1-(Benzyloxy)-5-[(*tert*-butyloxycarbonyl)amino]-piperidone (32). A mixture of *O*-benzyl 4-[(*tert*-butyloxycarbonyl)amino]-5-hydroxy-L-pentanohydroxamate (680 mg, 2 mmol), triphenylphosphine (629 mg, 2.4 mmol), and diethyl azodicarboxylate (418 mg, 2.4 mmol) in 50 mL of dry THF was stirred at room temperature for 24 h. The THF was removed under reduced pressure and the residue was purified by using MPLC with elution by EtOAc/hexane. Triphenylphosphine oxide and the reduced form of DEAD were coeluted with the main product, which was separated on repeated chromatography.

Product **32** was obtained in 62% yield: $[\alpha]^{25}_D$ −21.4° (*c* 0.5, acetone); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 1.7-1.93 (m, 2 H, CH_2), 2.4-2.6 (m, 2 H, CH_2), 3.1-3.15 (m, 1 H), 3.65 (dd, 1 H), 3.95 (m, 1 H, α-H), 4.5 (d, 1 H, NH), 5.0 (dd, 2 H, CH_2Ph), 7.4 (s, 5 H, Ph).

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.7; H, 7.6; N, 8.7. Found: C, 63.89; H, 7.44; N, 8.49.

A mixture of what appeared to be the *E* and *Z* isomers of O-alkylated products were obtained in 10% yield.

Acknowledgment. We thank the National Institutes of Health (Grant GM 26711) for support of this research. Appreciation is expressed to the Colorado State University Regional NMR Center (funded by National Science Foundation Grant No. CHE-8208821) for providing 360-MHz NMR spectra.

Registry No. **3**, 52816-29-2; **4**, 91229-86-6; **7**, 91279-50-4; **8**, 1676-73-9; **9**, 28812-54-6; **10**, 24277-39-2; **11**, 90194-99-3; **12**, 90195-02-1; **12**·trifluoroacetate salt, 91229-87-7; (*E*)-**13**, 91229-88-8; (*Z*)-**13**, 91229-89-9; **14**, 91237-84-2; **15**, 91229-90-2; **16**, 37513-14-7; **18**, 91229-91-3; **19**, 1499-55-4; **20**, 91229-93-5; **21**, 91229-94-6; **22**, 26048-86-2; **24**, 91229-92-4; **26**, 91229-95-7; **27**, 91229-96-8; **28**, 30924-93-7; **29**, 91229-97-9; **30**, 37787-77-2; **31**, 89545-84-6; **32**, 91229-98-0; di-*tert*-butyl dicarbonate, 24424-99-5; *O*-benzyl acetohydroxamate, 4797-81-3; *O*-benzyl-*N*-tosylhydroxylamine, 1576-39-2; N^{α}-(*tert*-butyloxycarbonyl)-γ-methyl-L-glutamic acid, 45214-91-3; O^{α}-benzyl N^2-(*tert*-butyloxycarbonyl)-γ-methyl-L-glutamic acid α-hydroxamate, 91229-99-1; N^{α}-(*tert*-butyloxycarbonyl)-γ-[-(trimethylsilyl)ethyl]-L-glutamic acid, 91230-00-1; O^{α}-benzyl N^{α}-(*tert*-butoxycarbonyl)-γ-[2-(trimethylsilyl)ethyl]-L-glutamic acid α-hydroxamate, 91230-01-2; N^{α}-(*tert*-butyloxycarbonyl)-L-proline, 15761-39-4; thiazolidine-2-thione, 96-53-7; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; 1-benzyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoate, 91230-02-3; *O*-benzyl (*S*)-2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoate hydroxamate, 91230-03-4; 2-[(*tert*-butyloxycarbonyl)amino]-5-acetoxypentanoic acid, 109-52-4; L-glutamic acid, 56-86-0.

Synthesis and Structural Studies of Certain Novel Imidazo[1,2-*b*]pyrazole Nucleosides[1,2]

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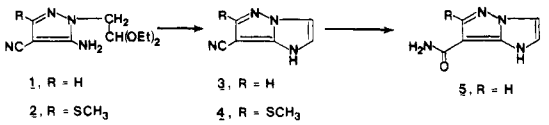
Received March 12, 1984

The first chemical syntheses of imidazo[1,2-*b*]pyrazole-7-carbonitrile (**3**), the corresponding ribonucleosides (**10** and **16**), and certain related derivatives of a new class of purine analogues containing a bridgehead nitrogen atom are described. Condensation of 2-hydrazinoacetaldehyde diethyl acetal with (ethoxymethylene)malononitrile and subsequent ring closure gave **3**. Direct glycosylation of the Me_3Si derivative of **3** with blocked ribofuranose (**8**) in the presence of trimethylsilyl triflate gave the blocked nucleosides **9** and **15**, which on further ammonolysis gave 1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (**10**) and the corresponding N-5 glycosyl isomer (**16**), the first known example of a nucleoside in which the glycon moiety is attached to a nitrogen adjacent to a bridgehead nitrogen atom. The isomeric ratio of **9** and **15** was found to be time dependent. Similarly, reaction of 2,2-bis(methylthio)-1-cyanoacrylonitrile with 2-hydrazinoacetaldehyde diethyl acetal gave 6-(methylthio)-imidazo[1,2-*b*]pyrazole-7-carbonitrile (**4**). Glycosylation of the Me_3Si derivative of **4** with **8** and subsequent debenzoylation gave 6-(methylthio)-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (**12**). The absolute structures of **10** and **16** were determined by single-crystal X-ray diffraction techniques employing Mo Kα radiation. The glycosidic bond in the kinetically less stable isomer **16** is considerably longer (1.505 Å) than the corresponding bond in the more stable isomer **10** (1.451 Å). The two five-membered azole rings in both **10** and **16** are planar and the dihedral angle between the planes in each compound is less than 1°.

As part of an ongoing synthetic program directed toward the preparation of novel azole nucleosides, we became interested in aromatic azapentalene nucleosides. Until the present work, nucleosides of this type have not been described, and we wish to report the first chemical synthesis and structural elucidation of certain imidazo[1,2-*b*]pyrazole nucleosides. Azapentalene ring systems, which contain two heteroaromatic five-membered rings fused together, can be construed to mimic purine analogues in which the six-membered pyrimidine ring has been contracted in size by one member. Nucleoside derivatives of these ring systems thus result in a class of compounds that may possibly exhibit interesting biological activity.

Scheme I



Replacement of the heterocyclic moiety in naturally occurring purine nucleosides with an appropriately substituted azapentalene ring will result in purine nucleoside

(1) A portion of this work was presented at the 184th American Chemical Society Meeting, Kansas City, MO, September, 1982. Wood, S. G.; Revankar, G. R.; Robins, R. K. "Abstracts of Papers", MEDI 34. This work is taken, in part from the Ph.D. Dissertation of S.G.W., Brigham Young University, 1983.

(2) This investigation was supported in part by U. S. Army Medical Research and Development Command Contract DAMD 17-79-C-9046. This is contribution number 1708 to the Army Research on Antiparasitic Drugs.

0022-3263/84/1949-3534$01.50/0

analogues with an altered geometry. Although the geometric configuration of the ring possessing the glycon moiety will presumably be similar to that of the natural purine nucleosides, the substituents in the adjoining ring will assume a slightly different spatial relationship with respect to the pyrimidine ring substituents.

In order to investigate this new class of nucleosides, imidazo[1,2-b]pyrazole-7-carbonitrile (3) was selected as the starting material for the glycosylation studies. Modification of a synthesis of this ring system[3,4] provided the hitherto unknown imidazo[1,2-b]pyrazole with a carbonitrile function which is amenable to further transformation reactions.

Methods and Discussion

One of the starting materials needed for the glycosylation studies, imidazo[1,2-b]pyrazole-7-carbonitrile (3), was prepared by the condensation of 2-hydrazinoacetaldehyde diethyl acetal with (ethoxymethylene)malononitrile, which gave the alkylated pyrazole 1 (Scheme I). Ring closure of 1 under acid-catalyzed hydrolytic conditions gave 3. The structure of 3 was confirmed by the inspection of its IR spectrum, which revealed a nitrile band at 2205 cm^{-1}. Further hydrolysis of 3 with polyphosphoric acid gave imidazo[1,2-b]pyrazole-7-carboxamide (5). The ^1H NMR and IR spectra are in support of this structure. The IR spectrum of 5 revealed the absence of the nitrile band and the presence of an amide carbonyl band at 1640 cm^{-1}. A similar condensation of 2,2-bis(methylthio)-1-cyanoacrylonitrile[5] with 2-hydrazinoacetaldehyde diethyl acetal gave the intermediate 5-amino-1-(2,2-diethoxyethyl)-3-(methylthio)pyrazole-4-carbonitrile (2), which in the presence of 1 N H_2SO_4 ring closed to 6-(methylthio)-imidazo[1,2-b]pyrazole-7-carbonitrile (4). The ring closure was apparent as evidenced by the appearance of aromatic proton resonance in the ^1H NMR spectrum (Me_2SO-d_6) at δ 7.38 and 7.77, which were assigned to C-2(H) and C-3(H), respectively.

For the glycosylation studies, the trimethylsilyl procedure, as described by Vorbrüggen and co-workers[6] was found to be successful. Glycosylation of the trimethylsilyl derivative of 3 (6) with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (8) in the presence of 1.4 mol equiv of trimethylsilyl trifluoromethanesulfonate (Me_3Si triflate) at ambient temperature for 3 days gave a 1:3 isomeric mixture of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[1,2-b]pyrazole-7-carbonitrile (9) and 5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[1,2-b]pyrazole-7-carbonitrile (15), respectively (Scheme II). Compounds 9 and 15 were separated on a silica gel column by using prepartive LC techniques. The structure of these blocked nucleosides were unequivocally established by single-crystal X-ray diffraction studies of the respective debenzoylated derivatives.

A more careful investigation of this glycosylation reaction revealed that the isomeric product distribution of 9 and 15 varied according to time and temperature. A study was done to obtain quantitative data concerning this observation. The imidazo[1,2-b]pyrazole-7-carbonitrile (3) was glycosylated in accordance with the above conditions. The reaction was allowed to stir at room temperature for 6 days. Periodically, a neutralized aliquot of the reaction

Scheme II

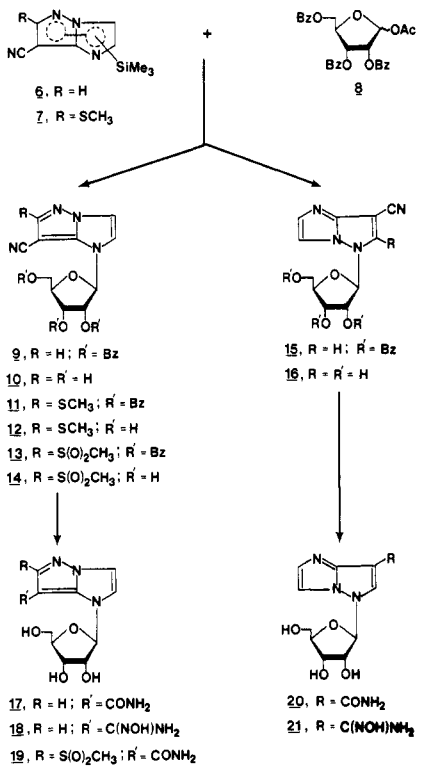


Table I. Isomeric Ratio of the Glycosylation Products of Imidazo[1,2-b]pyrazole-7-carbonitrile (3)

nucleoside	time				
	1 h	1 day	2 days	4 days	6 days
15	96%	93%	88%	72%	47%
9	4%	7%	12%	28%	53%

mixture was analyzed by HPLC. The isomeric ratio of 9:15 was computed by comparing relative peak heights and UV absorption values at 254 nm. The results of this study are shown in Table I. Initially isomer 15 is formed almost exclusively. Over a period of time, isomer 9 formed, until after six days the ratio of 9:15 is almost 1:1. This rearrangement of 15 to 9 could be accelerated by heating the reaction mixture itself or a solution of pure 15 in CH_3CN in the presence of Me_3Si triflate, but not without the formation of accompanying degradation products. This conversion of 15 to 9 is analogous to the rearrangement of 8-glycosyl-8-azapurines to 9-glycosyl-8-azapurines as reported by Montgomery and Elliott.[7] No other products or starting heterocycle could be detected by TLC in a sample taken 1 h after addition of Me_3Si triflate to the reaction mixture. These data suggest that under these glycosylation conditions, formation of the isomer 15 is kinetically controlled, whereas the formation of the isomer 9 is thermodynamically controlled. It is especially noteworthy that the glycon moiety in 15 is attached to a nitrogen adjacent to a bridgehead nitrogen atom. Such a direct glycosylation on a nitrogen adjacent to a bridgehead nitrogen has not been previously reported in the literature.[8]

Subsequent treatment of 9 and 15 with $MeOH/NH_3$ provided 1-β-D-ribofuranosylimidazo[1,2-b]pyrazole-7-carbonitrile (10) and the corresponding N-5 glycosyl derivative (16), respectively. Crystals suitable for single-

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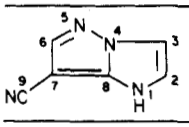
Table II. Carbon-13 Chemical Shifts from Internal Me_4Si[a]



	chemical shift, δ					
	C-2	C-3	C-6	C-7	C-8	C-9
3	119.6	109.4	146.1	65.8	140.9	115.2
5	119.6	108.5	141.9	93.6	139.9	164.4
10	114.7	110.6	146.5	66.4	140.1	114.7
16	113.3	109.2	138.8	69.8	143.6	113.3

[a] Carbon-13 spectra were obtained at 22.5 MHz with a JEOL FX 90Q spectrometer.

crystal X-ray analysis were obtained from samples of both of these deblocked nucleosides. The X-ray diffraction analysis confirmed the site of glycosylation and the β anomeric configuration for both **10** and **16**.

The ^1H NMR spectra of imidazo[1,2-*b*]pyrazole-7-carbonitrile (**3**) and the corresponding nucleosides **10** and **16** displayed some interestingly characteristics. The spectrum of **3** in Me_2SO-d_6 revealed three aromatic signals which were assigned by selective irradiation studies. In addition to the expected coupling between the adjacent imidazole ring protons, the C-6 proton ($J_{2,3}$ = 2.8 Hz) is coupled (J = 0.7 Hz) over 6 bonds with the C-2 proton. This type of long-range cross-ring coupling is characteristic of azapentalene systems.[3,9] The assignments of these proton resonances are based on first-order approximations. The ^1H NMR spectra of both **3** and **10** are quite similar in the aromatic region. The nucleoside **10** exhibited downfield shifts of 0.29 ppm for C-2(H), 0.16 ppm for C-3(H), and 0.08 ppm for C-6(H) with respect to **3**. The cross-ring coupling evident in the heterocycle **3** is also observed in the nucleoside **10**. The N-5 isomer **16** exhibited a considerable upfield shift for C-2(H) (0.19 ppm) and downfield shifts for C-3(H) (0.34 ppm) and C-6(H) (0.77 ppm) relative to **3**. All the signals appear as singlets with no cross-ring coupling evident, as well as no evidence of the more pronounced C-2(H) and C-3(H) coupling. The anomeric proton of **16** relative to **10** experienced a 0.12 ppm downfield shift.

In Table II the ^{13}C chemical shifts for **3**, **5**, **10**, and **16** are listed. The base **3** displayed the six peaks as expected. Selective irradiation of various proton resonances allowed the assignment of the signals. The bridgehead carbon (C-8) was assigned as the signal at 140 ppm region and the nitrile carbon (C-9) was found in the usual region, around 115 ppm. The signal at 65.8 ppm was initially assigned to C-7 by default. In order to verify the assignment of the aromatic C-7 signal as that of the abnormally upfield peak at 65.8 ppm, the ^{13}C spectrum of the carboxamide derivative **5** was obtained. The spectrum of **5** revealed the absence of the nitrile peak (115.2 ppm) and the appearance of the carbonyl carbon (C-9) signal at 164.4 ppm. In addition to the above difference, the presumed C-7 signal experienced a downfield shift of 27.8 ppm relative to **3**. The other signals were not significantly affected, thus demonstrating that the assignments were indeed correct. The ^{13}C NMR spectrum of **10**, like that of the ^1H NMR spectrum, was not markedly different from that of **3**. The C-2 and C-6 carbon chemical shift values for the N-5 isomer **16** were significantly different from those of the base **3**. The C-2 and C-6 resonances in **16** showed an upfield shift of 6.3 ppm and 7.3 ppm, respectively, with respect to **3**.

The UV and IR absorption spectra also revealed a striking difference between the positional isomers **10** and **16**. The UV spectrum of **10** (λ_{max} 242 nm in pH 1 and 7) is similar to that of **3** (λ_{max} 240 nm in pH 1 and 7). Compound **16** (λ_{max} 276 nm in pH 7 and 11), on the other hand, showed a considerable bathochromic shift (34 nm) in the UV absorption spectrum relative to that of isomer **10**. The IR spectra of **10** and **16** were quite different in appearance. Most notably the N-5 isomer **16** absorbed strongly at 1565, 1540, and 1110 cm^{-1}. Similar absorption at these frequencies was completely absent in the N-1 isomer **10**. However, the compound **10** absorbed strongly in the IR at 1610, 1595, and 1185 cm^{-1}, similar to the absorption of the base **3** (1620, 1585, and 1180 cm^{-1}).

The carbonitrile function of **10** and **16** was available for further functionalization by reaction with various nucleophiles. The carboxamides **17** and **20** were prepared by the treatment of **10** and **16** with NH_4OH/H_2O_2, respectively. Similarly, compounds **10** and **16** were converted to the *N*-hydroxylcarboximidamides (**18** and **21**) by reacting the respective nitrile compounds with free hydroxylamine in EtOH. Compound **17** showed a large downfield chemical shift (δ 6.90) for the anomeric proton as compared to **10** (δ 5.72). The observed 1.18 ppm downfield shift difference of the anomeric proton of **17** as compared to **10** can be attributed to the anisotropic effect of the carboxyl group on the anomeric proton in **17**.[10]

Several 6-methylthio-substituted imidazo[1,2-*b*]pyrazole nucleosides were also prepared. It was hoped that the methylthio group would serve as a useful leaving group, thus providing a site for nucleophilic substitution on the ring. Glycosylation of the trimethylsilyl derivative of **4** (**7**) with **8** in the presence of Me_2Si triflate at ambient temperature gave rise to products similar to those formed by glycosylation of **3**. The nucleoside formed initially was rearranged with time to yield the more stable product. This rearrangement occurs faster and more completely than was the case with **3**. Attempts to isolate the nucleoside formed initially failed. However, the more stable isomer 6-(methylthio)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazole-7-carbonitrile (**11**) was isolated in good yield as a crystalline solid. Oxidation of **11** with *m*-chloroperoxybenzoic acid in CH_2Cl_2 readily gave the corresponding methyl sulfone derivative **13**. Treatment of **11** with $MeOH/NH_3$ gave the debenzoylated nucleoside 6-(methylthio)-1-β-D-ribofuranosylimidazo[1,2-*b*]-pyrazole-7-carbonitrile (**12**). A similar debenzoylation of the blocked sulfone **13** furnished 7-cyano-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazol-6-yl methyl sulfone (**14**). Hydrolysis of the nitrile function of **14** with NH_4OH in the presence of H_2O_2 gave 7-carbamoyl-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazol-6-yl methyl sulfone (**19**). Attempts at nucleophilic displacement of the methylsulfonyl group in compounds **14** and **19** failed.

The site of glycosylation in **11** was assigned by analogy to compound **9**. When comparing the ^1H NMR of the base **4** with that of the nucleoside **12**, very little difference in chemical shift was noted. The small downfield shift difference for the C-2(H) was the most noatable (0.12 ppm). This difference parallels with those observed in compounds **3** and **10**. The UV spectrum of **12** was also very similar to that of **4**, which is in parallel with **3** and its nucleoside **10**. The most striking evidence that the blocked nucleoside **11** was indeed the N-1 isomer was found in the large difference in chemical shift values between the anomeric proton of **14** (δ 5.70) and the corresponding carboxamide derivative **19** (δ 6.69). This difference (0.99 ppm), which is due to the anisotropic effect of the carbonyl group on the anomeric proton, was very similar to the difference

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Table III. Comparison of Observed Bond Lengths of the Aglycon of Isomers 10 and 16 with Theoretical Values[a]

	compd 10			compd 16		
bond	bond order	calcd bond length, Å	obsd bond length,Å	bond order	calcd bond length,Å	obsd bond length, Å
N(1)–C(2)	0.359	1.385	1.399 (2)	0.470	1.365	1.376 (5)
C(2)–C(3)	0.884	1.350	1.352 (3)	0.831	1.360	1.349 (8)
C(3)–N(4)	0.344	1.388	1.397 (2)	0.411	1.376	1.384 (7)
N(4)–N(5)	0.326	1.408	1.374 (2)	0.184	1.435	1.369 (5)
N(5)–C(6)	0.785	1.309	1.329 (3)	0.483	1.363	1.344 (7)
C(6)–C(7)	0.528	1.410	1.418 (2)	0.718	1.381	1.380 (7)
C(7)–C(8)	0.610	1.400	1.401 (2)	0.466	1.430	1.431 (7)
C(8)–N(1)	0.416	1.375	1.363 (2)	0.690	1.326	1.337 (5)
N(4)–C(8)	0.481	1.363	1.353 (2)	0.438	1.371	1.358 (7)
C(7)–C(9)	0.449	1.430	1.422 (2)	0.430	1.433	1.429 (7)
C(9)–N(9)	1.855	1.136	1.142 (2)	1.868	1.134	1.136 (8)

[a] Calculated using standard Streitwieser[13] values for h_x and K_{xy}, except as listed below. For **10** and **16**: h_x, N(9) 0.70, C(9) 0.20; K_{xy}, N(4)–N(5) 0.75, C(9)–N(9), 1.30. For **10**: K_{xy}, N(5)–C(6) 1.10. For **16**: K_{xy}, N(1)–C(8) 1.10.

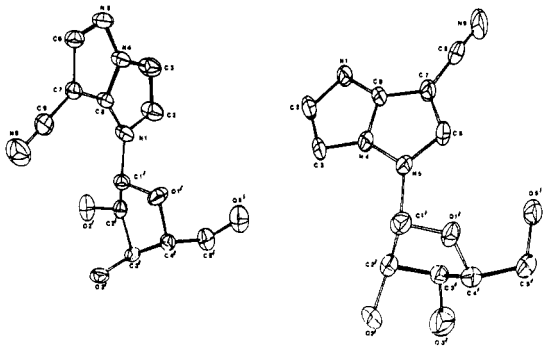

Figure 1. ORTEP drawings of the N-1 ribosyl isomer **10** and the N-5 ribosyl isomer **16**.

observed between **10** and **17** (1.18 ppm).

X-ray Crystallographic Analysis. An X-ray structural study of the two isomers **10** and **16** clearly showed that the N-5 isomer **16** did contain a bridgehead nitrogen adjacent to the glycosidic bond. The conformations and the atom labels of the molecules are shown in Figure 1. Both the isomers possess β configurations about the anomeric carbon. The bond lengths and angles in the glycon moiety are normal.[11] The sugar conformations of the two isomers, however, differ. The sugar in the N-5 isomer has the $^3T_2$ conformation with the torsion angles O(5′)–C(5′)–C(4′)–O(1′) and O(5′)–C(5′)–C(4′)–C(3′) being −59.8° and +60.3°, respectively. The sugar in the N-1 isomer has the $_3T^2$ conformation with the O(5′)–C(5′)–C(4′)–O(1′) and O(5′)–C(5′)–C(4′)–C(3′) torsion angles having the values of −63.2° and +62.7°, respectively. The glycosidic torsion angles in **16**, i.e., O(1′)–C(1′)–N(5)–N(4), is −174.2°, while in **10**, i.e., O(1′)–C(1′)-N(1)-C(8), is 101.0°. The bond lengths of the heterocyclic portions of the two molecules are of interest and will be discussed and compared with theoretical values obtained from Hückel calculation. It is significant that the glycosidic bond in the less stable isomer **16** is considerably longer than the corresponding bond in the more stable isomer **10** (1.505 (6) and 1.451 (2) Å, respectively). This difference supports the observation that the glycosidic bond in **16** is readily cleaved and that on standing for several hours in the presence of Me_3Si triflate, **15** is converted to **9**.

Least-squares planes were calculated for each five-membered ring of the fused ring systems for the two isomers. In each case, the five-membered rings are planar. The largest deviation of any atom from its five-membered ring plane is 0.015 Å, the distance N(1) deviates from the plane calculated for N(1), C(2), C(3), N(4), C(8) in **10**. The dihedral angle between the least-squares planes in **10** is 0.84°, while it is 0.87° in **16**. Similar dihedral angles found in other fused five-membered ring systems are 1.6° in 1,6-dimethyl-7-(ethoxycarbonyl)pyrazole[1,5-*d*]tetrazole[12] and 3.6° in 3-amino-1-β-D-ribofuranosyl-*s*-triazolol[5,1-*c*]-*s*-triazole.[13]

The molecules of each isomer are linked by intermolecular hydrogen bonds. The donor atoms in each case are the alcoholic oxygen atoms of the sugar as each molecule forms hydrogen bonds with three other molecules. In the N-5 isomer, O(2′) is hydrogen bonded to N(9), O(3′) to O(5′), and O(5′) to N(1) of different molecules. In the N-1 isomer, O(2′) is hydrogen bonded to O(3′), O(3′) to N(5), and O(5′) to O(2′) of different molecules. The hydrogen bond data are listed in the supplementary talbes.

Table III lists the X-ray (observed) and theoretical bond distances for the heterocyclic portion of each isomer. The theoretical values were obtained from Hückel calculations. The bond distances between chemically equivalent atoms in the portions of the heterocycles containing N(1), C(2), C(3), N(4), and N(5) are similar, but comparison of bond distances in the remainder of the heterocycle shows significant differences. In order to compare these bond lengths to theoretical values and to correlate some spectroscopic results obtained with the isomers, Hückel molecular orbital calculations were carried out for 1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile and 5*H*-imidazo-[1,2-*b*]pyrazole-7-carbonitrile. The standard atom and bond values of Streitwieser[14] were used to obtain the secular determinant except as noted in Table III. The theoretical values obtained by this treatment are in good agreement with the observed chemical, spectroscopic, and X-ray data. The model predicts the 1-H compound to be the more stable tautomer by 0.08 eV, and this is substantiated by the fact that the N-1 glycosyl isomer **10** is thermodynamically more stable. The model is also predictive of the longer wavelengths observed for the N-5 isomer **16** with respect to **10** in the UV spectrum. The ratio of the energy differences between the highest occupied orbital (HOMO) and the lowest unoccupied orbital (LUMO) for **16** as compared to **10** is 1:1.12. The ratio of the observed UV transition energies for **16** to **10** is 1:1.14. The model predicts a π electron density of greater than

(11) Tables of atomic parameters, bond length and angles, least-squares plane, and hydrogen bond data are available as supplementary material.

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(13) Wood, S. G.; Dalley, N. K.; George, R. D.; Robins, R. K.; Revankar, G. R. *Nucleosides Nucleotides* **1984**, *3*, 187–194.

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1.1 on C-7 in both cases. This is reflected in the upfield ^{13}C NMR chemical shifts for this carbon (~65 ppm). Finally, good agreement exists between the bond lengths observed by X-ray and those calculated from the predicted bond orders, except for the N(4)–N(5) bond.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H NMR) spectra were determined at 89.6 MHz with a JEOL FX 90Q spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The presence of solvent as indicated by elemental analysis was verified by ^1H NMR. Infrared spectra (IR) were obtained on a Beckman Acculab 2 spectrophotometer and ultraviolet spectra (UV, sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and Robertson Labs, Florham Park, NJ. Thin-layer chromatography (TLC) was run on silica gel 60 F-254 plates (EM Reagents). J. T. Baker silica gel (70–230 mesh) was used for column chromatography. Preparative liquid chromatography (LC) was run utilizing the Waters Prep 500 LC system. All solvents used were reagent grade. Detection of components on TLC was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 30 °C.

5-Amino-1-(2,2-diethoxyethyl)pyrazole-4-carbonitrile (1). To a solution of 2-hydrazinoacetaldehyde diethyl acetal[3] (12.0 g, 81 mmol) in ethanol (25 mL) was added a solution of (ethoxymethylene)malononitrile (9.8 g, 80 mmol) in ethanol (100 mL) and the mixture was stirred at room temperature for 2 days. The solvent was evaporated and the residual syrup was dissolved in ether (150 mL). The insoluble solid was removed by filtration and discarded. Hexane (about 10% by volume) was added to the ether solution resulting in the precipitation of a dark oil. The oil was extracted with ether (2 × 75 mL) and the combined organic layer was evaporated to dryness. On standing, the residual oil crystallized (15.2 g, 85%). This product was used without further purification for subsequent ring closure. An analytical sample was prepared by recrystallization from hexane/ethyl acetate: mp 84–85 °C; IR (KBr) ν 1230 (CHOEt), 2200 (CN), 2900–3400 (NH_2) cm^{-1}; UV λ_{max} (EtOH) 228 nm (ϵ 9300); ^1H NMR (acetone-d_6) δ 1.18 (t, 6, CH_3), 3.70 (m, 4, CH_2), 4.22 (d, 2, CH_2), 4.85 (t, 1, CH), 5.80 (s, 2, NH_2), 7.56 (s, 1, C_3H). Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.88; H, 7.47, N, 25.03.

Imidazo[1,2-*b*]pyrazole-7-carbonitrile (3). A solution of 1 (11.20 g, 50 mmol) in 1 N HCl (100 mL) was heated on a steam bath for 30 min. On cooling (0–5 °C), the solid that separated was collected and crystallized from EtOH as needles: yield 4.0 g (60%); mp >250 °C dec; IR (KBr) ν 2205 (CN) cm^{-1}; UV λ_{max} (pH 1) 240 nm (ϵ 6200); UV λ_{max} (pH 7) 240 nm (ϵ 6600); UV λ_{max} (pH 11) 268 nm (ϵ 4600); ^1H NMR (Me_2SO-d_6) δ 7.43 (d, 1, J = 3.0 Hz, C_2H), 7.82 (d, 1, J = 3.0 Hz, C_3H), 8.12 (s, 1, C_6H). Anal. Calcd for $C_6H_4N_4$: C, 54.55; H, 3.04; N, 42.41. Found: C, 54.46; H, 3.13; N, 42.52.

Imidazo[1,2-*b*]pyrazole-7-carboxamide (5). Compound 3 (1.32 g, 10 mmol) was added to polyphosphoric acid (4.0 g) and the mixture was heated on a hot plate (150 °C) until the resulting syrup was clear (~15 min). The reaction mixture was cooled (0–5 °C) and carefully diluted with ice water (50 mL). The clear aqueous solution was neutralized with solid $NaHCO_3$ and concentrated to ~10 mL. The solid that precipitated was collected and washed with cold water (5 mL). Concentration of the filtrates gave a second crop of the material. The combined solids were crystallized from H_2O/EtOH as needles: yield 0.90 g (60%); mp 248–249 °C; IR (KBr) ν 1640 (C=O) cm^{-1}; UV λ_{max} (pH 1) 237 nm, (sh) (ϵ 6500), 258 (8200); UV λ_{max} (pH 7) 245 nm, (sh) (ϵ 7500), 263 (12 300); UV λ_{max} (pH 11) 222 nm (ϵ 9400), 267 (8200); ^1H NMR (Me_2SO-d_6) δ 6.90 (br s, 2, $CONH_2$), 7.36 (d, 1, J = 1.5 Hz, C_2H), 7.74 (d, 1, J = 2.0 Hz, C_3H), 8.26 (s, 1, C_6H), 13.50 (br s, 1, NH). Anal. Calcd for $C_6H_6N_4O$: C, 48.01; H, 4.03; N, 37.32. Found: C, 48.00; H, 4.35; N, 36.97.

5-Amino-1-(2,2-diethoxyethyl)-3-(methylthio)pyrazole-4-carbonitrile (2). In the same manner as for 1, the title compound was prepared using 2,2-bis(methylthio)-1-cyanoacrylonitrile[5] (11.5 g, 68 mmol) and 2-hydrazinoacetaldehyde diethyl acetal (10.0 g, 68 mmol) in EtOH (115 mL) to yield 15.55 g (85%): mp 68–69 °C; IR (KBr) ν 1240 (CHOEt), 2200 (CN), 3320, 3400 (NH_2) cm^{-1}; UV λ_{max} (pH 1, 7 and 11) 240 nm, (sh) (ϵ 5800); ^1H NMR (acetone-d_6) δ 1.05 (m, 6, CH_3), 2.30 (s, 3, SCH_3), 3.80 (d, 2, J = 4.0 Hz, CH_2), 4.60 (m, 4, CH_2), 4.75 (t, 1, CH), 5.65 (br s, 2, NH_2). Anal. Calcd for $C_{11}H_{18}N_4O_2S$: C, 48.87; H, 6.71; N, 20.72; S, 11.86. Found: C, 49.15; H, 6.70; N, 20.62; S, 11.91.

6-(Methylthio)imidazo[1,2-*b*]pyrazole-7-carbonitrile (4). In the same manner as for 3, treatment of 2 (15.0 g, 48 mmol) with 1 N H_2SO_4 gave 4.70 g (55%) of the title compound: mp 187 °C (sinters); IR (KBr) ν 2210 (CN) cm^{-1}; UV λ_{max} (pH 1) 257 nm (ϵ 7400); UV λ_{max} (pH 7) 257 nm (ϵ 8000); UV λ_{max} (pH 11) 260 nm (sh) (ϵ 6200); ^1H NMR (Me_2SO-d_6) δ 2.60 (s, 3, SCH_3), 7.38 (d, 1, J = 2.7 Hz, C_2H), 7.77 (d, 1, J = 2.7 Hz, C_3H). Anal. Calcd for $C_7H_6N_4S$: C, 47.17; H, 3.40; N, 31.43. Found: C, 47.02; H, 3.38; N, 31.54.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazole-7-carbonitrile (9) and 5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazole-7-carbonitrile (15). A mixture of dry 3 (5.0 g, 38 mmol), hexamethyldisilazane (HMDS, 60 mL), and $(NH_4)_2SO_4$ (0.10 g) was heated under reflux for 3 h with the exclusion of moisture. Excess HMDS was removed by distillation to provide the crystalline Me_3Si derivative 6. To a solution of 6 in dry CH_3CN (200 mL) was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (8, 19.15 g, 28 mmol) and trimethylsilyl trifluoromethanesulfonate (Me_3Si triflate, 9.7 mL, 53 mmol). The reaction mixture was stirred for 3 days at ambient temperature. The CH_3CN was evaporated and the residue was dissolved in EtOAc (300 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ solution (3 × 50 mL) and dried over Na_2SO_4. The organic layer was evaporated and the resulting syrup was purified by preparative LC and eluted with acetone:hexane (35:65, v/v). Compound 9 was found in the first fractions followed by compound 15. Evaporation of the solvent gave 2.2 g (10%) of 9 and 6.0 g of 15 (27%).

The above procedure was modified to obtain a 95% yield of 15 by adding the Me_3Si triflate catalyst to a cold (0–5 °C) solution of 6 and the blocked ribofuranose (8) in CH_3CN. After stirring 1 h in the cold, the solution was poured into saturated $NaHCO_3$ solution (150 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed. The residual oil was purified on a silica gel column with $CHCl_3$:H_3CCOCH_3 (9:1, v/v) as the solvent to afford 15. Compound 9 partially crystallized out of the crude syrupy mixture upon the addition of acetone.

Compound 9: mp 166–167 °C; IR (KBr) ν 1725 (C=O), 2220 (CN) cm^{-1}; ^1H NMR (acetone-d_6) δ 5.50 (d, 1, J = 5.0 Hz, $C_1'H$), 6.70 to 7.60 (m, 18, C_2H, C_3H, C_6H, 3 COC_6H_5) and other sugar protons. Anal. Calcd for $C_{32}H_{24}N_4O_7$: C, 66.66; H, 4.19; N, 9.71. Found: C, 66.66; H, 4.16; N, 9.70.

Compound 15 was obtained as an amorphous powder: IR (KBr) ν 1725 (C=O), 2220 (CN) cm^{-1}; ^1H NMR (acetone-d_6) δ 5.97 (d, 1, J = 5.0 Hz, $C_1'H$), 6.50 (s, 1, C_2H), 6.60 to 7.60 (m, 16, C_3H, 3 COC_6H_5), 8.0 (s, 1, C_6H) and other sugar protons. Anal. Calcd for $C_{32}H_{24}N_4O_7$: C, 66.66; H, 4.19; N, 9.71. Found: C, 66.59; H, 4.31; N, 9.63.

1-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (10). A solution of 9 (3.0 g, 5.2 mmol) in MeOH/NH_3 (saturated at 0 °C, 100 mL) was allowed to stir at room temperature for 16 h in a pressure bottle. The solvent was removed and the residue was triturated with boiling benzene (3 × 50 mL) to remove the benzamide. The residual gum was crystallized from EtOH to yield 0.96 g (70%): mp 182–183 °C; IR (KBr) ν 2205 (CN) cm^{-1}; UV λ_{max} (pH 1) 242 nm (ϵ 17 700); UV λ_{max} (pH 7) 242 nm (ϵ 18 500); UV λ_{max} (pH 11) 242 nm (ϵ 18 200); ^1H NMR (Me_2SO-d_6) δ 5.72 (d, 1, J = 5.0 Hz, $C_1'H$), 7.72 (d, 1, J = 2.0 Hz, C_2H), 7.98 (d, 1, J = 2.0 Hz, C_3H), 8.20 (s, 1, C_6H) and other sugar protons. Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.57; N, 21.20. Found: C, 50.13; H, 4.75; N, 20.85.

5-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (16). Following the procedure as described for 10, compound 15 (2.50 g, 43 mmol) yielded 0.80 g (75%) of the title compound, which was crystallized from EtOH: mp 149–150 °C; IR (KBr) ν 2205 (CN) cm^{-1}; UV λ_{max} (pH 1) 255 nm (ϵ 11 900); UV λ_{max} (pH

7) 276 nm (ε 10 200); UV λ_{max} (pH 11) 276 nm (ε 11 900); ^{1}H NMR (Me_2SO-d_6) δ 5.84 (d, 1, J = 5.0 Hz, $C_{1'}H$), 7.24 (s, 1, C_2H), 8.16 (s, 1, C_3H), 8.89 (s, 1, C_6H) and other sugar protons. Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.57; N, 21.20. Found: C, 49.92; H, 4.75; N, 20.90.

1-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carboxamide (17). Compound **10** (1.50 g, 5.68 mmol) was placed in concentrated NH_4OH solution (20 mL) and 30% H_2O_2 (1.0 mL) was added. The reaction mixture was stirred at room temperature for 16 h and the excess H_2O_2 was destroyed by stirring with 10% Pd/C. The Pd/C was removed by filtration on a Celite pad and the filtrate was evaporated to dryness. The residue was crystallized from H_2O/EtOH to yield 1.2 g (75%): mp 252–253 °C; IR (KBr) ν 1660 (C=O) cm^{-1}; UV λ_{max} (pH 1) 248 nm (ε 10 400); λ_{max} (pH 7) 248 nm (ε 11 000); λ_{max} (pH 11) 248 nm (ε 11 150); ^{1}H NMR (Me_2SO-d_6) δ 6.90 (d, 1, J = 4.7 Hz, $C_{1'}H$), 7.00 (br s, 2, $CONH_2$), 7.50 (m, 1, C_2H), 7.70 (d, 1, J = 3.0 Hz, C_3H), 8.03 (d, 1, J = 1.0 Hz, C_6H) and other sugar protons. Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.80; H, 5.00; N, 19.85. Found: C, 46.49; H, 5.14; N, 19.62.

5-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-carboxamide (20). In the same manner as for **17**, 1.50 g (5.68 mmol) of **16** gave 0.80 g (50%) of **20**: mp 145–146 °C; IR (KBr) ν 1640 (C=O) cm^{-1}; UV λ_{max} (pH 1) 213 nm (ε 12 300), 258 (5400); UV λ_{max} (pH 7) 217 nm (ε 11 000), 272 (4000); UV λ_{max} (pH 11) 220 nm (ε 11 600), 279 (4700); ^{1}H NMR (Me_2SO-d_6) δ 1.20 and 4.20 (t and m, CH_3CH_2OH), 5.75 (d, 1, J = 6.0 Hz, $C_{1'}H$), 7.15 and 7.45 (br s, 2, $CONH_2$), 7.20 (m, 1, C_2H), 8.02 (d, 1, J = 1.4 Hz, C_3H), 8.42 (d, 1, J = 1.0 Hz, C_6H) and other sugar protons. Anal. Calcd for $C_{11}H_{14}N_4O_5 \cdot {}^1/_2$EtOH: C, 47.21; H, 5.61; N, 18.35. Found: C, 47.24; H, 5.66; N, 18.20.

1-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-*N*-hydroxycarboximidamide (18). To a solution of **10** (1.6 g, 6.0 mmol) in absolute EtOH (50 mL) was added free hydroxylamine (3.0 g) and the mixture was heated under reflux for 1.5 h with the exclusion of moisture. The reaction mixture was cooled, filtered, and evaporated to dryness. The residue was triturated with cold EtOH (10 mL), filtered, and the solid crystallized from aqueous EtOH to yield 1.0 g (59.3%): mp 195 °C dec; IR (KBr) ν 1540, 1590, 1640 (C=NOH) cm^{-1}; UV λ_{max} (pH 1) 251 nm (ε 9800); λ_{max} (pH 7) 251 nm (ε 8900); λ_{max} (pH 11) 247 nm (ε 7000); ^{1}H NMR (Me_2SO-d_6) δ 5.65 (br s, 2, NH_2), 6.82 (d, 1, J = 4.0 Hz, $C_{1'}H$), 7.51 (m, 1, C_2H), 7.50 (d, 1, J = 3.0 Hz, C_3H), 7.88 (d, 1, J = 1.0 Hz, C_6H), 9.10 (br s, 1, NOH) and other sugar protons. Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.51; H, 5.15; N, 23.41.

5-β-D-Ribofuranosylimidazo[1,2-*b*]pyrazole-7-*N*-hydroxycarboximidamide (21). In the same manner as for **18**, treatment of **16** (2.0 g, 7.6 mmol) with NH_2OH (4.5 g) in EtOH (50 mL) gave 1.20 g (53%) of **21**: mp 151–153 °C dec; IR (KBr) ν 1640 (C=NOH) cm^{-1}; UV λ_{max} (pH 1) 261 nm (ε 8000); UV λ_{max} (pH 7), 267 nm (ε 8300); UV λ_{max} (pH 11) 274 nm (ε 7730); ^{1}H NMR (Me_2SO-d_6) δ 5.65 (d, 1, J = 5.5 Hz, $C_{1'}H$), 5.70 (br s, 2, NH_2), 7.16 (s, 1, C_2H), 7.95 (d, 1, J = 0.8 Hz, C_3H), 8.12 (s, 1, C_6H), 9.35 (br s, 1, NOH) and other sugar protons. Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.33; H, 5.20; N, 23.24.

6-(Methylthio)-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazole-7-carbonitrile (11). A mixture of dry **4** (1.78 g, 10 mmol), HMDS (25 mL), and $(NH_4)_2SO_4$ (10 mg) was heated under reflux for 1.5 h with the exclusion of moisture. Excess HMDS was removed by distillation to provide the trimethylsilyl derivative (**7**), which was dissolved in anhydrous CH_3CN (50 mL). To the solution was added **8** (5.05 g, 10 mmol), followed by Me_3Si triflate (3.11 g, 14 mmol), and the mixture was stirred at ambient temperature for 2 days. TLC (silica gel, $CHCl_3$:H_3CCOCH_3, 8:2) of an ethanolized aliquot indicated completion of the reaction. The reaction mixture was evaporated to dryness, and the residue dissolved in EtOAc (200 mL) and poured into a 5% aqueous $NaHCO_3$ solution (200 mL). The organic layer was separated and washed with 5% aqueous $NaHCO_3$ solution (2 × 75 mL), followed by water (3 × 50 mL). The dried (Na_2SO_4) organic phase was evaporated and the resulting syrup was dissolved in a small amount of CH_2Cl_2. It was chromatographed on a silica gel column (2.5 × 50 cm) using H_3CCOCH_3:CH_2Cl_2 (1:1, v/v) as the solvent. The fast-moving, homogeneous fractions containing the nucleoside product were pooled, solvent evaporated, and the residual syrup was triturated with hexane. The syrup crystallized as white crystals to yield 5.50 g (88.5%): mp 79–80 °C; IR (KBr) ν 1720 (C=O), 2220 (CN) cm^{-1}; UV λ_{max} (EtOH) (saturated solution) 228 nm; ^{1}H NMR (Me_2SO-d_6) δ 2.56 (s, 3, SCH_3), 5.88 (d, 1, J = 4.5 Hz, $C_{1'}H$), 6.32 (d, 1, J = 2.4 Hz, C_2H), 7.02 (d, 1, J = 2.4 Hz, C_3H), 7.40 to 8.00 (m, 15, 3 COC_6H_5) and other sugar protons. Anal. Calcd for $C_{33}H_{26}N_4O_7S$: C, 63.66; H, 4.21; N, 9.00; S, 5.15. Found: C, 63.70; H, 4.14; N, 8.77; S, 4.91.

6-(Methylthio)-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazole-7-carbonitrile (12). A solution of **11** (6.22 g, 10 mmol) in MeOH/NH_3 (saturated at 0 °C, 150 mL) was stirred at room temperature in a pressure bottle for 18 h. The precipitated solid was collected and the filtrate was evaporated to dryness. Trituration of the residue with hot benzene (3 × 50 mL) gave an oil, which solidified on treatment with MeOH. Crystallization of the combined solids from MeOH gave 2.80 g (90.5%) of analytical sample: mp 211–212 °C; IR (KBr) ν 2210 (CN) cm^{-1}; UV λ_{max} (pH 1) 221 nm (ε 13 000), 252 (sh) (8700); UV λ_{max} (pH 7) 221 nm (ε 15 500), 252 (sh) (9900); UV λ_{max} (pH 11) 220 nm, (sh) (ε 19 200), 252 (11 600); ^{1}H NMR (Me_2SO-d_6) δ 2.50 (s, 3, SCH_3), 5.50 (d, 1, J = 5.0 Hz, $C_{1'}H$), 7.50 (d, 1, J = 2.0 Hz, C_2H), 7.80 (d, 1, J = 2.0 Hz, C_3H) and other sugar protons. Anal. Calcd for $C_{12}H_{14}N_4O_4S$: C, 46.45; H, 4.55; N, 18.05; S, 10.33. Found: C, 46.75; H, 4.49; N, 17.92; S, 10.44.

7-Cyano-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[1,2-*b*]pyrazol-6-yl Methyl Sulfone (13). To a solution of **11** (6.22 g, 10 mmol) in CH_2Cl_2 (250 mL) was added *m*-chloroperoxybenzoic acid (3.80 g, 22 mmol). After stirring at room temperature for 1 h, the precipitated white solid was collected. The filtrate was taken to dryness and the residue was triturated with ether (2 × 50 mL). Upon adding hexane, the residual syrup crystallized. The combined solids were crystallized from a mixture of ethanol/hexane to yield 6.3 g (96%): mp 99–100 °C; IR (KBr) ν 1310 and 1120 (SO_2CH_3), 1720 (C=O), 2220 (CN) cm^{-1}; UV λ_{max} (EtOH) (saturated solution) 225 nm, 265; ^{1}H NMR (Me_2SO-d_6) δ 3.30 (s, 3, SO_2CH_3), 6.44 (d, 1, J = 5.0 Hz, $C_{1'}H$), 7.20–8.10 (m, 18, C_2H, 3 COC_6H_5) and other sugar protons. Anal. Calcd for $C_{33}H_{26}N_4O_9S$: C, 60.73; H, 4.02; N, 8.59; S, 4.91. Found: C, 60.68; H, 4.01; N, 8.34; S, 4.75.

7-Cyano-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazol-6-yl Methyl Sulfone (14). A solution of **13** (3.27 g, 5 mmol) in MeOH/NH_3 (100 mL) was stirred at room temperature for 18 h. Methanolic ammonia was evaporated and the residue was triturated with boiling benzene (3 × 50 mL). The residual syrup solidified upon treatment with EtOH. The solid was collected and crystallized from EtOH to yield 1.30 g (76%): mp 180–182 °C; IR (KBr) ν 1125 and 1320 (SO_2CH_3), 2210 (CN) cm^{-1}; UV λ_{max} (pH 1 and 11) 220 nm (ε 20 000), 273 (6300); UV λ_{max} (pH 7) 220 nm (ε 20 500), 273 (6700); ^{1}H NMR (Me_2SO-d_6) δ 3.38 (s, 3, SO_2CH_3), 5.70 (d, 1, J = 4.0 Hz, $C_{1'}H$), 8.13 (d, 1, J = 2.0 Hz, C_3H) and other sugar protons. Anal. Calcd for $C_{12}H_{14}N_4O_6S$: C, 42.11; H, 4.12; N, 16.36; S, 9.36. Found: C, 42.35; H, 4.20; N, 16.15; S, 9.23.

7-Carbamoyl-1-β-D-ribofuranosylimidazo[1,2-*b*]pyrazol-6-yl Methyl Sulfone (19). To a solution of **14** (2.2 g, 7.0 mmol) in concentrated NH_4OH (30 mL) was added 30% H_2O_2 (3 mL) and the mixture was stirred at room temperature overnight. The solid that separated was collected, washed with cold EtOH, and crystallized from H_2O/EtOH to yield 0.95 g (41%): mp 182–184 °C; IR (KBr) ν 1140 and 1310 (SO_2CH_3), 1725 (C=O) cm^{-1}; UV λ_{max} (pH 1, 7 and 11) 240 nm, (sh) (ε 5800), 274 (6100); ^{1}H NMR (Me_2SO-d_6) δ 3.44 (s, 3, SO_2CH_3), 6.69 (d, 1, J = 4.0 Hz, $C_{1'}H$), 7.55 (br s, 2, NH_2), 7.85 (d, 1, J = 2.7 Hz, C_2H), 7.98 (d, 1, J = 2.7 Hz, C_3H) and other sugar protons. Anal. Calcd for $C_{12}H_{16}N_4O_7S$: C, 40.00; H, 4.47; N, 15.54; S, 8.89. Found: C, 40.18; H, 4.56; N, 15.63; S, 8.79.

Single-Crystal X-ray Diffraction Analysis of 10 and 16. Slow crystallization of **10** and **16** from EtOH gave X-ray quality crystals. Data for the determination of lattice parameters and for the structural studies were collected by utilizing a Nicolet P3 auto-diffractometer using graphite monochromated Mo Kα radiation (λ 0.71069 Å). The lattice parameters for both compounds were obtained by using a least-squares technique of 15 centered 2θ values and the space groups were determined by use of systematic extinction data. Single-crystal data were collected by using

Table IV. Crystal Data and Experiment Parameters

	N-5 isomer	N-1 isomer
formula	$C_{11}H_{12}N_4O_4$	$C_{11}H_{12}N_4O_4$
space group	$P2_12_12_1$	$P2_1$
a	7.507 (1) Å	8.651 (5) Å
b	9.015 (5)Å	7.031 (3) Å
c	16.907 (7) Å	10.133 (7) Å
β	90°	97.79 (5)°
V, Å^3	1148.8	611.1
Z	4	2
d_{meas}, g/cc	1.53	1.44
μ, cm^{-1}	0.76	0.76
max 2θ	45°	50°
cut off for obsd reflection	2.5σ (F)	2σ (F)
measured data	1059	2559
observed data	822	2254

a $\theta - 2\theta$ scan technique with variable scan rates. No absorption correction was made for either compound as $\mu = 0.76$ cm^{-1}. The experimental data are summarized in Table IV.

Both structures were solved by using the direct methods program of the SHELX-76 program package.[15] In both structures the major portion of the non-hydrogen atoms were apparent in the first E map and the remaining heavy atoms were located using Fourier techniques. Refinement proceeded normally with all twelve hydrogen atoms of each isomer eventually located in difference maps. Non-hydrogen atoms were refined anisotropically while hydrogen atoms were refined isotropically. The quantity minimized was $\sum w(|FO| - |F_c|)^2$ with w being calculated from counting statistics. The final residual values are, for **16**, $R = 0.050$ and $R_w = 0.023$ and, for **10**, $R = 0.046$ and 0.031. The final difference map for both structures showed no significant features.

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Acknowledgment. We are grateful to Drs. Charles R. Petrie for ^{13}C NMR spectrum, Richard L. Snow, and James L. Bills for molecular orbital calculations.

Registry No. **1**, 91296-17-2; **2**, 91296-18-3; **3**, 91296-19-4; **4**, 91296-20-7; **5**, 91296-21-8; **6**, 91296-34-3; **7**, 91296-36-5; **8**, 14215-97-5; **9**, 91296-22-9; **10**, 91296-23-0; **11**, 91311-06-7; **12**, 91296-24-1; **13**, 91311-07-8; **14**, 91296-25-2; **15**, 91296-26-3; **16**, 91296-27-4; **17**, 91296-28-5; **19**, 91296-30-9; **18**, 91296-29-6; **20**, 91296-31-0; **21**, 91296-32-1; 2-hydrazinoacetaldehyde diethyl acetal, 42351-81-5; (ethoxymethylene)malononitrile, 123-06-8.

Supplementary Material Available: Tables of positional and thermal parameters of the atoms of **10** and **16** (V and VI), bond lengths and angles for the two isomers (VII), least-squares planes of the heterocyclic portion of each isomer (VIII), and hydrogen bond data for the two isomers (IX) (5 pages). Ordering information is given on any current masthead page.

The Rugulovasines: Synthesis, Structure, and Interconversions

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Received March 9, 1984

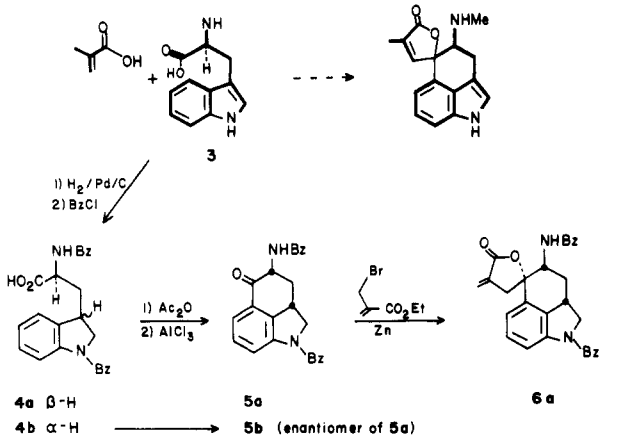
Experimental details are provided for the synthesis of the rugulovasine alkaloids from tryptophan. Optically active rugulovasine A is prepared for the first time and details concerning its conformation, racemization, and isomerization to rugulovasine B are presented.

It was not until X-ray crystallographic analysis[1] established rugulovasine A to be *racemic* that the remarkable behavior of these naturally occurring substances was fully exposed. First obtained[2] from *Pennicillium concavo-rugulosium*, and then[3] from *Pennicillium islandicum*, these alkaloids were formulated[4] as **1** and **2** on the basis of chemical and spectroscopic evidence. Their *interconversion*, combined with their racemic form was efficiently described by the ingenious mechanism shown[1] (Figure 1). Our access to optically active ergot alkaloids through synthesis from L-tryptophan[5] put us in a unique position to study these isomerization so we felt obliged to do so. This is an account of our experiences.

Synthesis

The combination of tryptophan and methacrylate provided the necessary skeletal features of the rugulovasines (Scheme I), while the stereochemical details emerged from the high selectivities of the reactions involved. Specifically, hydrogenation[6] of tryptophan followed by benzoylation led to the diastereomeric **4a** and **4b** each of which gave a single enantiomer of the tricyclic ketone **5** on Friedel–Crafts reactions of the corresponding azalactones. Reformatsky[7] reaction produced the methylene lactone **6**.

Scheme I



There are no stereochemical challenges here, since cis *hetero*atoms in the methylene lactone **6** lead to rugulo-

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