% ethanol (200 mL) containing 1 N hydrochloric acid (10 mL) and hydrogenolysed with palladium hydroxide (4.0 g) at room temperature and 50 psi over 6 h. The catalyst was filtered off and propylene oxide (10 mL) added to the filtrate. After 30 min the solution was concentrated to dryness at reduced pressure to an oil (1.6 g) that contained two products (TLC). This was taken up in methanol and reevaporated under high vacuum to a mixture of oil and hard foam. The foam (0.65 g, still a mixture) was separated mechanically from the oil, which was a single component. The oil was dissolved in methanol (90 mL) and treated at 0°C with 90% trifluoroacetic acid, whereupon a solid began to form. It was diluted with ether to produce the debenzylated acetonide as a tan solid (0.24 g, 15%); MS: 348 (M + 1), 176 (agylcone). Treatment of the foam with 90% trifluoroacetic acid at 0°C produced an intractable mixture. The desired intermediate was deprotected cleanly with 90% trifluoroacetic acid (2.5 mL) at 0°C in 1 h and, on dilution with ether, a tan solid salt of **21** was obtained (0.16 g, 47%), mp 120–124°C (dec.); $[\alpha]_D^{25}$ −31.95 (*c* = 1.13, DMSO); IR: 3359, 3185, 3152, 2800–2500 (br), 1677, 1659, 1198, 723; ^{1}HMR: 3.0 (dd, CH_2), 3.75 (dd, CH_2), 3.8 (m, 5′-CH_2), 4.25 (m, 4′-H + 3′-H), 4.4 (m, 2′-H), 5.85 (d, 1′-H), 8.1 (s, H at 2); MS: 308 (M + 1, weak), 176 (aglycone). Anal. $C_{13}H_{17}N_5O_4 \cdot 2CF_3COOH$: C, H, N.

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