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Synthesis and Antiinflammatory Activity of 6-Oxo-1-(β-D-ribofuranosyl)nicotinic Acid and Related Derivatives

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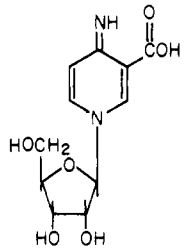
5-Substituted 1-(β-D-ribofuranosyl)pyridin-2-ones (6-oxonicotinic acid nucleosides) were prepared by direct glycosylation of 5-nitro-, 5-carbomethoxy-, 5-carboxamido-, 5-amino-, 5-carbobenzyloxyamino-, and 5-acetamido-2-trimethylsilyloxy or corresponding 2-methoxypyridine derivatives by the Hilbert–Johnson method. The glycosylation products were deblocked by conventional procedures and substituents at the 5 position were modified to give the 5-carboxamide, carboxyhydrazide, and carboxylic acid. Only 1-(β-D-ribofuranosyl)pyridin-2-one-5-carboxylic acid [1-(β-D-ribofuranosyl)-6-oxonicotinic acid] (**12**), showed significant activity in treating adjuvant-induced arthritis in rats.

Nicotinamide and related derivatives have shown a variety of interesting biological activities including anti-RNA and DNA virus,[1] antiinflammatory,[2] coronary vasodilator,[3] antifibrillatory,[3] spasmolytic,[3] and hypertensive[3] activity. Niacin derivatives have also been demonstrated to inhibit, among other enzymes, tumor tRNA methylase[4] and glucose-phosphate isomerase.[5] It is possible that nicotinamide derivatives in some cases may act by virtue of their conversion to the corresponding nucleoside or nucleotide (NAD) analogue.

For example, 2-hydroxynicotinic acid, an inhibitor of cholesterol and fatty acid synthesis in the rat,[6] has been shown to be converted to 1-(β-D-ribofuranosyl)-2-oxonicotinic acid by dogs and rats[7] when administered orally. The isolation of labeled 1-(β-D-ribofuranosyl)-2-oxonicotinic acid from the urine accounted for over 75% of the administered 2-hydroxynicotinic acid.[7] The isolation of nicotinic acid ribonucleoside from extracts of *Aspergillus niger* has recently been reported.[8] A new nucleoside, 1-(β-D-ribofuranosyl)-4-iminonicotinic acid, named clitidine, has recently been isolated from the Japanese



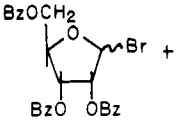
clitidine

mushroom *Clitocybe acromelalga*.[9] Clitidine causes marked hyperemia and hyperesthesia in various parts of the body. Since clitidine, a 4-substituted nicotinic acid, and 1-(β-D-ribofuranosyl)-2-oxonicotinic acid carry no charge on the pyridine nitrogen, it was of interest to synthesize the 6-oxonicotinic acid **12** and other related derivatives to determine their potential biological activity.

A number of *N*-glycosylpyridine derivatives have been reported, including several glycosylpyridin-2-ones[10,11] and pyridine nucleoside analogues[12–14] of the naturally occurring pyrimidine nucleosides. Several methods of glycosylation have been employed in the synthesis of these pyridine nucleosides, most notably the silver salt and the mercury salt methods,[11] rearrangement of the corresponding *O*-glycosides,[15] and the Hilbert–Johnson method.[12] The Hilbert–Johnson method and the silyl modification thereof were selected for this study because of their versatility and the often observed absence of side products.

Discussion

Glycosylation of 2-trimethylsilyloxy-5-nitropyridine (**2**) in acetonitrile at ambient temperature with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide (**1**) gave 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitro-2-pyridone (**8**). Similarly, **1** and 2-trimethylsilyloxy-5-carbomethoxy-



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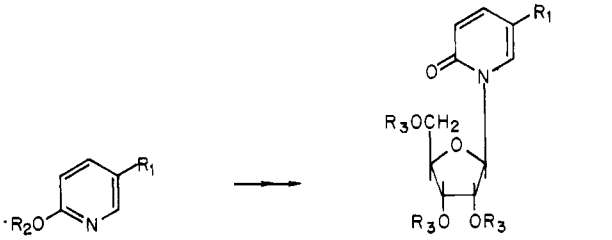

	R_1	R_2
2	$-NO_2$	$-Si(CH_3)_3$
3	$-CO_2CH_3$	$-Si(CH_3)_3$
4	$-CONH_2$	$-CH_3$
5	$-NH_2$	$-CH_3$
6	-NHCBz	$-CH_3$
7	-NHAc	$-CH_3$

	R_1	R_3
8	$-NO_2$	-Bz
9	$-NO_2$	-H
10	$-CO_2CH_3$	-Bz
11	$-CO_2CH_3$	-H
12	$-CO_2H$	-H
13	$-CONHNH_2$	-H
14	$-CONH_2$	-Bz
15	$-CONH_2$	-H
16	-NHBz	-H
17	-NHCbz	-H
18	-NHAc	-H

Bz = benzoyl; Ac = acetyl; Cbz = carbobenzyloxy

pyridine (**3**) gave **10** in excellent yield. A negative Fehling's test demonstrated the absence of any *O*-glycoside in the major nucleoside products isolated. Debenzoylation of **8**

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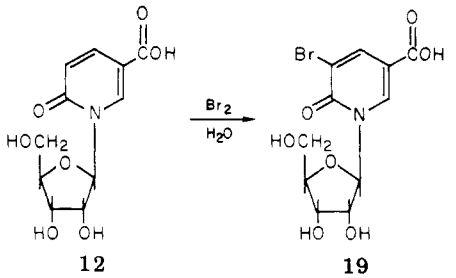
Table I. ^{1}H NMR Chemical Shifts[a] and Coupling Constants for 5-Substituted 1-(β-D-Ribofuranosyl)pyridin-2-ones

1-(β-D-Ribofuranosyl)pyridin-2-one derivative	Chemical shifts, ppm				Coupling constants, Hz		
	H-1′	H-3	H-4	H-5	$J_{1',2'}$	$J_{4,5}$	$J_{4,6}$
5-Nitro- (9)	5.98 (s)	6.53 (d)	8.17 (q)	9.68 (d)		10	3
5-Methoxycarbonyl- (11)	6.03 (d)	6.46 (d)	7.84 (q)	9.03 (d)	2	9.5	3
5-Carboxylic acid (12)	6.06 (d)	6.45 (d)	7.83 (q)	8.83 (d)	2.5	9.5	2.5
5-Carboxyhydrazide (13)	6.08 (d)	6.45 (d)	7.84 (q)	8.45 (d)	3	10	2.5
5-Carboxamide (15)	6.07 (d)	6.46 (d)	7.90 (q)	8.57 (d)	3	9.5	3
5-Benzamido- (16)	6.27 (d)	6.40 (d)	b	8.19 (d)	3	9.5	3
5-Carbobenzyloxyamino- (17)	6.10 (d)	6.41 (d)	7.5 (q)[b]	7.97 (d)	3	10	2.5
5-Acetamido- (18)	6.10 (d)	6.41 (d)	7.46 (q)	8.17 (d)	3	10	3

[a] Spectra were recorded with a Hitachi R-20A NMR spectrometer at 25 °C using Me_2SO-d_6 as the solvent with DSS as an internal standard. [b] (Partially) obscured by benzyl (benzoyl) resonance.

with methanolic ammonia and **10** with sodium methoxide gave 5-nitro-1-(β-D-ribofuranosyl)pyridin-2-one (**9**) and 5-carbomethoxy-1-(β-D-ribofuranosyl)pyridin-2-one (**11**), respectively. Treatment of the blocked methyl 6-oxonicotinate nucleoside **10** with methanolic ammonia or hydrazine gave the corresponding 1-(β-D-ribofuranosyl)-pyridin-2-one-5-carboxamide (**15**) or -5-carboxyhydrazide (**13**), respectively. When 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-carbomethoxy-2-pyridone (**10**) was treated with sodium ethoxide containing a small amount of water, 1-(β-D-ribofuranosyl)pyridin-2-one-5-carboxylic acid [1-(β-D-ribofuranosyl)-6-oxonicotinic acid] (**12**) was obtained in good yield.

Similarly, glycosylation of 2-methoxy-5-carboxamidopyridine (**4**), 2-methoxy-5-carbobenzyloxyaminopyridine (**6**), and 2-methoxy-5-acetamidopyridine (**7**) by the Hilbert–Johnson method gave the corresponding nucleoside derivatives after deblocking with methanolic ammonia. The glycosylation products of **4**, **6**, and **7** were, as expected, 5-carboxamido- (**15**, identical with the sample prepared from the methyl nicotinate nucleoside **10** vide supra), 5-carbobenzyloxyamino- (**17**), and 5-acetamido- (**18**) 1-(β-D-ribofuranosyl)pyridin-2-one, respectively. Glycosylation of 2-methoxy-5-aminopyridine (**5**) and debenzoylation with methanolic ammonia produced a nucleoside **16** which still possessed one benzoyl group (^{1}H NMR and elemental analysis). If the benzoxy group remained as an ester on one of the sugar hydroxyl groups, the primary hydroxyl on C-5 would be the most likely location of the ester linkage. Since the H-5′,5″ chemical shift of **16** appeared as a multiplet at 3.64 ppm instead of the region near 4.5 ppm (the usual position for hydrogen on primary carbon bound in an ester linkage), the benzoyl group could not be attached to the carbohydrate portion of the molecule and was therefore assigned to the only other possible site, the 5-amino group. This unusual benzoyl migration to form 5-benzamido-1-(β-D-ribofuranosyl)pyridin-2-one (**16**) is possibly due to the stronger basic character of 3-aminopyridines compared to many other heterocyclic amines. Bromination of **12** with bromine water gave 3-



12 **19**

bromo-1-(β-D-ribofuranosyl)pyridin-2-one (**19**) in 71% yield. The position of the bromine at position 3 was established due to the absence of the C_3 proton resonance at 6.45 ppm.

Examination of the ^{1}H NMR spectra of the pyridin-2-one nucleosides revealed that the H-1′ and H-3 chemical shifts were very consistent but that the H-4 chemical shifts and particularly the H-6 chemical shifts were somewhat variable. A number of nonsteroidal antiinflammatory drugs have been shown to inhibit nicotinate phosphoribosyltransferase[2] and the formation of nicotinic acid mononucleotide. It seemed, therefore, that the nucleosides of nicotinic acid prepared here should be evaluated as antiinflammatory agents. This appeared especially important since 2-hydroxynicotinic acid and indomethacin both significantly inhibit nicotinate phosphoribosyltransferase.[2] Gaut and Solomon postulate that this inhibition of NAD biosynthesis may restrain mucopolysaccharide biosynthesis and thereby reduce inflammatory responsiveness.[2]

The nucleosides (deblocked) were administered orally at 30 mg/kg/day to rats which had arthritis induced into both hind feet by a microbacterial adjuvant.[16] The percentage inhibition of swelling was measured by the displacement of mercury as compared to control,[16] on days 3 and 14. Of the compounds tested, 1-(β-D-ribofuranosyl)pyridin-2-one-5-carboxylic acid (**12**) [1-(β-D-ribofuranosyl)-6-oxonicotinic acid] showed a significant inhibition of adjuvant-induced arthritis of 37% on day 14. The number of secondary lesions, though smaller, was approximately the same as the control. Naproxen in the same test gives an inhibition of about 65%. These data lend support to the concept[2] that there may be a biochemical relationship between nicotinic acid metabolism and the inflammatory response.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ultraviolet spectra were recorded on a Cary 15 spectrophotometer, optical rotations were determined with a Perkin-Elmer 141 polarimeter, and the mass spectra were determined with a Perkin-Elmer 270 mass spectrometer. Trimethylsilyl derivatives were prepared with hexamethyldisilizane by the method of Wittenburg.[14] Column chromatography was performed with silica gel (70–325 mesh; E. Merck, Darmstadt, Germany), used without pretreatment. The ratio of the weight of substance to the weight of absorbent was 1:60 to 1:80. Ascending TLC was performed on plates coated with Merck silica gel F-254. The compounds described herein were homogeneous on TLC and satisfactory analytical data (C, H, and N within ±0.4% of theoretical values) were formed under diminished pressure with the bath temperature below 40 °C.

5-Nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridin-2-one (8). A solution of **1** [prepared from 25.2 g (50 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose] in dry acetonitrile (80 mL) was added to the trimethylsilyl derivative of 2-hydroxy-5-nitropyridine (**2**) [prepared from 7.0 g (50 mmol) of 2-hydroxy-5-nitropyridine]. The solution was stirred for 2 days at room temperature. After 12 h some product began to crystallize from the reaction mixture. The crystalline product was collected by filtration and recrystallized from acetonitrile. The filtrate and the mother liquor of recrystallization were combined and the

Table II. Activity of 1-(β-D-Ribofuranosyl)pyridin-2-one-5-carboxylic Acid vs. Adjuvant-Induced Arthritis

Compd	Dose (by mouth)	% inhibn		Secondary lesions, day 14	Wt change, day 0-1/14
		Day 3	Day 14		
12	30 mg/kg/day	21	37	4, 3, 2	+22
Controls				3, 2, 2	+19
				4, 4, 4	
				4, 2, 2	
				4, 2, 3	

solvent was evaporated. The residue was triturated with chloroform, and the chloroform and chloroform-insoluble material were removed by filtration to afford a quantitative recovery of the unreacted pyridine derivative. The volume of the chloroform solution was reduced prior to resolution on a silica gel column (eluent, chloroform). The product was collected and crystallized from acetonitrile to give a total of 13.39 g (46%) of **8** as needles: mp 187–188 °C; $[\alpha]^{25}_D$ −73.0° (*c* 1.0, DMF). Anal. ($C_{31}H_{24}N_2O_{10}$) C, H, N.

5-Nitro-1-(β-D-ribofuranosyl)pyridin-2-one (9). To a solution of methanol (150 mL) and DMF (100 mL), which had been presaturated with ammonia at 0 °C, was added **8** (4.0 g, 6.8 mmol). The mixture was stored in a pressure bottle at room temperature for 3.5 days. The resulting solution was evaporated to dryness and the residue was triturated with chloroform. The precipitated product was collected by filtration, washed with chloroform, and crystallized from methanol to give 1.28 g (69%) of **9** as granules: mp 223–225 °C; $[\alpha]^{25}_D$ −65.7° (*c* 1.0, DMF); UV λ_{max}^{pH1} 302 nm (ε 11 100), λ_{max}^{pH11} 302 nm (ε 10 500). Anal. ($C_{10}H_{12}N_2O_7$) C, H, N.

Methyl 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-pyridin-2-one-5-carboxylate (10). A solution of 1 [prepared from 25.2 g (50 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose] in dry acetonitrile (100 mL) was added to the trimethylsilyl derivative of methyl 6-hydroxynicotinate (**3**) [prepared from 6.9 g (45 mmol) of methyl 6-hydroxynicotinate]. The solution was stirred for 3 days at room temperature and the solvent was evaporated. The residue was dissolved in EtOAc (500 mL) and washed consecutively with water (1 × 300 mL), 6 M $NaHCO_3$ (2 × 300 mL), and water (2 × 300 mL). EtOAc was evaporated and the remaining traces of water were removed by coevaporations with absolute EtOH. The residue was dissolved in a minimum amount of CH_2Cl_2 and chromatographed on a silica gel column (eluent, CH_2Cl_2). The product was collected and crystallized from EtOAc–Et_2O–petroleum ether to give 20.4 g (76%) of **10** as needles: mp 135–136 °C; $[\alpha]^{25}_D$ −42.7° (*c* 1.0, DMF). Anal. ($C_{33}H_{27}NO_{10}$) C, H, N.

Methyl 1-(β-D-Ribofuranosyl)-2-pyridone-5-carboxylate (11). Compound **10** (3.0 g) was treated with NaOMe in MeOH (0.40 g of sodium in 100 mL of methanol) for 1 h at room temperature and then 18 h at 0 °C. The sodium ions were removed with Amberlite IR-120 (H^+) ion-exchange resin. The MeOH was evaporated in vacuo and the residue was dissolved in water (300 mL), washed with Et_2O (3 × 250 mL), and lyophilized. The lyophilized product was crystallized from acetone to give 1.80 g (68%) of **11** as needles, mp 118–120 °C. Additional product (0.39 g, 15%) was obtained from the mother liquor: $[\alpha]^{25}_D$ −2.7° (*c* 1.0, DMF); UV λ_{max}^{pH1} 260 nm (ε 16 100), λ_{max}^{pH11} 260 nm (ε 15 900). Anal. ($C_{12}H_{15}NO_7$) C, H, N.

1-(β-D-Ribofuranosyl)pyridin-2-one-5-carboxylic Acid [6-Oxo-1-(β-D-ribofuranosyl)nicotinic Acid] (12). A solution of **10** (3.0 g, 5 mmol) in MeOH (100 mL) containing NaOMe (1.65 g) and water (1.5 mL) was heated for 60 min at 80 °C. The solution was cooled and the sodium ions were removed with Amberlite IR-120 (H^+) ion-exchange resin. The solution was evaporated and traces of remaining water were removed by coevaporation with absolute EtOH. The residue was triturated with Et_2O and the product was collected by filtration and washed with Et_2O. Crystallization from MeOH gave 0.96 g (71%) of **12** as needles: mp 217–219 °C; $[\alpha]^{25}_D$ −3.5° (*c* 1.0, DMF); UV λ_{max}^{pH1} 259 nm (ε 15 900), λ_{max}^{pH11} 252 and 300 nm (ε 12 600 and 5600). Anal. ($C_{11}H_{13}NO_7$) C, H, N.

1-(β-D-Ribofuranosyl)pyridin-2-one-5-carboxyhydrazide (13). A solution of **10** (3.0 g, 5 mmol) in MeOH (25 mL) was treated with 85% hydrazine hydrate (50 mL) for 15 h at room temperature. The solution was heated to boiling for 5 min and cooled, and the solvent and the excess reagent were evaporated. The syrupy residue was dissolved in water (150 mL) and washed with chloroform (3 × 250 mL). The solution was concentrated to a small volume by evaporation and then lyophilized. The lyophilized product was crystallized and recrystallized from methanol to give 1.1 g (78%) of **13** as granules: mp 220–224 °C; $[\alpha]^{25}_D$ +11.4° (*c* 1.0, DMF); UV λ_{max}^{pH1} 261 and 295 nm (ε 14 700 and 5600), λ_{max}^{pH11} 255 and 295 nm (ε 14 200 and 5600). Anal. ($C_{11}H_{15}N_3O_6$) C, H, N.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)pyridin-2-one-5-carboxamide (14). 6-Methoxynicotinamide (**4**, 2.5 g, 16.4 mmol) was added to a solution of 1 [prepared from 8.3 g (16.4 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose] in dry DMF (50 mL). The solution was stirred for 3 days at room temperature. The solvent was evaporated and the residue was dissolved in a minimum amount of $CHCl_3$ and chromatographed on a silica gel column [eluent, acetone–$CHCl_3$ (1:9)]. The product was collected, crystallized, and recrystallized from MeOH to give 6.0 g (63%) of **14** as needles: mp 231–233 °C; $[\alpha]^{20}_D$ −30.2° (*c* 1.0, DMF). Anal. ($C_{32}H_{26}N_2O_9$) C, H, N.

1-(β-D-Ribofuranosyl)pyridin-2-one-5-carboxamide [6-Oxo-1-(β-D-ribofuranosyl)nicotinamide] (15). Method I. To MeOH (200 mL) presaturated with NH_3 at 0 °C was added **10** (3.0 g, 5 mmol). The mixture was allowed to stand in a pressure bottle for 3.5 days at room temperature. The resulting solution was evaporated and the residue was triturated with $CHCl_3$. The precipitated product was collected by filtration, washed with $CHCl_3$, and crystallized from MeOH to give 1.2 g (84%) of **15** as needles: mp 215–217 °C; $[\alpha]^{25}_D$ +21.6° (*c* 1.0, DMF); UV λ_{max}^{pH1} 257 and 295 nm (ε 13 800 and 5300), λ_{max}^{pH11} 257 and 295 nm (ε 13 800 and 5300). Anal. ($C_{11}H_{14}N_2O_6$) C, H, N.

Method II. A solution of **14** (1.0 g, 1.7 mmol) in methanol (150 mL) containing a catalytic amount of sodium (35 mg) was allowed to stand for 20 h at room temperature. The reaction mixture was cooled in an ice bath and neutralized with cold 2 N HCl. The solvent was evaporated and traces of remaining water were removed by coevaporation with absolute EtOH. The residue was triturated with Et_2O and the solid was crystallized from MeOH to give 0.36 (77%) of **15** as needles: mp 215–127 °C; mmp (of products from methods I and II) 215–217 °C; $[\alpha]^{25}_D$ +21.7° (*c* 1.0, DMF).

5-Benzamido-1-(β-D-ribofuranosyl)pyridin-2-one (16). A solution of 1 [prepared from 20.2 g (40 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose] in dry acetonitrile (200 mL) was added to the trimethylsilyl derivative of 5-amino-2-methoxypyridine (**5**) [prepared from 5.0 g (40 mmol) of 5-amino-2-methoxypyridine]. The solution was stirred for 2.5 days at room temperature. The solvent was evaporated and the residue was dissolved in chloroform. Substances insoluble in $CHCl_3$ were filtered and discarded. The $CHCl_3$ solution was condensed to a small volume and chromatographed on a silica gel column [eluent, MeOH–$CHCl_3$ (1:19)]. After solvent removal, the nucleoside fractions were treated with MeOH (400 mL) presaturated with ammonia at 0 °C. The solution was kept 7 days at room temperature in a pressure bottle. The solvent was evaporated and the residue was triturated with $CHCl_3$. The resultant solid was filtered, washed with $CHCl_3$, and crystallized from MeOH to give 4.4 g (32%) of **16** as needles: mp 197–198 °C; the ^1H NMR spectrum of **16** showed the presence of 1 mol of MeOH/mol; $[\alpha]^{25}_D$ +9.5° (*c* 1.0, DMF); UV λ_{max}^{pH1} 270 nm (ε 11 400), λ_{max}^{pH11} 270 nm (ε 11 100). Anal. ($C_{17}H_{18}N_2O_6 \cdot CH_3OH$) C, H, N.

5-Carbobenzyloxyamino-1-(β-D-ribofuranosyl)pyridin-2-one (17). 3-Carbobenzyloxyamino-5-methoxypyridine (**6**, 15.0 g, 58.1 mmol) was added to a solution of 1 [prepared from 33.0

g (65.4 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose] in dry acetonitrile (350 mL). The solution was stirred for 3 days at room temperature. The solvent was evaporated and the residue was dissolved in a minimum amount of $CHCl_3$ and chromatographed on a silica gel column [eluent, acetone–$CHCl_3$ (1:9)]. The fractions containing the glycosylation product were pooled, evaporated to dryness, and treated with MeOH (400 mL), presaturated with NH_3 at 0 °C. The solution was stored in a pressure bottle for 1 week at room temperature. The solvent was evaporated and the residue was triturated with $CHCl_3$. The flocculent precipitate was collected by filtration and reprecipitated from a MeOH solution with Et_2O. The precipitate was crystallized from acetone to give 11.4 g (52%) of **17** as needles: mp 120–122 °C; $[\alpha]^{25}_D$ +24.1° (*c* 1.0, DMF); UV λ_{max}^{pH1} 234 and 315 nm (ϵ 13 500 and 4700), λ_{max}^{pH11} 237 and 315 nm (ϵ 13 200 and 4700). Anal. ($C_{18}H_{20}N_2O_7$) C, H, N.

5-Acetamido-1-(β-D-ribofuranosyl)pyridin-2-one (18). 5-Acetamido-2-methoxypyridine (**7**, 5.0 g, 30 mmol) was added to a solution of **1** [prepared from 15 g (30 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose] in dry acetonitrile (65 mL). The solution was stirred for 3 days at room temperature. The insoluble pyridinium salt was removed by filtration. The filtrate was then diluted with $CHCl_3$ (350 mL) and washed with water (3 × 200 mL). The $CHCl_3$ solution was evaporated to dryness and the residue freed from water by coevaporation with absolute EtOH. The syrupy residue was dissolved in a minimum amount of $CHCl_3$ and chromatographed on a silica gel column [eluent, MeOH–$CHCl_3$ (1:19)]. The fractions containing the glycosidation products, **18** tribenzoate, were pooled, evaporated to dryness, and treated with MeOH (300 mL), presaturated with NH_3 at 0 °C. The solution was stored in a pressure bottle for 1 week at room temperature. The solvent was evaporated and the residue was dissolved in water (200 mL), washed with chloroform (3 × 240 mL), and evaporated. The syrupy residue was crystallized and recrystallized from MeOH–$CHCl_3$ to give 5.20 g (61%) of **18** as needles: mp 179–181 °C; the ^1H NMR spectrum of this crystalline sample showed the presence of 0.75 mol of water/mol; $[\alpha]^{25}_D$ −5.6° (*c* 1.0, DMF); UV λ_{max}^{pH1} 248 and 314 nm (ϵ 9100 and 4300), λ_{max}^{pH11} 248 and 314 nm (ϵ 9100 and 4300). Anal. ($C_{12}H_{16}N_2O_6 \cdot 0.75\ H_2O$) C, H, N.

3-Bromo-1-(β-D-ribofuranosyl)pyridin-2-one-5-carboxylic Acid (19). Compound **12** (0.43 g, 1.6 mmol) was treated with 20 mL of bromine water (bromine in water was saturated at room temperature). The reaction mixture was kept 45 min at room temperature. Presence of an excess bromine was indicated by the persistent yellow color of the solution. Bromine and water were evaporated in vacuo. During evaporation of the solvent much of the product began to crystallize out. The product was recrystallized from water. This gave 0.40 g (71%) of **20** as needles: mp 219–220 °C; $[\alpha]^{25}_D$ +42.6° (*c* 1.0, *N*,*N*-dimethylformamide); λ_{max}^{pH11} 214, 265, and 307 nm (ϵ 18 600, 11 450, and 7300); λ_{max}^{pH7} 212, 257, and 213 nm (ϵ 18 050, 8850, and 7350); λ_{max}^{pH1} 257 and 213 nm (ϵ 8850 and 7350). Anal. ($C_{11}H_{12}NO_7Br$) C, H, N.

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Potential Antitumor Agents. 27. Quantitative Structure–Antileukemic (L1210) Activity Relationships for the ω-[4-(9-Acridinylamino)phenyl]alkanoic Acids

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Simple carboxylic acid derivatives of 9-anilinoacridine (e.g., **1**, R = –COOH) provide high experimental antileukemic (L1210) activity. The homologous 1′-$(CH_2)_n$COOH congeners also prove active, and there is a parabolic interrelationship between maximum increase in life span in L1210 tests and R_m values used as a measure of agent lipophilic–hydrophilic balance. The corresponding carboxamides [1′-$(CH_2)_n$$CONH_2$] provide a similar parabolic relationship, which has an optimum R_m value displaced from that of the acids. Earlier examined 1′-$NHSO_2(CH_2)_nCH_3$ variants, the 3-$NHCOCH_3$ congeners of these, and the carboxamide [1′-$(CH_2)_n$$CONH_2$] and sulfonamide [1′-$(CH_2)_n$$SO_2NH_2$] homologues can be treated as one group and a correlation equation derived that is identical with that for the carboxamide variants alone. The optimum R_m value for this group is displaced from that of the acids by the equivalent of 1.8 log *P* units on the octanol–water scale. In this drug series a carboxylic acid residue acts as an acceptable hydrophilic unit, providing a log *P* contribution intermediate between that of the un-ionized acid and the totally ionized carboxylate anion. Quantitative effects of acridine ring substituents on L1210 activity differ in analogues containing either carboxylic acid or alkanesulfonanilide side chains, supporting the view that different site-binding orientations may be involved with these two drug classes.

Earlier the high experimental antileukemic (L1210) activity of some simple carboxylic acid derivatives of 9-anilinoacridine was described.[1] Carboxylate residues were only acceptable when attached at the 1′ position (e.g.,

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