Synthesis and Antiviral Evaluation of Nucleosides of 5-Methylimidazole-4-carboxamide[1]

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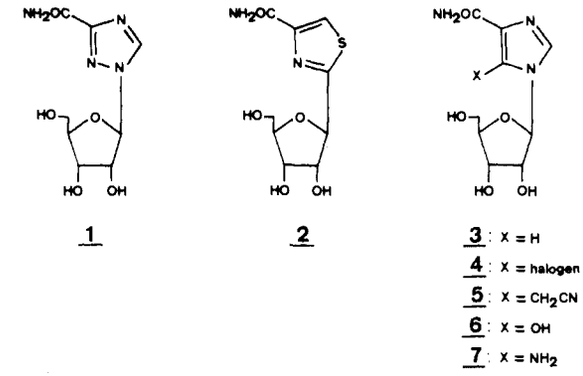
Due to the antiviral activity of certain 5-substituted imidazole nucleosides related to ribavirin, 5-methylimidazole-4-carboxamide nucleosides having β-D-ribofuranosyl, 2-deoxy-β- and -α-D-ribofuranosyl, and (2-hydroxyethoxy)methyl moieties have been prepared and tested as antiviral agents. 1-β-D-Ribofuranosyl-5-methylimidazole-4-carboxamide (**12**) was obtained by deacetylation of the corresponding tri-*O*-acetyl nucleoside **11** or by deacetylation and ammonolysis of the blocked ethyl 5-methylimidazole-4-carboxylate nucleoside **10**, which was prepared from the stannic chloride catalyzed condensation of the trimethylsilyl derivative of ethyl 4(5)-methylimidazole-5(4)-carboxylate (**8**). Glycosylation of 4(5)-methylimidazole-5(4)-carboxamide (**13**) with 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-*erythro*-pentofuranosyl chloride via mercuric cyanide method provided an anomeric mixture of the blocked 5-methylimidazole-4-carboxamide deoxynucleoside **14** along with an anomeric mixture of the 4-methyl 5-carboxamide isomer **15**. Separation of compound **14** into the corresponding β and α anomers was achieved by conversion to the 3′,5′-di-*O*-acetyl derivatives **17** and **18**, which after chromatographic separation were deacetylated to give 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (**19**) and its α anomer **20**. 1-[(2-Hydroxyethoxy)methyl]-5-methylimidazole-4-carboxamide (**23**) was prepared by alkylation of the imidazole **13** with (2-acetoxyethoxy)methyl bromide followed by treatment with methanolic ammonia. All these imidazole nucleosides were tested in HeLa cell cultures against type 1 herpes simplex and vesicular stomatitis viruses. The ribofuranosyl derivative **12** showed a significant activity against type 1 herpes simplex virus.

The success of ribavirin (**1**) as a broad-spectrum antiviral agent has stimulated the synthesis and testing of a large number of nucleosides of related five-membered heterocycles.[2,3] Studies on structure–activity relationships of these compounds have shown that the presence of a carboxamide group situated β to the site of glycosylation and adjacent to a nitrogen of the heterocycle is necessary for antiviral activity.[4,5] These features are found in the C-glycosyl thiazole **2** (tiazofurin),[5,6] the imidazole-4-carboxamide nucleoside **3**,[4,7] and the 5-substituted imidazole-4-carboxamide nucleosides **4**[4,8] and **5**,[9] which, although less active than ribavirin, showed antiviral activities, being, up to date, the 5-fluoro derivative **4** (X = F), the most potent antiviral imidazole nucleoside. The monophosphate of the 5-cyanomethyl derivative **5** is a potent inhibitor of IMP dehydrogenase, although as antiviral agent is less effective than its ring-closed derivative 3-deazaguanosine. Studies on the possibility that the antiviral activity of **5** could be due to an enzymatic cyclization to the corresponding 3-deazaguanosine seemed to demonstrate that the imidazole **5** possesses antiviral activity by itself, independently of the possible cyclization.[9] While substitution at the 5-position of the imidazole-4-carboxamide moiety gives nucleosides having antiviral (e.g., **4** and **5**) or antibiotic activities (e.g., bredinin **6**) or other important naturally occurring nucleosides (AICA ribonucleoside **7**), substitution at the 2-position of this moiety (e.g., 1-β-D-ribofuranosyl-2-methylimidazole-4-carboxamide[10]) or at the related 5-position of ribavirin gives compounds devoid of antiviral activity.[11] The lack of activity of the mentioned 2-methylimidazole nucleoside was attributed to a possible conformational change of the imidazole ring about the ribosyl bond, as postulated in the case of 5-substituted ribavirin derivatives.[12] All of these facts prompted us to prepare and test as antivirals some 5-substituted imidazole-4-carboxamide nucleosides, particularly 5-methyl-substituted compounds, having ribofuranosyl, 2-deoxyribofuranosyl, and (2-hydroxyethoxy)methyl (the acyclic sugar analogue of acycloguanosine) as sugar moieties.



Chemistry. 1-β-D-Ribofuranosyl-5-methylimidazole-4-carboxamide (**12**)[13] was obtained by deacetylation and

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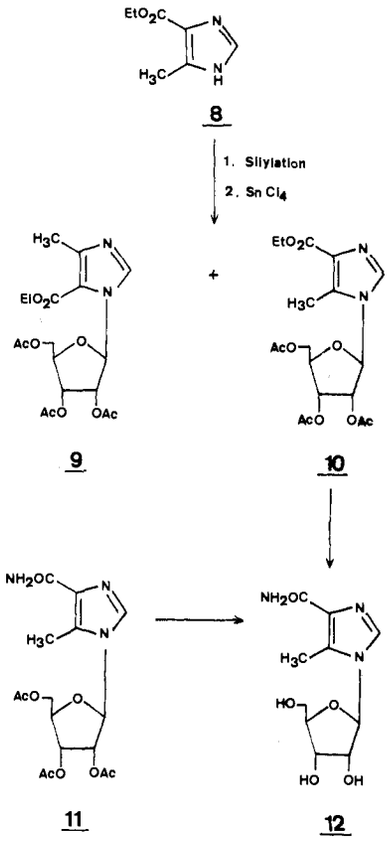
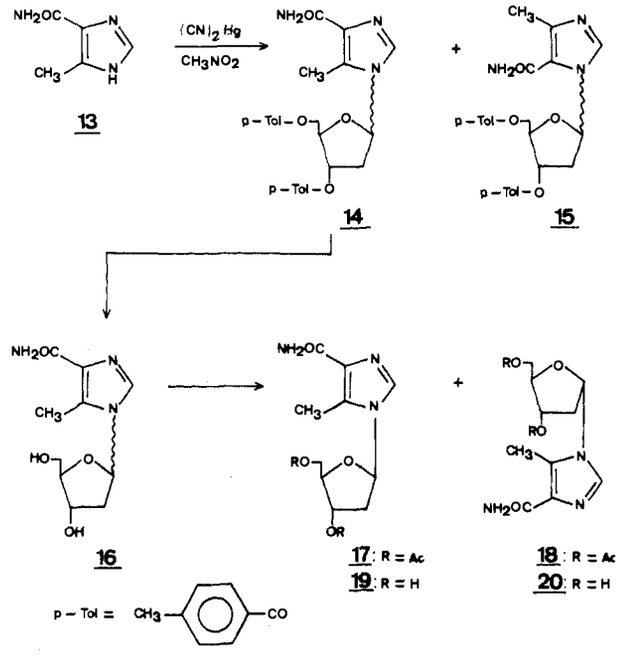
Scheme I



ammonolysis of ethyl 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-methylimidazole-4-carboxylate (**10**) or by deacetylation of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-methylimidazole-4-carboxamide (**11**) (Scheme I). The synthesis of both per-O-acetylated nucleosides in 66% or 48% yield had been previously reported by ribosylation of ethyl 4(5)-methylimidazole-5(4)-carboxylate (**8**) or 4-(5)-methylimidazole-5(4)-carboxamide (**13**) via mercuric cyanide method.[14] Now, ribosylation of the trimethylsilyl derivative of **8** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose has been investigated as an alternate route to compound **12**. However, the yield (43%) of the 4-carboxylate-substituted nucleoside **10**, which leads to the desired compound **12**, was lower than that with the previously reported glycosylation method. Therefore, the synthesis of the 2′-deoxyribonucleosides was achieved by the mercuric cyanide procedure. Reaction of the carboxamide-substituted imidazole **13**[14] with 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-*erythro*-pentofuranosyl chloride[15] gave a mixture of nucleosides which was separated by preparative TLC to provide 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (**14**) and 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-4-methylimidazole-5-carboxamide (**15**) in 32% and 6% yield, respectively (Scheme II). Structural assignments of these 2′-deoxyribonucleosides were made on the basis of their ^{1}H NMR spectra. Due to the deshielding effect of the

Scheme II



glycosyl moiety,[16] the signal for the methyl group of the 5-methyl-substituted derivative **14** showed a downfield shift as compared with that of the 4-methyl-substituted isomer **15**. A similar effect has been observed with other 4- and 5-methyl-substituted imidazole nucleosides.[14] Further support for this assignation of the glycosylation site will be given later by the ^{13}C NMR data of the resulting deblocked 5-methyl-substituted deoxynucleosides **19** and **20**. In both compounds, **14** and **15**, the anomeric proton appeared as a complex multiplet with a peak width of 18 and 25 Hz, respectively, only consistent with an anomeric mixture of 2′-deoxyribonucleosides.[16] Although in many cases the use of *p*-toluoyl protecting groups has facilitated the separation of anomers formed in the synthesis of 2′-deoxyribonucleosides, all attempts to separate **14** or **15** into their corresponding anomers by preparative TLC were unsuccessful. In an effort to obtain the 2′-deoxyribonucleoside analogue of **12**, as a pure β anomer, compound **14** was converted into the corresponding anomeric mixture of 2-deoxy-3,5-di-*O*-acetyl-D-*erythro*-pentofuranosyl derivatives by treatment with methanolic ammonia followed by acetylation of the resulting deblocked deoxynucleosides **16** with acetic anhydride and 4-(dimethylamino)pyridine. Further evidence for the assignment of **14** as an anomeric mixture came from the ^{1}H NMR spectrum of its deprotected analogue **16**, which showed the presence of two different signals at δ 7.83 and 7.90 for the C-2 protons. The anomeric mixture of di-*O*-acetylated deoxyribonucleosides was separated by preparative TLC to provide the pure β- and α-anomers **17** and **18** in 34% and 41.5% yield, respectively, from **14**. Deacetylation of **17** and **18** with methanolic ammonia gave 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (**19**) and 1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (**20**), respectively. The anomeric configuration of **17**–**20** was determined by ^{1}H NMR spectroscopy (Table I). According to the "triplet–quartet-peak" width rule,[16] the H-1′ protons of the β-anomers **17** and **19** appeared as a triplet having peak widths of 13.5 and 12.5 Hz, respectively.

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Table I. ^1H NMR Data

no.	solvent	δ(H-2)	δ(H-1′)	$J_{1',2'}$, Hz	δ(CH_3)	others
12	Me_2SO	7.90	5.55	5	2.50	
14	$CDCl_3$	7.58	6.03 (m)[a]	a	2.62	2.40 (s, CH_3 of toluoyl)
15	$CDCl_3$	7.43	6.28 (m)[a]	a	2.50	2.40 (s, CH_3 of toluoyl)
17	$CDCl_3$	7.61	5.91 (t)	6.7	2.61	
18	$CDCl_3$	7.66	6.01 (q)	7.8; 2.4	2.61	
19	Me_2SO	7.83	5.91 (t)	6.2	2.50	2.11–2.56 (CM, H-2′, H-2″)
20	Me_2SO	7.90	5.93 (q)	7.8; 3.0	2.50	1.93–2.94 (SM, H-2′, H-2″)
21	$CDCl_3$	7.4			2.62	5.30 (s, OCH_2 base)
22	$CDCl_3$	7.60			2.50	5.62 (s, OCH_2 base)
23	Me_2SO	7.71			2.46	5.33 (s, OCH_2 base)

[a] Multiplet with a peak width of 18 Hz for 14 and 25 Hz for 15, corresponding in both compounds to an anomeric mixture.

Table II. ^{13}C Chemical Shifts (ppm) of the Base Anion 13 and Its Nucleosides 12, 19, and 20[a]

no.	C=O	C-2	C-4	C-5	CH_3
13	168.77	140.03	128.72	139.12	13.67
12	165.39	133.61 (133.03)	130.99[b] (130.72)	131.51[b] (132.12)	9.14
19	165.38	134.10 (133.03)	130.87[b] (130.72)	131.07[b] (132.12)	9.14
20	165.29	134.10 (133.03)	131.11 (130.72)	133.32 (132.12)	9.06

[a] Values in parentheses are theoretical chemical shifts, using α- and β-substitution shifts of +7 and −2 ppm, respectively. [b] Since the experimental values of C-4 and C-5 are very similar, this assignment could be interchangeable in 12 or/and 19.

The H-1′ of the α anomers 18 and 20 appeared as a doublet of doublets with peak widths of 10.2 Hz (J = 2.4 and 7.8 Hz) for 18 and 10.8 Hz (J = 3.0 and 7.8 Hz) for 20. On the other hand, it has been shown[17] that the difference in chemical shift between the two H-2′ methylene protons of α-deoxyribonucleosides is bigger than that of the corresponding β anomers. Thus, the signals of H-2′a and H-2′b for 20 appeared as a set of separate multiplets (SM) between δ 1.93 and 2.94 (band width δ 1.01), whereas 19 displayed a clustered multiplet (CM) between 2.11 and 2.56 (band width δ 0.45). The results of the two criteria are consistent with the assignment of β-anomeric configuration to 17 and 19 and α configuration to 18 and 20. Finally, evidence for the assignment of the glycosylation site of 19 and 20, and therefore of 14, 17, and 18, was obtained from ^{13}C NMR spectroscopy. Table II shows the ^{13}C chemical shifts of the anion of the base 13 and of its 2′-deoxyribonucleosides 19 and 20. Data of the 5-methylimidazole ribonucleosides 12, the structure of which has been unequivocally established,[14] are also included for comparison. Assignments of the ^{13}C chemical shifts of 13 were based on general rules of ^{13}C NMR[18,19] and on the comparison with related imidazole anions.[20] Theoretical values for the chemical shifts of nucleosides 12, 19, and 20 were calculated with use of a substitution shift parameter of 7 ppm upfield for the carbons in the α-position to the substituted nitrogen and a downfield shift of 2 ppm for the carbons in the β-position.[21] A reasonable agreement between the experimental and theoretical values is only obtained when the above nucleosides are assigned as 2-methylimidazole-4-carboxamides. Comparison of the ^1H and ^{13}C NMR chemical shifts of 19 and 20 with those of 12 further confirms this assignment. Attempts were not made to separate the mixture of anomers of 15 because of the low yield in which this compound was obtained.

Finally, alkylation of 13 with (2-acetoxyethoxy)methyl bromide[22] in nitromethane and in the presence of mercuric cyanide gave 1-[(2-acetoxyethoxy)methyl]-5-methylimidazole-4-carboxamide (21) in 48% yield along with traces of the 4-methyl 5-carboxamide isomer 22 (Scheme III). The position of substitution in these isomers was determined from their ^1H NMR spectra (Table I). Due to the anisotropy of the carboxamide group, the singlet for the methylene group attached to the imidazole ring of the 5-carboxamide-substituted compound 22 appeared at lower field than that of the 5-methyl-substituted isomer 21. On the other hand, and as described earlier for the positional isomers 14 and 15, the signal for the methyl group of 21 showed a downfield shift as compared with that of 22. Deacetylation of 21 with methanolic ammonia afforded 1-[(2-hydroxyethoxy)methyl]-5-methylimidazole-4-carboxamide (23).

Scheme III

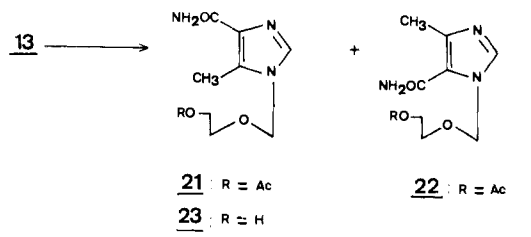

Table III. Antiviral Data of Nucleosides of 5-Methylimidazole-4-carboxamide in HeLa Cell Cultures

	HSV-1		VSV	
no.	CPE_{50}, μg/mL	Tox_{50}, μg/mL	CPE_{50}, μg/mL	Tox_{50}, μg/mL
12	75	>400	125	>400
13	>200	>200		
19	150	300	150	>400
20	>200	>200	150	>400
23	>200	>200	180	>200
1	75	400	15	400

Antiviral Results and Discussion

Deprotected nucleosides 12, 19, 20, and 23 and the corresponding free imidazole 13 were tested for inhibition of herpes simplex virus type 1 (HSV-1) and vesicular stomatitis virus (VSV). For comparative purposes, ribavirin (1) was included as reference material. Table III

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represents the concentration of the compound that protects by 50% the CPE induced by the corresponding virus (CPE_{50}) and the concentration that induces 50% cell toxicity (Tox_{50}). As it is shown, the ribofuranosyl derivative **12** displayed, under these test conditions, an activity against HSV-1, similar to that of ribavirin but a lower toxicity. However, its activity against VSV was clearly lower as the reference compound. Compound **12** was also tested against polio I virus, encephalomyocarditis virus, and Semliky Forest virus. In the three cases, it was found to be inactive up to a concentration of 200 μg/mL. Substitution of the ribofuranosyl moiety of compound **12** by the 2′-deoxy-β-D-ribofuranosyl moiety reduced the activity against HSV-1 substantially. Neither the 2-deoxy-α-D-ribofuranosyl derivative **20** nor the acyclic nucleoside **23** showed activity against HSV-1 up to a concentration of 200 μg/mL. In contrast to 1,2,4-triazole-3-carboxamide, the heterocyclic base of ribavirin, 4(5)-methylimidazole-5(4)-carboxamide was inactive.[3] The finding that compound **12** does not possess a broad spectrum of antiviral activity suggests that its mode of action is different from that of ribavirin.

Experimental Section

Chemical Methods. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 90 MHz on a Varian EM-390 spectrometer and at 300 MHz on a Varian XL-300 spectrometer with Me_4Si as the internal standard. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 300 MHz in Me_2SO-d_6 on a Varian XL-spectrometer with Me_4Si as the internal reference. The values are given in parts per million (ppm) downfield from Me_4Si. The anion of imidazole **13** was formed by neutralization with LiOH in Me_2SO-d_6. Analytical thin-layer chromatography was performed on aluminum sheets coated with a 0.2-mm layer of silica gel 60 F_{254} (Merck) and preparative-layer chromatography was performed on 20 × 20 cm glass plates coated with a 2-mm layer of silica gel PF_{254} (Merck). The compounds were detected with UV light (254 nm) or by spraying the plates with 30% sulfuric acid in ethanol and heating at ca. 110 °C.

Biological Methods. Antiviral Activity. HeLa cells were grown in plastic petri dishes until confluency was reached. The cells were infected or mock-infected with herpes simplex virus type 1 (HSV-1) (0.5 PFU/cell) or vesicular stomatitis virus (VSV) (0.01 PFU/cell) and different concentrations of the compound were added. The cytopathic effect (CPE) was estimated under a phase-contrast microscope either after 48 h (HSV-1) or after 24 h (VSV).

1-β-D-Ribofuranosyl-5-methylimidazole-4-carboxamide (12). Ethyl 4(5)-methylimidazole-5(4)-carboxylate (**8**; 1.54 g, 10 mmol) was converted to its trimethylsilyl derivative by refluxing **8** under anhydrous conditions for 2 h with hexamethyldisilazane (50 mL) and trimethylchlorosilane (1 mL). The excess hexamethyldisilazane was removed under reduced pressure and the resulting trimethylsilyl derivative was dissolved in dry 1,2-dichloroethane (50 mL). 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose (3.5 g, 11 mmol) was added to the solution followed by addition of anhydrous $SnCl_4$ (1.5 mL, 13 mmol). The reaction solution was refluxed for 2 h and then poured slowly into a stirred 5% $NaHCO_3$ solution (100 mL). Chloroform (100 mL) was added and stirring continued for 0.5 h. The mixture was filtered through Celite and the organic layer was removed. The aqueous layer was extracted with chloroform (50 mL), and the combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent gave a syrup, which was chromatographed on preparative TLC with use of chloroform–ethyl acetate (1:1). The fastest moving band afforded 0.25 g (6%) of **9**.[14] The slowest moving band gave 1.76 g (43%) of **10**, identical in all respects with that previously described.[14]

A solution of **10** (1.23 g, 3 mmol) in dry methanol (50 mL) was treated with liquid ammonia (10 mL) and stored in a stainless steel pressure bottle at 120 °C for 3 days. On cooling, the solvent was evaporated to give a solid, which was recrystallized from methanol to afford 0.76 g (100% yield from **10**) of **12**: mp 178 °C. Anal. ($C_{10}H_{15}N_3O_5$) C, H, N.

From 11. A solution of **11**[14] (1.15 g, 3 mmol) in methanol (100 mL) saturated at 0 °C with ammonia was allowed to stand at room temperature overnight. Evaporation of the solvent and crystallization of the residue gave **12** in quantitative yield, identical in all respects with that described above.

1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (14) and 1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl)-4-methylimidazole-5-carboxamide (15). To a mixture of 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride[15] (5.8 g, 15 mmol), mercuric cyanide (2.5 g, 10 mmol), and molecular sieve in dry nitromethane (150 mL) was added 4(5)-methylimidazole-5(4)-carboxamide (**13**;[14] 1.25 g, 10 mmol). The mixture was refluxed for 6 h. After this, it was filtered while still hot to remove the insoluble residue, which was washed with hot nitromethane (50 mL). The filtrate was evaporated and the residue obtained was treated with chloroform (300 mL) and filtered to separate the solid formed. The chloroform extract was washed with 30% KI solution (100 mL) and water (100 mL) and then dried over Na_2SO_4. The residue obtained after removing the solvent was chromatographed on preparative TLC with use of ethyl acetate–hexane–chloroform (2:1:1). The fastest moving band yielded 0.28 g (6%) of the anomeric mixture **15** as a foam. Anal. ($C_{26}H_{27}N_3O_6$) C, H, N.

The slowest moving band afforded 1.53 g (32%) of the anomeric mixture **14** as a solid, which was recrystallized from ethyl acetate–hexane: mp 89–92 °C. Anal. ($C_{26}H_{27}N_3O_6$) C, H, N.

1-(2-Deoxy-3,5-di-*O*-acetyl-β-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (17) and 1-(2-Deoxy-3,5-di-*O*-acetyl-α-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (18). A solution of **14** (0.95 g, 2 mmol) in methanolic ammonia (100 mL) was allowed to stand at room temperature overnight. Evaporation of the solvent left a residue, which was purified by preparative TLC with use of chloroform–methanol (3:1) and crystallized from ethanol to give 0.40 g (84%) of a solid, which was identified by ^{1}H NMR as the anomeric mixture of deprotected deoxynucleosides **16**. A solution of **16** (0.4 g, 1.66 mmol) and 4-(dimethylamino)pyridine (0.24 g, 2 mmol) in acetic anhydride (20 mL) was allowed to stand at room temperature for 3 days. After this time the solution was added to crushed ice (30 g) and extracted with chloroform (3 × 20 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (20 mL) and dried over Na_2SO_4. Removal of the solvent left a residue, which was chromatographed on preparative TLC with use of ethyl acetate–hexane–methanol (8:2:1). The fastest moving band gave a solid which was recrystallized from ethyl acetate to provide 0.22 g (34% from **14**) of **17**: mp 142 °C. Anal. ($C_{14}H_{19}N_3O_6$) C, H, N.

The slowest moving band yielded a solid, which was recrystallized from ethyl acetate to give 0.27 g (41.5% from **14**) of **18**: mp 172 °C. Anal. ($C_{14}H_{19}N_3O_6$) C, H, N.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (19). Treatment of **17** (0.16 g, 0.5 mmol) with a saturated solution of methanolic ammonia (50 mL) at room temperature for 20 h, followed by evaporation, gave a residue which was crystallized from ethanol–ether to afford 0.12 g (100%) of **19**: mp 150–151 °C. Anal. ($C_{10}H_{15}N_3O_4$) C, H, N.

1-(2-Deoxy-α-D-*erythro*-pentofuranosyl)-5-methylimidazole-4-carboxamide (20). By a method identical with that described above, compound **18** (0.16 g, 0.5 mmol) furnished 0.12 g (100%) of **20**: mp 208 °C (from ethanol). Anal. ($C_{10}H_{15}N_3O_4$) C, H, N.

1-[(2-Acetoxyethoxy)methyl]-5-methylimidazole-4-carboxamide (21) and 1-[(2-Acetoxyethoxy)methyl]-4-methylimidazole-5-carboxamide (22). To a mixture of 2-(acetoxyethoxy)methyl bromide[22] (2.24 g, 11 mmol), mercuric cyanide (2.2 g, 8 mmol), and molecular sieve in dry nitromethane (80 mL) was added 4(5)-methylimidazole-5(4)-carboxamide (**13**;[14] 1 g, 8 mmol). The mixture was refluxed for 4 h. After this, it was filtered while still hot and the insoluble residue was washed with hot nitromethane (40 mL). The filtrate was evaporated and the residue obtained was treated with chloroform (250 mL) and filtered. The chloroform extract was washed with 30% KI solution (75 mL) and water (75 mL) and then dried over Na_2SO_4. The

residue obtained after removing the solvent was chromatographed on preparative TLC with use of methanol–chloroform (0.5:9.5). Elution of the fastest and major band gave a solid which recrystallized from ethanol to yield 0.92 g (48%) of **21**: mp 140–141 °C. Anal. ($C_{10}H_{15}N_3O_4$) C, H, N.

The slowest moving band afforded 20 mg (~1%) of **22**, which was identified by ^1H NMR spectroscopy.

1-[(2-Hydroxyethoxy)methyl]-2-methylimidazole-4-carboxamide (23). A solution of **21** (0.73 g, 3 mmol) in methanolic ammonia (45 mL) was allowed to stand at room temperature for 24 h. Evaporation of the solvent and coevaporation with ethanol gave a solid which was recrystallized from methanol to yield 0.59 g (98%) of **23**: mp 137–138 °C. Anal. ($C_8H_{13}N_3O_3$) C, H, N.

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Registry No. **8**, 51605-32-4; **9**, 77421-54-6; **10**, 77421-55-7; **11**, 77421-58-0; **12**, 85665-04-9; **13**, 77421-51-3; α-**14**, 95936-32-6; β-**14**, 95936-33-7; α-**15**, 95936-30-4; β-**15**, 95936-31-5; **17**, 95936-36-0; **18**, 95936-37-1; **19**, 95936-35-9; **20**, 95936-34-8; **21**, 95936-38-2; **22**, 95936-39-3; **23**, 95936-40-6; 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, 13035-61-5; 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride, 3601-89-6; (2-acetoxyethoxy)methyl bromide, 81777-40-4.

Book Reviews

Antimalarial Drugs I (Handbook of Experimental Pharmacology, Vol. 68/1). Biological Background, Experimental Methods, and Drug Resistance. Edited by W. Peters and W. H. G. Richards. Springer-Verlag, New York. 1984. xviii + 484 pp. 17 × 24.5 cm. ISBN 0-387-12616-3. $143.50.

This is the first of two monographs devoted to antimalarial drug development. The present one is concerned with the biological and clinical aspects of the subject, whereas the second is devoted primarily to a discussion of the various classes of compounds which have shown potential.

The 22 authors of Part I are specialists in their respective fields and, for the most part, have written their chapters in a lucid manner. The editors managed not only to bring cohesiveness to their contributions but also to minimize overlap of subject matter without incurring any obvious omissions. This is not a book for adherents to the off-the-shelf screening school of drug development. Rather, it is a guide for those who are interested in acquiring the biological background for intelligent antimalarial drug design.

In Chapter 1, P. C. C. Garnham describes the life cycles of various *Plasmodia* that infect humans, rodents, avia, and reptilia. The metabolic requirements of the malaria parasite and the characteristics of the host–parasite relationship are given by I. W. Sherman in Chapter 2. W. H. G. Richards, in Chapter 3, outlines the latest in vitro culture methods for malaria parasites and discusses their applicability in drug testing. In Chapter 4, G. H. Mitchell deals with the immune response to the malaria parasite at its various stages of development. A description of the clinical pathology of the disease is given in Chapter 5, written by V. Boonpucknavig, T. Srichaikul, and S. Punyagupta, and is accompanied by numerous black and white photographs showing the typical histological characteristics of the parasites. In Chapter 6, R. E. Desjardins describes recent in vitro culture technology, with emphasis on a semiautomated technique that is currently being used in antimalarial drug screening. Chapter 7, by W. H. G. Richards, is devoted to avian malaria and informs us that over 400 species of birds have been found to be afflicted with the disease. Details are given of how avian malaria models have been exploited for drug development. A. L. Ager, Jr., in Chapter 8, describes rodent malaria, first reported in 1948, and the manner in which the *Plasmodium berghei* model is used in primary and secondary screens. In Chapter 9, concerned with simian malaria, R. N. Rossan discusses the ability of the Colombian owl monkey to support *P. falciparum* infection and the application of this model to drug evaluation. S.-C. Chou and his collaborators in Chapter 10 describe alternative models for antimalarial testing, including isolated enzyme systems, use of protozoa other than *Plasmodia* for drug screens, and drug-induced clumping inhibition. In Chapter 11, G. A. T. Targett outlines the relationship between immune responses and antimalarial chemotherapy. Chapter 12, by M. H. Heiffer, D. F. Davidson, Jr., and D. W. Korte, Jr., details the organization of the Walter Reed antimalarial drug development program and considers the steps required to transform a promising lead into a drug for human therapy. Chapter 13, on phase I and II clinical trials by M. Fernex, lists the technical and ethical problems encountered in performing drug evaluations in human subjects. In the chapter which follows, the same author tells of the manner in which subjects are selected and in which field trials are conducted. H. M. Gilles in Chapter 15 details the pharmacogenetic factors which must be considered when testing antimalarial drugs. Chapter 16, by W. Peters, gives the history and present status of drug resistance and Chapter 17, by K. H. Rieckmann, tells how it is evaluated. The means of producing experimental drug resistance is reviewed by W. Peters in Chapter 18.

The book appears to verify an unwritten law which states that the greater the number of contributors to a monograph, the further out-of-date it will be on publication. With few exceptions, the latest references are to papers which appeared in 1981; two chapters stop at 1980. The impression that one is left with is that, for whatever reason, the book is not quite as current as one would wish. Nevertheless, it is an excellent and highly recommended resource for malaria researchers and others interested in acquiring a good foundation in antimalarial chemotherapy.

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Comprehensive Heterocyclic Chemistry. Volumes 1-8. The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds. Set Editors: Alan R. Katritzky and Charles W. Rees. Pergamon Press, Oxford, England, 1984. xvi + 1111 pp. 19.5 × 28 cm. ISBN 0-080-30708-6. $2200 for set, cannot be purchased individually.

The review, which consists of seven volumes devoted to the chemistry of heterocyclic compounds and one volume of indexes, is a masterful addition to the previous comprehensive reviews of inorganic (1973), organic (1979), and organometallic (1982) chemistry. One can appreciate the magnitude of the undertaking when one begins to consider all the permutations of heteroatoms, ring sizes, and sites of unsaturation possible. However, as the reader who examines this will attest, the editorial board has utilized well the choice of authors in achieving a truly comprehensive review of a field that is fascinating to chemists, particularly those involved with the design, synthesis, or evaluation of novel biologically active compounds.

Although comprised of eight volumes, the set is divided into six parts (including the indexes) in which ring size is the primary determinant and, in this way, it distinguishes itself from the more familiar pattern of heterocyclic reviews based on the identity of the heteroatom. Part 1 (Volume 1) provides an introduction to