Perkin-Elmer R-20B NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 70 eV. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama Chemistry Department. Melting points are uncorrected.

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# Nucleosides of 4-Substituted Imidazoles

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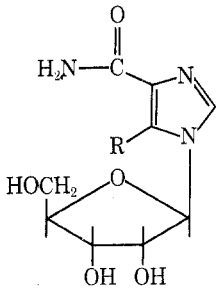
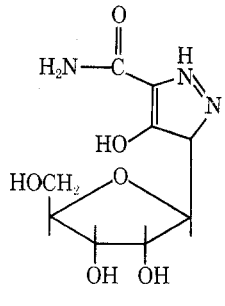
The synthesis of 1-(β-D-ribofuranosyl)imidazole nucleoside analogs via the deamination of the corresponding 5-aminoimidazole nucleosides is described. 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid, on treatment with acid anhydrides, was ring closed to 5-substituted nucleoside analogs of imidazo[4,5-*d*][1,3]oxazin-7-one. The intermolecular dimerization of methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate, to provide 2-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-yl]adenosine, is also described.

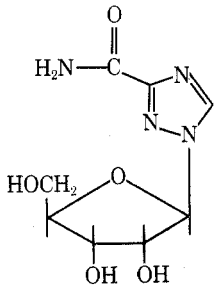
The nucleoside antibiotic bredinin isolated from the culture filtrate of *Eupenicillium brefeldianum* has recently been reported as an immunosuppressive agent.[1] This antibiotic has been shown to possess structure **1** which is essentially an isomer of pyrazomycin[2] (**2**). The synthetic triazole nucleoside, ribavirin (**3**), which has close resemblance to **1** and **2**, has been reported from these laboratories to exhibit broad spectrum antiviral activity.[3] These data suggest that



bredinin (**1**, R = OH)
AICA riboside (**4**, R = $NH_2$)



pyrazomycin (**2**)



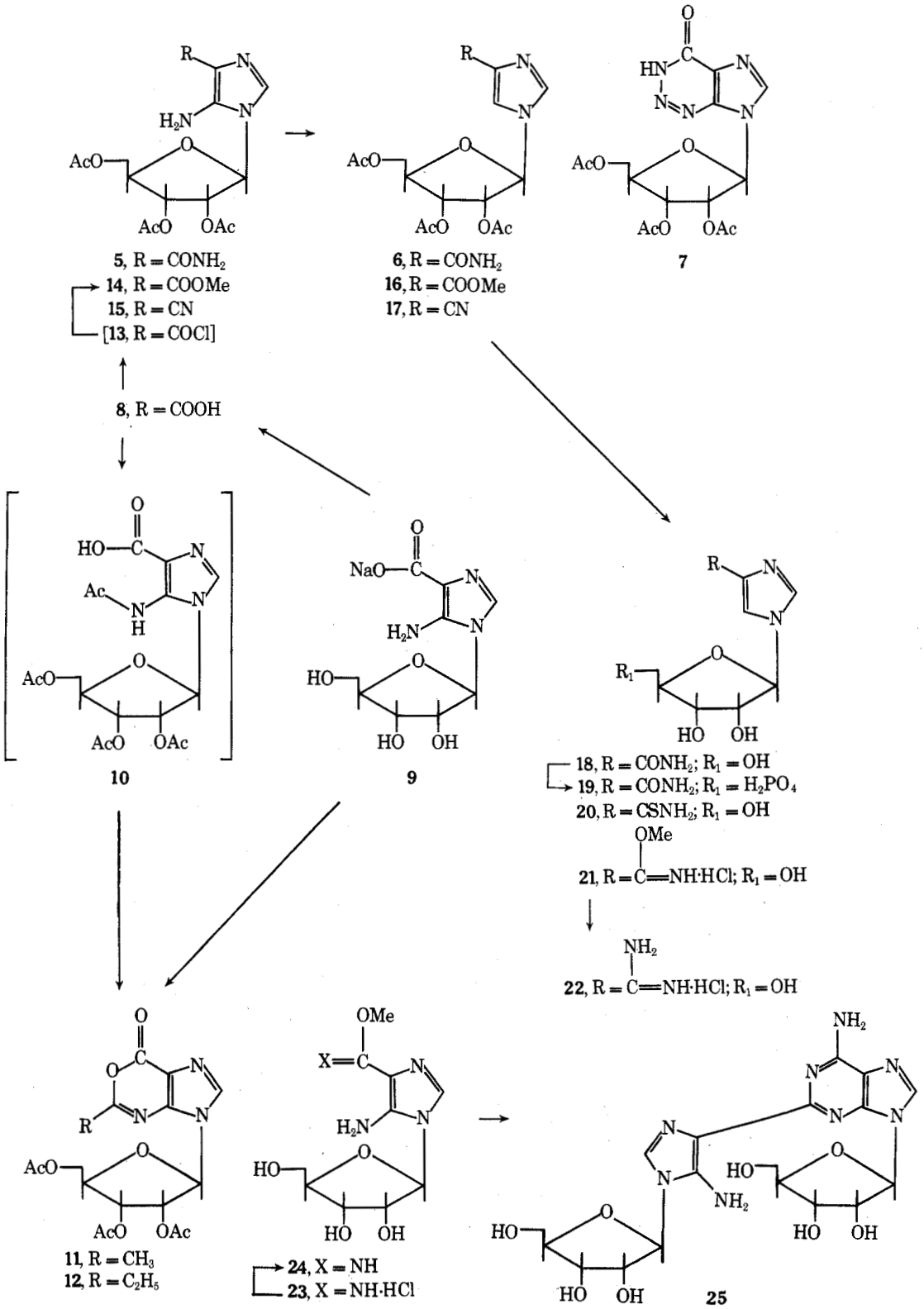
ribavirin (**3**)

nucleoside derivatives of five-membered heterocycles are of potential chemotherapeutic importance. The naturally occurring 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate (AICAR), a central intermediate in de novo purine biosynthetic pathway,[4] bears close resemblance to these derivatives; therefore, chemical modification of this molecule was considered from a biological standpoint. The commercial availability[5] of the corresponding nucleoside, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside, **4**) has led us to study this approach in detail.[6-8]

In the present paper we describe the synthesis of some novel 4-substituted imidazole nucleosides related to ribavirin via diazotization of AICA riboside. In the past, this modification has proven rather difficult and attempts at altering the 5 position of **4** via diazotization under strongly acidic conditions have resulted in facile ring closure to give 2-azainosine.[9] This reaction was well utilized, however, in preparing 2-substituted 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide derivatives.[7] Further attempts were made to reductively deaminate the 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide[10] (**5**) using hypophosphorous acid and sodium nitrite. Although some deaminated product, 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (**6**), was indeed formed, extensive cyclization occurred to give 7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*]-*v*-triazin-4-one (**7**) as the major product. The formation of **7** was not unexpected, since the synthesis of this compound has previously been reported from this laboratory.[9] In order to circumvent this ring closure, modification of the 4-carboxamide function of AICA riboside into a nonreactive group like the methyl carboxylate was investigated. The precursor, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (**8**), was obtained via the treatment of sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (**9**) with pyridine and acetic anhydride at a low temperature (10 ± 5°).[6] Repeated experiments revealed that the control of temperature in this reaction was extremely important. At a high temperature (>30°) the 5-amino function of **9** was acetylated generating the corresponding tetraacetyl derivative (**10**) in situ, which immediately cyclized to furnish 5-methyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (**11**). In an experiment when **8** was heated at 100° in pyridine in the presence of acetic anhydride compound **11** was formed in almost theoretical yield within 1 hr. In a similar experiment when acetic anhydride was replaced by propionic anhydride the corresponding 5-ethyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (**12**) was obtained in quantitative yield. These novel nucleosides could provide potential intermediates for the synthesis of 1,2-disubstituted purine nucleosides if treated with the requisite amine.

The synthesis of the desired compound **14** was accomplished via treatment of **8** with dimethylformamide, thionyl chloride, and pyridine at −20° to generate the acid chloride **13** in situ, which was treated with methanol to yield

**Scheme I**




compound **14**. The usefulness of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**) for deamination studies was obvious owing to the presence of a nitrile group at the 4 position and it was synthesized as described in a patent.[10]

The subsequent reductive deamination of **14** and **15** was able to be carried out successfully via diazotization using hypophosphorous acid and sodium nitrite. These reactions were achieved at a low temperature (≤20°) to avoid excessive cleavage of the glycosidic bond. Methyl 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**16**) and 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**17**) were isolated by silicic acid column chromatography as a syrup and a crystalline product, respectively, in 60–65% yields. Treatment of **16** with methanol and ammonium hydroxide readily provided 1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**18**). Compound **18** was also obtained when **17** was treated with hydrogen peroxide in the presence of concentrated ammonium hydroxide. Nucleoside **18** is the first example of the synthesis of 2-deaziriba-

virin. The synthesis of 1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate (**19**) was also of interest and was achieved in 63% yield by selective 5′-phosphorylation of **18** in the presence of triethyl phosphate and phosphorus oxychloride.

The synthesis of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**17**) provided the possibility of further modifications at the 4 position of 1-β-D-ribofuranosylimidazole. The treatment of **17** with potassium hydrosulfide and hydrogen sulfide in methanol at 80–90° gave 1-(β-D-ribofuranosyl)imidazole-4-thiocarboxamide (**20**) as a crystalline compound in 75% yield. When **17** was treated with dry hydrogen chloride in methanol at 0°, it was deacetylated in situ and provided the interesting methyl 1-(β-D-ribofuranosyl)imidazole-4-carboximidate hydrochloride (**21**). The latter compound was further converted into 1-(β-D-ribofuranosyl)imidazole-4-carboxamidine hydrochloride (**22**) when treated with methanolic ammonia at 100°.

Although the synthesis of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamidine has been previously reported,[11] we wanted to develop an alternate synthesis starting from 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**). When **15** was treated with dry hydrogen chloride in methanol at 0° methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate hydrochloride (**23**) was obtained. The basic methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate (**24**) could be liberated in the crystalline form when an aqueous ethanolic solution of **23** was gradually adjusted with triethylamine to pH 7. We observed an unusual, although not entirely unexpected, intermolecular cyclization[12] when **24** was treated with liquid ammonia at 100° and 2-[5-amino-1-(β-D-ribofuranosyl)imidazole-4-yl]adenosine (**25**) was obtained as a crystalline compound in 25% yield. The structure of compound **25** was assigned on the basis of uv, NMR, and elemental analysis. The desired 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamidine was not isolated in this experiment.

## Experimental Section

All the deamination reactions were performed at a temperature of −23 ± 3° to avoid hydrolysis of the glycosyl bond. The physical properties were determined with the following instruments: melting points, Thomas-Hoover apparatus (uncorrected); $^1$H NMR, Hitachi Perkin-Elmer R-20A spectrometer (DSS); uv spectra, Cary 15 uv spectrophotometer (pH 1 and pH 11). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich. Silica gel (Woelm, 0.063–0.2 mm) was used for column chromatography. Solvent systems (A) ethyl acetate–chloroform–acetone (5:3:2 v/v) and (B) ethyl acetate–1-propanol–water (4:1:2 v/v, top layer) were used respectively to check the homogeneity of the blocked and deblocked nucleosides on thin layer chromatography. Presence of exchangeable protons was confirmed by NMR spectroscopy in absolute $Me_2SO$-$d_6$ by exchange with $D_2O$ followed by reintegration.

**1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (6).** 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxamide (**5**, 1.152 g, 3.00 mmol) was dissolved in 50% $H_3PO_2$ (20 ml) at −20° with vigorous stirring. To this was added dropwise a solution of $NaNO_2$ (227 mg, 3.3 mmol) in water (2 ml). The reaction mixture turned deep purple. After 2 hr of stirring the reaction mixture was adjusted to pH 6 by careful addition of ammonium hydroxide. It was extracted with ethyl acetate (4 × 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue (1.01 g) was applied to a dry column of silica gel (2 × 40 cm). It was eluted with EtOAc–$CH_2Cl_2$–MeOH (350:125:25 v/v) and 20-ml fractions were collected. Fraction 2 contained 190 mg of compound **7** (found identical, in every respect, with an authentic sample[9]).

Fractions 4, 5, and 6 were evaporated in vacuo to give crude compound **6** (280 mg). This was purified by rechromatography through a silica gel column (1 × 20 cm, packed in $CHCl_3$) and elution with $CHCl_3$–EtOAc (60:40 v/v). Upon evaporation, fractions 3–10 (20 ml each) gave 120 mg of pure compound **6** in the form of a thick syrup: NMR ($CDCl_3$–$D_2O$) δ 5.85 (d, 1, $J$ = 4.5 Hz, $C_{1'}H$) and 7.69 and 7.87 ppm [s (pair), 2, $C_2H$ and $C_5H$].

Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.55; H, 5.28; N, 11.10.

**5-Methyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (11). Method A.** 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid[6] (**8**, 385 mg, 1 mmol) was gently refluxed in pyridine (5.3 ml) and acetic anhydride (2.7 ml) for 2 hr. The reaction mixture was concentrated to dryness in vacuo. The residue was dissolved in ethyl acetate (20 ml) and washed with water. The ethyl acetate portion was dried ($MgSO_4$) and evaporated in vacuo. The residue thus obtained was crystallized from benzene–petroleum ether to give 360 mg (90%) of **11** in the form of fine needles: mp 115°; NMR ($Me_2SO$-$d_6$) δ 2.51 (s, 3, $CH_3$), 6.19 (d, 1, $J$ = 5 Hz, $C_{1'}H$), and 8.39 ppm (s, 1, $C_2H$).

Anal. Calcd for $C_{17}H_{19}N_3O_9$: C, 49.88; H, 4.68; N, 10.27. Found: C, 49.87; H, 4.61; N, 10.04.

**Method B.** Compound **11** was also obtained when sodium 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate[6] (**9**) was treated as reported in method A. The yield in this case was 30% and the product characterized as for method A.

**5-Ethyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*d*][1,3]oxazin-7-one (12).** In this experiment 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid was treated with propionic anhydride in pyridine. The reaction and isolation was performed in the same manner as for **11** in method A. The product **12** was crystallized from carbon tetrachloride: mp 136°; NMR ($Me_2SO$-$d_6$) δ 1.29 (s, 3, $J$ = 7.5 Hz, $CH_3$ of 5-ethyl), 2.81 (d, 2, $J$ = 7.5 Hz, $CH_2$ of 5-ethyl), 6.21 (d, 1, $J$ = 4 Hz, $C_{1'}H$), and 8.35 ppm (s, 1, $C_2H$).

Anal. Calcd for $C_{18}H_{21}N_3O_9$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.28; H, 5.23; N, 9.74.

**Methyl 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole-4-carboxylate (14).** Under nitrogen atmosphere and anhydrous conditions, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (**8**, 770 mg, 2 mmol) and pyridine (158 mg, 0.161 ml, 2 mmol) were dissolved in dry DMF (8 ml). This mixture was cooled to −20°. A precooled (−10°) solution of DMF–$SOCl_2$ (0.144 ml of $SOCl_2$ in DMF to make the total volume 0.3 ml) was added to the mixture. The reaction mixture was stirred at −20 ± 3°) for 2 hr. After this period methanol (10 ml) was added dropwise to the reaction solution and after complete addition (10 min) the reaction was allowed to come to room temperature. After 8 hr of additional stirring, the solvents were evaporated in vacuo. The residue thus obtained was dissolved in $CH_2Cl_2$ and washed with water and the organic phase was dried ($MgSO_4$). Compound **14** crystallized when the syrup, obtained after evaporating the solvent in vacuo, was treated with benzene (15 ml). The product was recrystallized from chloroform–ether or 2-propanol to yield 335 mg (42%): mp 145°; NMR ($Me_2SO$-$d_6$) δ 3.71 (s, 3, $COOCH_3$), 5.97 (d, 1, $J$ = 6 Hz, $C_{1'}H$), 6.25 [s (br), 2, $NH_2$], and 7.47 ppm (s, 1, $C_2H$).

Anal. Calcd for $C_{16}H_{21}N_3O_9$: C, 48.12; H, 5.30; N, 10.52. Found: C, 47.99; H, 5.36; N, 10.73.

**Methyl 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate (16).** Compound **14** (799 mg, 2 mmol) was added to a precooled (−20°) stirred solution of hypophosphorous acid (48–50%, 20 ml) containing a few drops of hydrochloric acid. To the above clear solution was added slowly (8 min) a solution of $NaNO_2$ (345 mg, 5.00 mmol) in water (3 ml). The stirring was continued for 3 hr at −20°. The reaction solution was adjusted to pH 6 by careful addition of a saturated solution of sodium bicarbonate. The final reaction mixture was extracted with ethyl acetate (4 × 40 ml) and the organic layer in turn was washed thoroughly with water (2 × 50 ml). The ethyl acetate portion was dried ($MgSO_4$) and the crude residue was chromatographed through a silica gel column (2 × 35 cm, packed in $CHCl_3$). The first $CHCl_3$ eluate (250 ml) was rejected. The column was again eluted with $CHCl_3$–EtOAC (75:25 v/v) and fractions (25 ml) were collected. Fractions 3–10, on evaporation, gave 450 mg (60%) of pure compound **16** as a syrup: NMR ($Me_2SO$-$d_6$) δ 3.8 (s, 1, $COOCH_3$), 6.13 (d, 1, $J$ = 5 Hz, $C_{1'}H$), and 8.09 and 8.22 ppm [s (pair), 2, $C_2H$ and $C_5H$].

Anal. Calcd for $C_{16}H_{20}N_2O_9$: C, 50.00; H, 5.25; N, 7.29. Found: C, 49.93; H, 5.48; N, 7.08.

**1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (17).** A solution of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-

ribofuranosyl)imidazole-4-carbonitrile[16] (3.7 g, 10.00 mmol) in methanol (20 ml) was added to a precooled (−20 to −25°) solution of hypophosphorous acid (48–50%, 100 ml) containing a few drops of concentrated hydrochloric acid. To this was added a solution of sodium nitrite 3.5 g in water (8 ml). The reductive deamination and the isolation of product **17** was performed exactly the same way as described for the synthesis of **16**. The syrup thus obtained by column chromatography was crystallized from methanol to give the pure product **17**: yield 2.3 g (65%); mp 122–123°; $\lambda_{max}$ (pH 1) 218 nm ($\epsilon$ 13,330); $\lambda_{max}$ (pH 11) 226 nm ($\epsilon$ 7694); $\nu_{max}$ (KBr) 2234 $cm^{-1}$ (C≡N); NMR ($CDCl_3$ $\delta$ 5.85 (d, 1, $J$ = 4 Hz, $C_1$'H) and 7.75 and 7.81 ppm [s (pair), 2, $C_2$H and $C_5$H].

Anal. Calcd for $C_{15}H_{17}N_3O_7$: C, 51.28; H, 4.88; N, 11.96. Found: C, 51.30; H, 4.76; N, 11.98.

**1-(β-D-Ribofuranosyl)imidazole-4-carboxamide (18). Method A (from 6 or 16).** The blocked compounds **6** and **16** (1 mmol) were respectively treated with a solution of methanol–$NH_4OH$ (10 ml, 1:1 v/v) for 5 hr at room temperature (in case of **16** the reaction went to completion only after 5 days owing to slow reactivity of methyl ester). The solvent was removed in vacuo and the residue was dried in vacuo (0.1 mm) at 40° for 5–7 hr. The residue could then easily be crystallized from methanol. The product **18** obtained from **6** was identical in all respects with the one obtained from **16**: yield 70–75%; mp 156–157°; $\lambda_{max}$ (pH 1) 213 nm ($\epsilon$ 12,900); $\lambda_{max}$ (pH 11) 235 nm ($\epsilon$ 10,200); NMR ($Me_2SO$-$d_6$–$D_2O$) $\delta$ 5.65 (d, 1, $J$ = 5.0 Hz, $C_1$'H) and 7.92 and 7.99 [s (pair), 2, $C_2$H and $C_5$H].

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.24; H, 5.25; N, 17.13.

**Method B (from 17).** Compound **17** (350 mg, 1 mmol) was suspended in 10 ml of ammonium hydroxide. The suspension was cooled to 0° in ice and a 30% solution of hydrogen peroxide (0.5 ml) was added. The suspension was stirred overnight to give a clear solution. The solvent was evaporated and the residue was triturated with acetone. The supernatant was decanted and the resultant residue was crystallized from water, yield 180 mg (74%). The product was found to be identical with that isolated by method A.

**1-(β-D-Ribofuranosyl)imidazole-4-carboxamide 5'-Phosphate (19).** To a stirred suspension of 1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**18**, 1.216 g, 5 mmol) in triethyl phosphate (20 ml) was added $POCl_3$ (1.6 g) at −5 to 5°. After complete addition (5 min) the reaction mixture was stirred for 5 hr at 0°. This was poured into ice–water (15 ml) and the mixture was diluted with $H_2O$ (50 ml). The solution was adjusted to pH 1.5 by adding 2 *N* NaOH, applied to a Dowex X1 (formate) column (2 × 15 cm), and eluted with water (1000 ml), and the eluate was discarded. The column was subsequently eluted with 0.5 *N* formic acid and 20-ml fractions collected. Fractions 5–11 were evaporated to dryness in vacuo. The residue was triturated well with acetone (3 × 15 ml) and the supernatant was discarded. The residue thus obtained was crystallized from water to yield 1.0 g (63%): mp 197°; NMR ($Me_2SO$-$d_6$–$D_2O$) $\delta$ 5.7 (d, 1, $J$ = 5 Hz, $C_1$'H) and 7.92 and 8.08 ppm [s (pair), 2, $C_2$H and $C_5$H].

Anal. Calcd for $C_9H_{14}N_3O_8P$: C, 33.45; H, 4.37; N, 13.00. Found: C, 33.40; H, 4.41; N, 13.02.

**1-(β-D-Ribofuranosyl)imidazole-4-thiocarboxamide (20).** Compound **17** (500 mg, 1.42 mmol) and KOH (200 mg) in methanol (10 ml) were saturated with $H_2S$ at 0° and heated in a bomb at 100° for 4 hr. After removal of the solvent the residue was taken into water (2 ml) and adjusted to pH 5 by adding dilute HCl. The mixture was cooled in ice for 10–15 min and the separated solid collected by filtration. The crude product was recrystallized from water to give 280 mg of white needles (75%): mp 185°; $\lambda_{max}$ (pH 1) 246 nm ($\epsilon$ 9603) and 298.5 (9982); $\lambda_{max}$ (pH 11) 256 (12,585) and 301.5 (11,372); NMR ($Me_2SO$-$fd_6$–$D_2O$) $\delta$ 5.64 (d, 1, $J$ = 5 Hz) and 8.0 and 8.07 ppm [s (pair), 2, $C_2$H and $C_5$H].

Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21; S, 12.37. Found: C, 41.58; H, 4.96; N, 16.05; S, 12.51.

**Methyl 1-(β-D-Ribofuranosyl)imidazole-4-carboximidate Hydrochloride (21).** A solution of **17** (1.9 g, 5.00 mmol) in methanol (30 ml) was saturated with dry hydrogen chloride at 0°. The reaction mixture was allowed to stand overnight at −10°. The separated product was filtered, washed with dry ether, and dried in vacuo to yield 1.4 g (50%) of the hydrochloride **21** as a white solid. The product was recrystallized from acetone–water, mp 155–158° dec.

Anal. Calcd for $C_{10}H_{15}N_3O_5HCl$: C, 40.89; H, 5.49; N, 14.31. Found: C, 40.75; H, 5.30; N, 14.21.

**1-(β-D-Ribofuranosyl)imidazole-4-carboxamidine Hydrochloride (22).** Compound **21** (1.45 g, 5 mmol) after drying in vacuo over $P_2O_5$ for 24 hr at room temperature was treated with liquid ammonia (10 ml) in a bomb at 80°. The ammonia was evaporated and the residue was treated with absolute ethanol. The ethanol was evaporated in vacuo and the residue was crystallized from ethanol to give **22** in the form of white crystals: yield 850 mg (60%); mp 166–167° (213° dec); $\lambda_{max}$ (pH 1) 243 nm ($\epsilon$ 10,800); $\lambda_{max}$ (pH 11) 242 (10,450); NMR ($Me_2SO$-$d_6$) $\delta$ 5.76 (d, 1, $J$ = 4.5 Hz, $C_1$'H), 8.3 and 8.61 [s (pair), 2, $C_2$H and $C_5$H], and 8.7–9.5 ppm (m, 4, HN=$CNH_2$·HCl).

Anal. Calcd for $C_9H_{14}N_4O_4$·HCl: C, 38.79; H, 5.42; N, 20.10. Found: C, 38.50; H, 5.60; N, 19.89.

**Methyl 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate Hydrochloride (23).** 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**, 3.6 g, 10 mmol) was dissolved in methanol (25 ml). This solution was saturated with dry HCl at 0° and allowed to stand at the same temperature for 24 hr. The separated white solid was filtered, washed with acetone, and dried in vacuo ($P_2O_5$) to give 2.7 g (90%) of the product **23** which was recrystallized from acetone–water: mp 113° dec; NMR ($Me_2SO$-$d_6$–$D_2O$) $\delta$ 4.18 (s, 3, $CH_3$ of carboximidate), 5.62 (d, 1, $J$ = 6.5 Hz, $C_1$'H), and 7.67 ppm (s, 1, $C_2$H).

Anal. Calcd for $C_{10}H_{16}N_4O_5$·HCl: C, 38.91; H, 5.55; N, 18.15. Found: C, 38.79; H, 5.42; N, 17.89.

**Methyl 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate (24).** An ice-cold aqueous methanolic solution of **23** was adjusted to pH 7 by adding triethylamine. The solution was stirred well and the liberated white solid was filtered and recrystallized from water to give **24** in the form of white crystals: mp 181° dec; $\lambda_{max}$ (pH 1) 293 nm ($\epsilon$ 20,700); $\lambda_{max}$ (pH 11) 260 (14,300); NMR ($Me_2SO$-$d_6$–$D_2O$) $\delta$ 3.81 (s, 3, $CH_3$ of carboximidate), 5.52 (d, 1, $J$ = 6.5 Hz, $C_1$'H), and 7.47 ppm (s, 1, $C_2$H).

Anal. Calcd for $C_{10}H_{16}N_4O_5$: C, 44.11; H, 5.92; N, 20.58. Found: C, 44.13; H, 6.02; N, 20.44.

**2-[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-yl]adenosine (25).** Methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboximidate (**24**, 272 mg, 1 mmol) was treated with liquid ammonia at 100° for 16 hr. After evaporation of ammonia the residue was crystallized from hot water to give 55 mg (20%) of compound **25**: mp 221° (dec; $\lambda_{max}$ (pH 1) 257 nm ($\epsilon$ 14,400) and 312 (19,200); $\lambda_{max}$ (pH 11) 252 (15,400) and 310 (20,200); NMR ($Me_2SO$-$d_6$–$D_2O$) $\delta$ 5.6 [s (br), 1, $C_1$'H of imidazole riboside], 5.98 [s (br), 1, $C_1$'H of adenosine], 7.42 [s (br), 1, $C_2$H], and 8.25 ppm [s (br), 1, $C_8$H].

Anal. Calcd for $C_{18}H_{24}N_8O_8$: C, 45.00; H, 5.04; N, 23.33. Found: C, 44.70; H, 5.05; N, 23.37.

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# Electrochemistry of Natural Products. V. Intramolecular Coupling of Phenolic Alkaloid Precursors[1]

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Intramolecular coupling of some diphenols by electrochemical oxidation is reported. Specifically, 1-(4-hydroxyphenylethyl)- and 1-(4-hydroxy-3-methoxyphenylethyl)-7-hydroxy-6-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinolines have been coupled to the corresponding dienones in yields of 20–40% and *N*-acyl-*N*-norreticulines have been coupled to *N*-acyl-*N*-norpallidines in yields of about 18%. Attempts to couple *N*-benzylphenylethylamines to alkaloids of the Amaryllidaceae type were not successful.

The important role played by phenol coupling in alkaloid biosynthesis has been thoroughly documented and reviewed.[3] In general, attempts to carry out phenol coupling reactions in vitro have been only partially successful, mainly owing to low yields caused by overoxidation. In an attempt to develop a more specific oxidizing system, we have been exploring controlled potential, electrochemical oxidation. Intermolecular coupling reactions have been carried out in good yields (50–95%) and our work has recently been summarized.[4] In this paper, we would like to report our more limited success with intramolecular coupling of diphenols. Such electrochemical reactions do not appear to have been previously reported. Although diphenols have not been coupled electrochemiccally before, their methyl ethers have been coupled recently[5] with considerable success. Yields have been high, and the reactions have been remarkably clean. Although these reactions have the greater potential as useful synthetic methods, the coupling of diphenols is more relevant to biosynthesis and biomimetic synthesis of natural products.

**The 1-Phenylethyltetrahydroisoquinolines.** The compounds oxidized were **7** and **8**, which were prepared (Scheme I) by the method generalized by Harmon and his coworkers.[6] The actual reactions used, however, are substantially different from those previously recorded[7-9] in that the side chain double bond is left in place until the final debenzylation step (**6** to **7** and **8**). Using this sequence, the intermediates were easier to crystallize and work with.

The oxidations of the hydrochlorides of **7** and **8** were carried out on a graphite felt anode in water using tetraethylammonium perchlorate as an electrolyte. The potentials were controlled at 0.7 V for **7** and at 0.8 V for **8** [as measured against a standard calomel electrode (SCE)]. The dienone **9** was obtained from **7** in 23% yield as compared with 19% using $FeCl_3$ as an oxidizing agent.[8] The two dienones, **10** and **11** (differing in the stereochemistry at the spiro ring system) were obtained in a combined yield of 36% as compared to 9% using $K_3Fe(CN)_6$[9] and 31% using $FeCl_3$.[10] The isomers, **10** and **11**, were separated as previously described,[9] but, unfortunately, there was no preponderance of one isomer. One of the isomers is the alkaloid kreysiginone.[10]

**The Acyl Reticuline Derivatives.** The oxidative ring closure of reticuline (**12**, Scheme II) to a dienone skeleton, **16**, and thence to morphine has been one of the major goals in alkaloid synthesis for many years. Although **16** was obtained once in very low yield,[11] the more usual product has been the isomeric dienone, **17**, albeit also in low yields (0–4%). The work has been well summarized.[3c]

Attempts to oxidize reticuline (**12**) and its nor derivative, **13**, electrochemically have yielded no isolable products and the starting material was destroyed either by extensive overoxidation or by some sort of fragmentation process.[12] Thus, the *N*-carbethoxy (**14**) and the *N*-carbobenzyloxy (**15**) derivatives of norreticuline were chosen for oxidation studies. Compound **14** was prepared from reticuline dibenzyl ether[13] and **15** was prepared from reticuline itself[14] by acylation. Compounds **12** and **13** were prepared by a general Bischler–Napieralski synthesis.[14]

Experimental conditions for the oxidation of **14** were explored extensively. The optimum conditions were found to be oxidation on a graphite felt anode in 50% aqueous *tert*-butyl alcohol with 4 molar equiv of potassium *tert*-butoxide and an equivalent amount of palladium chloride.[5d,15] The current was controlled at 0.2 V vs. SCE, and the oxidations were performed under nitrogen at 20° for a time equivalent to a two-electron oxidation. Under these conditions, the dienone **18** was obtained in a yield of 15.5%, corrected to 18% by recovery of starting material. Yields were lower in aqueous acetonitrile with tetraethylammonium perchlorate as electrolyte, at higher or lower temperatures, at higher or lower potentials, and in the absence of palladium chloride. Compound **18** was methylated to **20** with diazomethane, but all attempts to remove the carbethoxy group by hydrolysis or reduction failed to yield isolable products.

Although **18** and **20** were not crystalline, they gave satisfactory analyses and had spectroscopic properties corresponding to the structures. Both **18** and **20** had strong molecular ion peaks at *m/e* 385 and 399, respectively, with strong peaks corresponding to loss of ethyl, carbethoxy, and $CH_2NCO_2Et$. The uv spectra showed maxima at 283 and 236 nm in agreement with a cross-conjugated $\alpha$-methoxycyclohexadienone structure[16] and lacked a strong peak at 300 nm expected from any aporphine system.[3e] The ir spectra show three bands at 1665, 1635, and 1615 $cm^{-1}$