Some Selenium Derivatives of Imidazo[1,2-*a*]pyridines

Elli S. Hand and William W. Paudler*

Department of Chemistry, The University of Alabama, University, Alabama 35486

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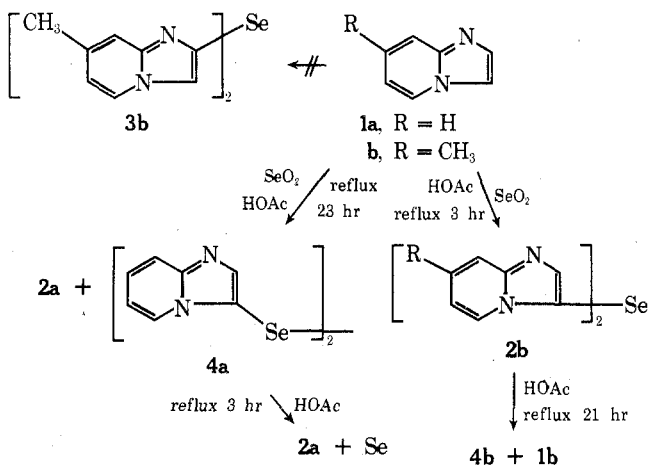
The reaction of imidazo[1,2-*a*]pyridine (**1a**) and its 7-methyl derivative (**1b**) with selenium dioxide affords 3,3′-di(imidazo[1,2-*a*]pyridyl) selenides (**2a,b**). Prolonged reaction time also yield the 3,3′-di(imidazo[1,2-*a*]pyridine) diselenide (**4a**) along with **2a**. The diselenide **4a** can be converted to the monoselenide **2a** by heating in glacial acetic acid, while the monoselenide **2b** affords a mixture of the diselenide **4b** and 7-methylimidazo[1,2-*a*]pyridine (**1b**) under similar reaction conditions. The monoselenide **2b** when treated with bromine yields, ultimately, 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**). When 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) is treated with selenium dioxide in acetic acid, monoselenide **2b**, diselenide **4b**, 5-(2-amino-4-methylpyridyl)-3-(7-methylimidazo[1,2-*a*]pyridyl) selenide (**6**), and the parent compound **1b** are obtained. The ^{1}H NMR spectra of the various compounds, as well as possible reaction paths to account for their formation, are described.

As part of a research project requiring the preparation of imidazo[1,2-*a*]pyridine carboxaldehydes, we had occasion to attempt a selenium dioxide oxidation of 7-methylimidazo[1,2-*a*]pyridine (**1b**). Surprisingly, no carboxaldehyde derivative was obtained. Instead, a compound of molecular composition $C_{16}H_{14}N_4Se$ was isolated in 90% yield. The ^{1}H NMR spectrum of this compound (see Table I) indicates that neither the methyl group nor any of the six-membered ring protons of 7-methylimidazo[1,2-*a*]pyridine (**1b**) were affected by the reaction. The presence of a singlet at δ 7.87 ppm indicates that substitution by a selenium atom has occurred at either C-2 or C-3 of the ring system. Therefore, we can conclude that the product has either structure **2b** or **3b** (see Scheme I).

An examination of Dreiding molecular models shows that if the compound had structure **3b**, assuming free rotation about the two carbon–selenium bonds, one would expect the chemical shifts of the six-membered ring protons in this compound to be very similar to those in 7-methylimidazo[1,2-*a*]pyridine (**1b**). On the other hand, if the compound had structure **2b**, the models indicate a potential ring–ring interaction which would produce a significant shift in the resonance position of H-2 and H-5. An examination of Table I shows that the latter instance prevails. Specifically, H-5 is more deshielded by 0.39 ppm in the selenium-containing compound **2b** than it is in the starting material (**1b**). A similar shift (0.38 ppm) is apparent for H-2. Thus, we are dealing with the 3-substituted derivative **2b**.

Scheme I



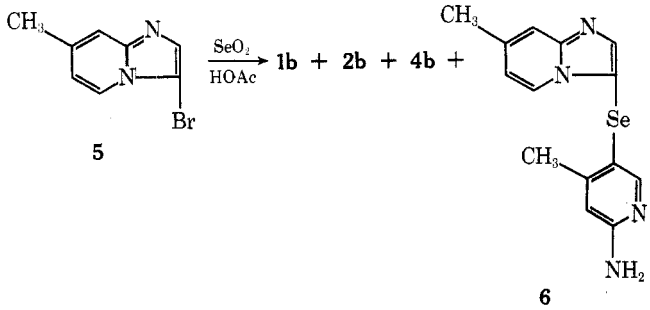
The parent imidazo[1,2-*a*]pyridine (**1a**) when treated with selenium dioxide affords the analogous monoselenide **2a** as well as a compound of molecular formula $C_{14}H_{10}N_4Se_2$ (**4a**). The ^{1}H NMR spectrum of this material differs from that of the monoselenide **2a** by increased shielding of H-2, H-5, and H-6 while maintaining the same splitting pattern. When this diselenide is heated in acetic acid, it is converted to the monoselenide. Consequently, the two compounds are structurally related to each other in terms of their sites of substitution. An analysis of the ^{1}H

Table I
Chemical Shifts[a] of Some Imidazo[1,2-*a*]pyridines[c]

	ArH[b] **1a**	ArBr	ArSeAr **2a**	$(ArSe)_2$ **4a**	Ar′H[b] **1b**	Ar′Br **5**	Ar′SeAr′[b] **2b**	$(Ar'Se)_2$ **4b**	**6**	
H_2	7.58	7.62	7.96	7.76	7.49	7.52	7.87	7.70	7.83	
H_3	7.63				7.55					
H_5	8.05	7.90	8.51	7.84	7.99	7.96	8.38	7.67	8.27	
H_6	6.78	6.75	6.93	6.64	6.61	6.72	6.75	6.48	6.72	
H_7	7.16	7.10	7.24	7.24						
H_8	7.62	7.57	7.60	7.68	7.37	7.34	7.38	7.40	7.42	
CH_3					2.38	2.39	2.39	2.40	2.40 & 2.42	2.23
H_3'									6.34	6.34
H_6'									8.06	7.99
NH_2									~4.55	~4.40
H_5'										6.50

[a] In δ (parts per million), dilute solutions in $CDCl_3$. [b] Extrapolated to infinite dilution. [c] Typical values of coupling constants: $J_{2,3}$ = 0–1; $J_{2,8}$ = 0; $J_{3,8}$ = <1; $J_{5,6}$ = 6.6–7; $J_{5,7}$ = 1–1.5; $J_{5,8}$ = 0–1.5; $J_{6,7}$ = 6.6–7; $J_{6,8}$ = 1–1.5; $J_{7,8}$ = 9 Hz.

Scheme II



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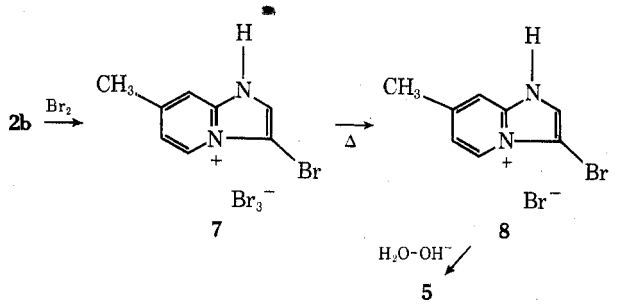
NMR spectrum of the diselenide **4a**[1] further confirms the substitution position of the hterocyclic rings, since an inspection of Dreiding models reveals that, assuming free rotation about the selenium–selenium bond, there will be ring–ring interactions affecting H-2, H-5, and H-6. A comparison of the chemical shifts of H-2 (δ 7.58 ppm), H-5 (δ 8.05 ppm), and H-6 (δ 6.78 ppm) of imidazo[1,2-*a*]pyridine with the corresponding protons in the diselenide, H-2 (δ 7.76 ppm), H-5 (δ 7.84 ppm), H-6 (δ 6.64 ppm), confirms this prediction.

When the monoselenide **2b** is refluxed in acetic acid in the presence or absence of selenium, it is converted to the diselenide **4b,** as well as the parent compound (**1b**). In the absence of selenium, larger amounts of the parent compound **1b** are formed.

The formation of these 3-substituted compounds prompted us to examine the behavior of an imidazo[1,2-*a*]pyridine blocked at that position. When 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) is refluxed in acetic acid in the presence of selenium dioxide, four compounds are isolated, namely, 7-methylimidazo[1,2-*a*]pyridine (**1b**), the monoselenide **2b,** the diselenide **4b,** and a compound, $C_{14}H_{14}N_4Se$ (**6**).

The ^1H NMR spectrum of compound **6** showed the same pattern as observed in the monoselenide **2b.** In addition to these absorptions, two sharp one-proton singlets (δ 6.34 and 8.06 ppm) and a broad two-proton band (δ 4.55 ppm) are observed. The methyl proton absorption of this compound integrates for six protons. Based upon these data we suggest structure **6** (see Scheme II). A comparison of the ^1H NMR spectrum of 2-amino-4-methylpyridine [H-3 (δ 6.34 ppm), H-6 (δ 7.99 ppm)] with the "extra" singlet protons in compound **6** confirms the structural assignment.

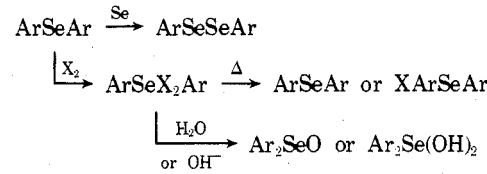
Since the bromine in compound **5** is readily displaced by selenium, it became of interest to examine the reactivity of the selenide **2b** toward bromine. When compound **2b** was treated with bromine in chloroform, a yellow precipitate formed instantaneously. This compound, $C_8H_8N_2Br_4$ (**7**), obtained in quantitative yield, when heated in wet benzene, formed a colorless material, $C_8H_8N_2Br_2$ (**8**). The ^1H NMR spectra of compounds **7** and **8** in Me_2SO-d_6 are identical. Treatment of compound **8** with cold dilute base afforded 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**). These various transformations can be depicted as follows.



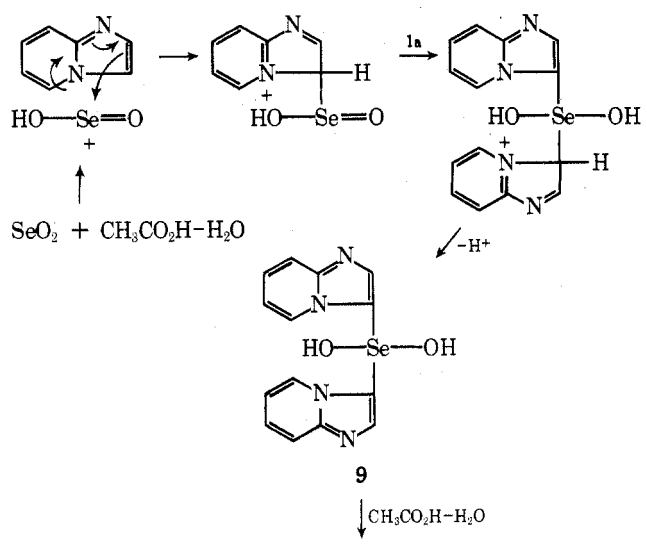
Discussion

The use of selenium dioxide in oxidations of olefins and "active" methyl and methylene groups is well known.[2,3] Some other uses of selenium dioxide in organic chemistry involve the formation of di-*p*-alkoxyphenyl selenides from aryl alkyl ethers[4] and analogous selenides from phenolic compounds.[5] Similar reactivity has been observed for selenium oxychloride, which leads to hydroxy[6] and alkoxy[6b] aryl selenides as well as another class of selenides, the *p*-dialkylaminophenyl derivatives.[7] Some unusual reactions of heterocyclic compounds with selenium dioxide are the formation of selenides from pyrazolones[8] and indoles.[9]

The chemistry of diaryl selenides, as applicable to our work, can be summarized by the following general reactions.[10,11]

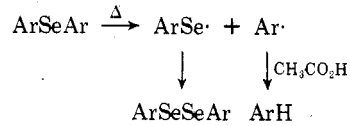


The formation of the diaryl selenides (**2a,b**) can be envisioned to occur by the following sequence of reactions.



The species $HO^+Se{=}O$ and $(HO)_3Se^+$ have been proposed[12] as the active moieties involved in the oxidation reactions of selenium dioxide in the presence of water. We are invoking the same species in the electrophilic substitutions of the imidazo[1,2-*a*]pyridines. A diarylhydroxy selenium intermediate, such as **9**, has been previously postulated, and its conversion to a diaryl selenide, in the presence of aqueous acetic acid and selenium, has been established.[4a]

The conversion of the monoselenides, ArSeAr, to a mixture of the diselenides, ArSeSeAr, and the starting compound, ArH, can be depicted by the following sequence.



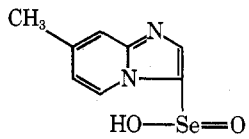
It is of interest to note that in this instance, contrary to other reports,[13] selenium is not required. The disproportionation of the diselenides **4a,b** to the monoselenides **2a,b** and selenium finds precedent in the literature.[14]

The formation of the monoselenide **2b** from 3-bromo-7-methylimidazo[1,2-*a*[pyridine (**5**) could possibly be a nu-

cleophilic or free-radical displaceme reaction at C-3. However, attempts at causing a nucleophilic displacement of bromine by methoxide (see Experimental Section), piperidine, or morpholine[15] were unsuccessful, and no evidence for the formation of free radicals in selenium dioxide oxidations has ever been obtained.[12] We therefore propose an electrophilic displacement reaction analogous to that described for the formation of the selenides **2a** and **2b**. Apparently, no precedence for this type of displacement reaction is available in the literature.

The concurrent formation of the diselenide **4b** and the parent compound (**5**) can then be rationalized as arising from the monoselenide **2b** as delineated in the previous paragraph.

The generation of the small amount of compound **6** may occur via the intermediacy of **10** and attack by 2-amino-4-



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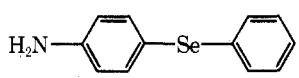
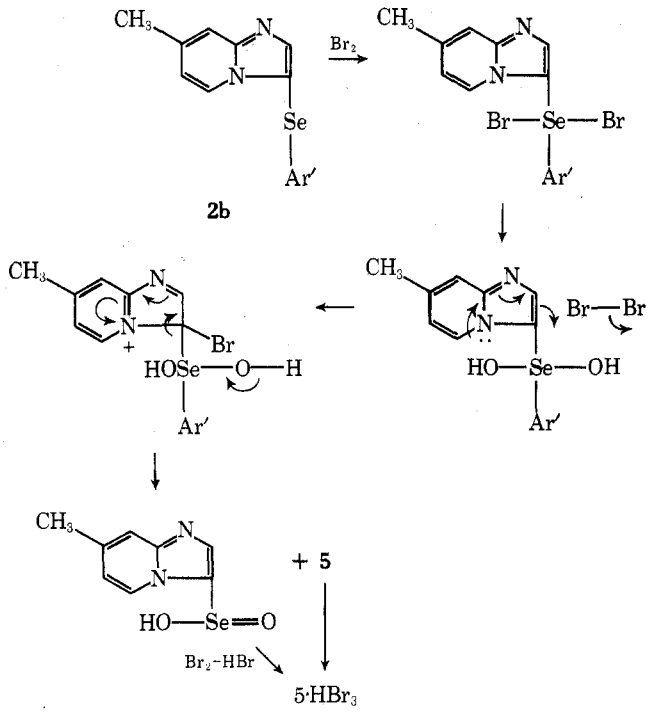
methylpyridine, generated by oxidative hydrolysis of compound **5**, on this species. In support of this path, the reaction of aniline with phenylseleninic acid to give **11** can be cited.[16]



11

The facile formation of 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**5**) from the reaction of the monoselenide **2b** with bromine appears to be novel[17] in that the reported reaction of bromine with diaryl selenides invariably affords $(Ar)_2SeBr_2$.[10,11] These compounds are transformed to BrArSeAr, BrArSeArBr, and ArSeAr derivatives at high temperatures. In the presence of water, or more easily in aqueous base, the dibromodiaryl selenides (Ar_2SeBr_2) are hydrolyzed to hydrated selenoxides, $Ar_2Se(OH)_2$.

Based upon the latter observation, we can depict the formation of the 3-bromo compound **5** by the following sequence of reactions.



It is of interest also to note that only π-excessive heterocyclic rings appear to be subject to electrophilic substitution by selenium dioxide. Thus, pyrazoles, indoles (vide infra), and, now, imidazo[1,2-*a*]pyridines have been shown to form similar diaryl selenides,[18] while pyridines[2] do not.

The reactivity of polyazaindenes and analogous π-excessive heterocyclic systems toward selenium dioxide, and the general synthetic utility of the displacement reaction with bromine and other potential electrophilic agents, are under active investigation.

Experimental Section[19]

Preparation of Compound 2b. To a solution of 2.92 g (26.5 mmol) of SeO_2[20] dissolved in 40 ml of ethanol was added 3.5 g (26.5 mmol) of 7-methylimidazo[1,2-*a*]pyridine (**1b**)[21a] and the solution was refluxed overnight. Since no Se had precipitated, the ethanol was displaced with 15 ml of glacial acetic acid containing 0.5 ml of water and the solution was refluxed for an additional 3 hr. The deep red solution became orange on cooling, and contained no precipitated Se. The solution was evaporated to dryness under reduced pressure, treated with ice-water and aqueous 10% NaOH until no further oil separated (pH ca. 6), and left to stand overnight, after which time the oil had solidified. The solid was collected, rinsed with H_2O, and dried [mp 230–232°, 3.6 g (90%)]. The filtrate yielded 0.53 g of starting material. The reaction product, dissolved in ethanol, was treated with charcoal and the filtrate was concentrated to ca. 10 ml, and water was then added to the hot solution to the saturation point. A further crystallization gave an analytical sample as glistening, colorless needles, mp 234–235.5°. Anal. Calcd for $C_{16}H_{14}N_4Se$: C, 56.31; H, 4.13; N, 16.42. Found: C, 55.98; H, 4.18; N, 16.17. Mass spectrum mol wt 342, 340, 339, 338, with typical distribution for Se isotopes 80, 78, 77, 76.[22]

Preparation of Compounds 2a and 4a. A solution of 2.4 g (22 mmol) of SeO_2 in 15 ml of glacial acetic acid, 1.5 ml of H_2O, and 2.4 g (20 mmol) of imidazo[1,2-*a*]pyridine[21b] was refluxed overnight and the solvents were removed under reduced pressure. The residue was treated with ice and aqueous 10% NaOH to pH 7. The orange solid was collected and rinsed with H_2O, absolute ethanol, and ether to give 2.55 g of a two-component mixture (TLC, alumina, 50% $CHCl_3$–C_6H_6). The mixture was twice treated with 10 ml of hot ethanol, cooled, and filtered to give 1.73 g (55%) of a colorless solid, compound **2a**, mp 268–270° dec. Two crystallizations from ethanol gave an analytical sample, mp 282–282.5° dec. Anal. Calcd for $C_{14}H_{10}N_4Se$: C, 53.68; H, 3.22; N, 17.89. Found: C, 53.86; H, 3.21; N, 17.79. Mass spectrum mol wt 314, 312, 311, 310.

The material in the organic wash liquids and mother liquors was percolated through 120 g of grade 3 neutral alumina in $CHCl_3$. Early fractions were two-component (mono- and diselenide) mixtures followed by 0.83 g (21%) of a single component which was dissolved in 200 ml of ethyl acetate. The solution was filtered and the filtrate was concentrated to 50 ml to give 0.54 g of a solid, compound **4a**, mp 191–192° dec. Recrystallization from 5 ml of ethanol afforded an analytical sample as a shiny orange solid, mp 192–193°. Anal. Calcd for $C_{14}H_{10}N_4Se_2$: C, 42.87; H, 2.57; N, 14.29. Found: C, 42.85; H, 2.63; N, 14.12. The ir spectra of the two materials were very similar and differed primarily in the intensities of the bands.

When a similar reaction mixture was allowed to stand at room temperature for 67 hr, no reaction occurred.

Reaction of 4a with Glacial Acetic Acid. When a solution of 150 mg of diselenide **4a** in 2 ml of glacial acetic acid was heated in an oil bath at 110° for 3 hr, Se deposited. The mixture was evaporated to dryness under reduced pressure. Water was added to the residue and the mixture was again evaporated to dryness. Extraction of the residue with $CHCl_3$ left a small amount of black Se (ca. 10 mg). The $CHCl_3$ extracts were concentrated to ca. 3 ml and the precipitated solid was filtered and rinsed with $CHCl_3$ and absolute ethanol. The nearly colorless solid (50 mg) was identified as the monoselenide **2a** by its melting point (265–270°) and ^1H NMR spectrum. The filtrate was evaporated to dryness, the residue was heated with 3 ml of absolute ethanol and cooled, and the precipitated solid was filtered to give 40 mg of starting material (**4a**), mp 194° dec. TLC of the filtrate (alumina, 25% $CHCl_3$–75% C_6H_6) indicated the presence of primarily starting material (**4a**), some monoselenide **2a**, and a trace of imidazo[1,2-*a*]pyridine (**1a**).

Reaction of Compound 2b with Selenium. A mixture of 0.34 g (1 mmol) of compound **2b**, 0.20 g (2.5 mmol) of black Se powder, and 20 ml of glacial acetic acid was refluxed for 23 hr. The Se was

removed by filtration, and the solvent was removed from the filtrate under reduced pressure. The residue was treated with ice–water and aqueous 10% NaOH to pH 8 and then extracted four times with $CHCl_3$ (30 ml total). The combined extracts were dried over anhydrous Na_2SO_4 and filtered and the filtrate was concentrated to a small volume and percolated through 40 g of grade 3 neutral alumina with $CHCl_3$. The early fractions contained 0.15 g (57%) of 7-methylimidazo[1,2-a]pyridine (**1b**), identified by TLC and ir spectral comparisons with an authentic sample. Later fractions contained a 1:1 mixture of compounds **2b** and **4b** (0.13 g, 34%) as shown by ^1H NMR spectral comparison with authentic samples.

Treatment of Compound 2b with Acetic Acid. A solution of 0.32 g (0.9 mmol) of the monoselenide **2b** in 15 ml of glacial acetic acid was refluxed for 24 hr. The solution rapidly turned yellow, then orange, and black Se precipitated. The Se was filtered (39 mg, 50%), and the filtrate was evaporated to dryness under reduced pressure. Water and aqueous 10% NaOH were added to the residue to pH 10. The mixture was extracted five times with $CHCl_3$ (40 ml total). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated to a small volume and percolated through 35 g of grade 3 neutral alumina with $CHCl_3$. The first fraction yielded 30 mg of a foul-smelling semisolid which had the same R_f (TLC on alumina, 50% C_6H_6–$CHCl_3$) as 7-methylimidazo[1,2-a]pyridine (**1b**). The next fractions contained 190 mg (80%) of **1b** contaminated with some of compound **2b**. This mixture was separated by sublimation in vacuo and its components were identified by ir and TLC comparisons with authentic samples of compounds **1b** and **2b**. The final fractions contained 40 mg (ca. 12%) of a 3:1 mixture of compounds **2b** and **4b** as shown by ^1H NMR comparison with authentic samples.

Reaction of 3-Bromo-7-methylimidazo[1,2-a]pyridine with Selenium Dioxide. A solution of 0.73 g (6.6 mmol) of SeO_2, 1.40 g (6.3 mmol) of 3-bromo-7-methylimidazo[1,2-a]pyridine[21a] (**5**), and 40 ml of ethanol was refluxed overnight. TLC (alumina, C_6H_6) indicated the presence of primarily starting material. The ethanol was therefore displaced with 15 ml of acetic acid and 0.5 ml of H_2O and the solution was refluxed for 23 hr, when it was deep red and black Se had precipitated. The latter was removed by filtration (0.25 g), and the filtrate was evaporated to dryness. The residue was treated with 15 ml of H_2O. A very fine, deep red powder (30 mg, Se) was removed by filtration. The filtrate was treated with aqueous 10% NaOH to pH 9 and extracted three times with $CHCl_3$ (30 ml total). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed. The residue was percolated through 120 g of grade 3 neutral alumina with 50% C_6H_6–$CHCl_3$. Starting material (80 mg) was eluted first, followed by 50 mg (6%) of 7-methylimidazo[1,2-a]pyridine identified by comparison with an authentic sample (TLC and ir spectra). Further elution gave 0.51 g (4) of compound **2b** identified by comparison with an authentic sample (TLC and ir spectra). After three treatments with charcoal in ethanol and addition of H_2O to the filtered hot ethanolic solution to the point of saturation, colorless needles (0.31 g), mp 234–235°, were obtained. Elution with $CHCl_3$ gave 0.14 g (11%) of yellow-orange compound **4b** which was twice crystallized from ethyl acetate to give fine, orange needles, mp 197° dec. Anal. Calcd for $C_{16}H_{14}N_4Se_2$: C, 45.73; H, 3.36; N, 13.33. Found: C, 45.46; H, 3.32; N, 13.07. Mass spectrum, a weak set of peaks near *m/e* 420 (M^+), and an intense set at 211, 209, 208, 207 (corresponding to $M^+/2$) with typical Se isotope distribution intensities.

Elution with 50% absolute ethanol–$CHCl_3$ gave 80 mg (8%) of a deep red oil which solidified on standing for several days. After treatment with charcoal in $CHCl_3$, addition of C_6H_6, and removal of a very small amount of flocculent precipitate, the filtrate was evaporated to dryness and the residue was twice crystallized from <1 ml of $CHCl_3$. A very pale yellow solid (**6**), mp 196–196.5°, was obtained. Anal. Calcd for $C_{14}H_{14}N_4Se$: C, 53.00; H, 4.45; N, 17.66. Found: C, 571; H, 4.45; N, 10. Ir (Nujol) indicates the presence of NH_2, 3400, 3220, and 3160 cm^{-1}, and contains all the absorption bands of the mono- and diselenides (**2b** and **4b**). Mass spectrum mol wt 318, 316, 315, 314 with typical Se isotope distribution.

Reaction of Compound 2b with Bromine. A solution of 100 mg (0.3 mmol) of the monoselenide **2b** in 5 ml of $CHCl_3$ was treated with a solution of 10 drops of Br_2 in 1 ml of $CHCl_3$. A yellow solid, which precipitated at once, was collected, rinsed with $CHCl_3$, and dried at room temperature in vacuo for 3 hr to give 0.28 g of solid **7** (mp 130–135° dec); green flame with Cu wire; ^1H NMR spectrum (Me_2SO-d_6) identical with that of 3-bromo-7-methylimidazo[1,2-a]pyridine hydrobromide (**8**); ir (Nujol), however, does not contain the bands typical of the latter. Anal. Calcd for $C_8H_8N_2Br_4$: C, 21.27; H. 1.78; N, 6.20. Found: C, 20.90, H, 1.75; N, 6.16. On attempted crystallization from C_6H_6 the yellow solid changed to a colorless material which was very soluble in H_2O and ethanol. It was twice crystallized by dissolution in hot ethanol and adding twice the volume of ethyl acetate; the solid (mp 220°, softens ca. 210°) had an ir spectrum identical with that of compound **8**.

A small amount of the above solid (**8**) was dissolved in 1 ml of H_2O, and 2 drops of aqueous 10% NaOH were added (pH 10) whereupon an oil separated. The oil was extracted with 3 × 0.5 ml of $CHCl_3$; the combined extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness to give 3-bromo-7-methylimidazo[1,2-a]pyridine (**5**), mp 72–76° (lit.[21a] 79.6–80.3°), as established by ir spectral comparison with an authentic sample.

3-Bromo-7-methylimidazo[1,2-a]pyridine Hydrobromide (8). A solution of ca. 100 mg of 3-bromo-7-methylimidazo[1,2-a]pyridine (**5**) in 48% HBr and ca. 5 ml of C_6H_6 was evaporated to dryness on a hot plate and under a stream of N_2. When the residue was treated with 2 ml of C_6H_6 and a few drops of absolute ethanol, colorless needles separated. These were twice crystallized from ca. 0.4 ml of absolute ethanol (mp 219–220°, softens ca. 210°). Anal. Calcd for $C_8H_8N_2Br_2$: C, 32.91; H, 2.76; N, 9.59. Found: C, 32.77; H, 2.78; N, 9.67.

Attempted Reaction of 3-Bromo-7-methylimidazo[1,2-a]pyridine with Sodium Methoxide. Na (0.33 g, 14 mmol) was added to 25 ml of dry methanol to afford 0.56 *M* $NaOCH_3$; 3-bromo-7-methylimidazol[1,2-a]pyridine (**5**, 0.42 g, 2 mmol) was then added and the solution was refluxed for 20 hr. TLC (alumina, 50% C_6H_6–$CHCl_3$) indicated the presence of only starting material. The solvent was removed in vacuo and the residue was treated with H_2O and extracted with four portions of $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was evaporated to dryness. The residue was distilled (100°, 0.02 Torr) to give 0.37 g (88%) of solid whose ir spectrum was identical with that of the starting material.

Registry No.—**1a**, 274-76-0; **1b**, 874-39-5; **2a**, 56051-28-6; **2b**, 56051-29-7; **4a**, 56051-30-0; **4b**, 56051-31-1; **5**, 56051-32-2; **6**, 56051-33-3; **7**, 56051-35-5; **8**, 56051-36-6; SeO_2, 7446-08-4; acetic acid, 64-19-7; selenium, 7782-49-2; bromine, 7726-95-6; sodium methoxide, 124-41-4.

References and Notes

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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

Prem C. Srivastava,* George A. Ivanovics, Robert J. Rousseau, and Roland K. Robins

ICN Pharmaceuticals Inc., Nucleic Acid Research Institute, Irvine, California 92664

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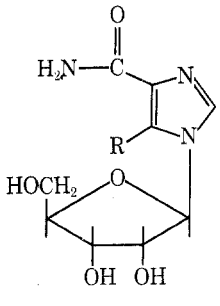
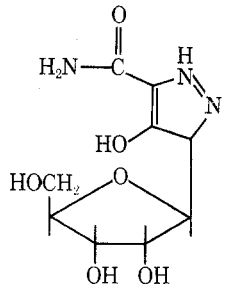
The synthesis of 1-(β-D-ribofuranosyl)imidazole nucleoside analogs via the deamination of the corresponding 5-aminoimidazole nucleosides is described. 5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid, on treatment with acid anhydrides, was ring closed to 5-substituted nucleoside 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.

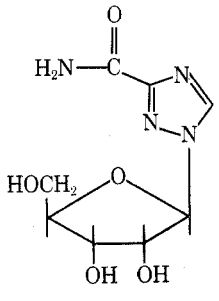
The nucleoside antibiotic bredinin isolated from the culture filtrate of *Eupenicillium brefeldianum* has recently been reported as an immunosuppressive agent.[1] This antibiotic has been shown to possess structure **1** which is essentially an isomer of pyrazomycin[2] (**2**). The synthetic triazole 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