# Studies of 2-Selenopyridine and Related Compounds[1]

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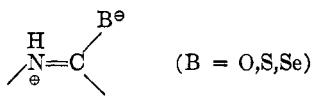
2-Selenopyridine, N-methyl-2-selenopyridine, 2-methylselenopyridine, and 2,2′-dipyridyl diselenide were synthesized. 2-Selenopyridine, which was shown to be in the zwitterionic selenamide form, forms a hydrogen-bonded dimer in benzene solution.

In a series of isologous oxo-, thio-, and seleno-ureides,[2] -purines,[3,4] and -pyrimidines[2,5] it was found that as oxygen is consecutively replaced with sulfur and with selenium, polarization of the type



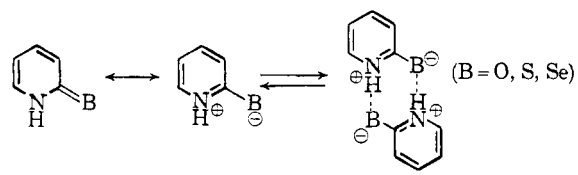

increases, as evidenced by bathochromic shifts in the ultraviolet spectrum and by decreasing p$K_a$ values. A similar increase in polarization accounts for the increased transacylating ability of seleno-acyl compounds, as compared to thioacyl compounds,[6] which in turn are better acylating agents[7] than are analogous esters.

The selenium-substituted heterocyclic compounds hitherto available are complex and in most cases insoluble in organic solvents, making difficult the determination of dipole moments and of infrared spectra in solution. For this reason the synthesis of 2-selenopyridine and related compounds seemed desirable.

Attempts to prepare 2-selenopyridine by the reaction of 2-halogenopyridines with selenourea or with sodium hydroselenide in boiling ethanol were unsuccessful, although the reaction of 2-bromopyridine N-oxide with hydroselenide in ethanol proceeded smoothly to yield 2-selenopyridine N-oxide; however, attempts to reduce the latter compound to selenopyridine failed.

The desired compound could be prepared by the addition of hydroselenide to 2-bromopyridine when the temperature was elevated by letting the reaction take place in boiling ethyleneglycol monoethyl ether. The product was converted to 2-methylselenopyridine with methyl iodide. N-Methyl-2-selenopyridine was prepared from N-methyl-2-bromopyridinium iodide.

Molecular weight determinations show 2-selenopyridine to be a dimer in benzene solution. Similarly, it was reported recently that 2-thiopyridine and 2-pyridone are dimeric in chloroform solution.[8] The ability of thio compounds and seleno compounds of this type to form hydrogen-bonded dimers is in accordance with the charge separation already mentioned




Ordinarily sulfur compounds have only weak hydrogen-bonding capacities. Since the molecular weight found in benzene was twice that of 2-selenopyridine, it was important to eliminate the possibility that this compound might have been oxidized to the corresponding diselenide. This was done by showing that selenopyridine readily reacted with chloroacetic acid to yield 2-carboxymethylselenopyridine and by synthesizing 2,2′-dipyridyl diselenide and showing that the diselenide has an ultraviolet spectrum different from that of 2-selenopyridine.

A comparison of the ultraviolet spectra of 2-selenopyridine, N-methyl-2-selenopyridine, and 2-methylselenopyridine was made. Since methyl groups attached to carbon, nitrogen, or sulfur, and presumably to selenium, are transparent in the ultraviolet region, such measurements indicate the tautomeric state of the unsubstituted compound. The following results were obtained (Table I).

It can be seen that, as in the case of the analogous 2-oxypyridines[9] and 2-thiopyridines,[10] the spectrum of the unsubstituted selenopyridine closely resembles that of its N-methyl derivative, but is rather different from that of 2-methylselenopyridine. These measurements indicate that 2-selenopyridine exists essentially in the form of the selenamide; comparison of its spectra with those of the analogous oxygen and sulfur compounds showed that again a bathochromic shift took place on descending the periodic table.

(1) This work was supported, in part, by grants from the National Science Foundation (G-19329) and the United States Public Health Service (CY-3937).

(2) H. G. Mautner and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 97 (1956).

(3) H. G. Mautner, *ibid.*, **78**, 5292 (1956).

(4) H. G. Mautner and J. J. Jaffe, *Biochem. Pharmacol.*, **5**, 343 (1961).

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(6) H. G. Mautner and W. H. H. Günther, *ibid.*, **83**, 3342 (1961).

(7) F. Lynen, *J. Cellular Comp. Physiol.*, **54**, suppl. 1, 33 (1959).

(8) A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 2950 (1960).

(9) S. F. Mason, *ibid.*, 5010 (1957).

(10) A. Albert and G. B. Barlin, *ibid.*, 2384 (1959).

TABLE I
ULTRAVIOLET SPECTRA

| | Molecules in neutral form (water) | | | Molecules in cationic form (70% sulfuric acid, pH 5.65) | |
|---|---|---|---|---|---|
| | $\lambda_{max}$ | $\epsilon_{max}$ | pH | $\lambda_{max}$ | $\epsilon_{max}$ |
| 2-Selenopyridine | 227 | 5600 | 5.7 | 242 | 5600 |
| | 285 | 5200 | | 308 | 7200 |
| | 358 | 4700 | | | |
| N—$CH_3$—Seleno-pyridine | 232 | 3800 | 5.7 | 238 | 4500 |
| | 287 | 4800 | | 306 | 8300 |
| | 357 | 5500 | | | |
| Se—$CH_3$—Seleno-pyridine | 245 | 5600 | 5.9 | 262 | 4930 |
| | 254 | 5500 | | 328 | 6350 |
| | 295 | 4100 | | | |

The acidic and basic dissocation constants of the selenium compounds were measured; the following table compares these constants with those of the isologous oxo and thio compounds (Table II). A calculation of tautomeric ratio[10] (lactam: lactim) based on the $pK'_a$ values of 2-selenopyridine and 2-methylselenopyridine shows 99.995% of 2-selenopyridine to be in the lactam form. This compares to values of 99.998% and 99.707% reported[10] for 2-thio- and 2-oxopyridine, respectively.

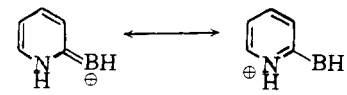
It is apparent that 2-selenopyridine is a stronger acid than 2-thiopyridine, which, in turn, is a stronger acid than 2-oxypyridine. Since these compounds have been shown to be in a tautomeric form in which the dissociating hydrogen is released from the ring nitrogen, ability to withdraw electrons from this nitrogen must increase as oxygen is replaced with sulfur and with selenium. This effect, which would not be expected from the electronegativities of the atoms involved, has been attributed to octet expansion in sulfur[11,12] and selenium[2,3] compounds.

TABLE II
IONIZATION OF SUBSTANCES

| | Proton gained ($pK'_a$) | Proton lost ($pK_a$) |
|---|---|---|
| Unsubstituted | | |
| 2-*O*-Pyridine | 0.75[a] | 11.62[b] |
| 2-*S*-Pyridine | −1.07[10], −1.38[c] | 9.97[10] |
| 2-*Se*-Pyridine | −1.00 | 9.36 |
| N—$CH_3$— | | |
| 2-*O*-Pyridine | 0.32[a] | |
| 2-*S*-Pyridine | −1.22[10] | |
| 2-*Se*-Pyridine | [d] | |
| B—$CH_3$— (B=O,S,Se) | | |
| 2-*O*-Pyridine | 3.28 | |
| 2-*S*-Pyridine | 3.23,[c] 3.62[10] | |
| 2-*Se*-Pyridine | 3.30 | |

[a] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956). [b] A. Albert and A. Hampton, *ibid.*, 505 (1954). [c] R. A. Jones and A. R. Katritzky, *ibid.*, 3610 (1958). [d] Rapid alteration of the spectrum of this compound in sulfuric acid solutions prevented the determination of its $pK'_a$.

The basic dissociation constants of these compounds were measured in sulfuric acid solution. It appears that in this solvent resonance of the type:



(B = O, S, Se)

is of importance. The relative instability of the 3*p* $\pi$-bonds of sulfur[13] and presumably of the 4*p* $\pi$-bonds of selenium, with a concommitant decrease of resonance stabilization in the diprotonated forms of 2-thio- and 2-selenopyridine, respectively, might account for the observation that 2-pyridone is a stronger base than its sulfur and selenium analogs.

## Experimental

**2-Selenopyridine N-Oxide.**—A solution of 0.41 g. (0.0178 g.-atom) of sodium in 20 ml. of absolute ethanol was chilled in an ice bath and saturated with freshly generated hydrogen selenide. After the addition of 1.5 g. (0.0071 mole) of 2-bromopyridine N-oxide[14] the mixture was heated to reflux for 30 min. After cooling, 8 ml. of water was added and the solution filtered. Acidification with acetic acid resulted in the precipitation of selenium. After filtration a clear, yellow solution was obtained the volume of which was reduced to 10 ml. under aspirator suction at room temperature. On cooling a yield of 0.73 g. (59%) of yellow crystalline product melting at 69–70° was obtained. Recrystallization from absolute ethanol raised the m.p. to 72.5–73.0°. Similarly to 2-thiopyridine *N*-oxide[14] the product produced a dark blue color on being added to ferric chloride solution.

*Anal.* Calcd. for $C_5H_5NOSe$: C, 34.50; H, 2.90; N, 8.05. Found: C, 34.61; H, 3.03; N, 8.07.

**2-Selenopyridine.**—A solution of 3.2 g. (0.139 g.-atom) of metallic sodium in 100 ml. of ethylene glycol monoethyl ether was chilled in an ice bath; hydrogen selenide, generated by the addition of dilute hydrochloric acid to aluminum selenide, was bubbled through the solution for 4 hr. To the dark red liquid 10 g. (0.064 mole) of 2-bromopyridine were added. The mixture was refluxed for 19 hr., and the solids were removed by filtration. The filtrate was evaporated to dryness under reduced pressure at 70°. The residue was dissolved in 80 ml. of water and 20 ml. of glacial acetic acid were added. The resultant red precipitate was filtered off with the aid of Celite and washed with water and methanol. The clear yellow filtrate was evaporated under reduced pressure until yellow needles began to form and then was cooled. The product was washed with cold water and dried over phosphorus pentoxide under vacuum to give 6.05 g. (61.4% monomer). It was recrystallized from benzene to give yellow needles; m.p. 132–137°.[15]

*Anal.*[16] Calcd. for $C_5H_5NSe$: C, 37.93; H, 3.18; N, 8.86; Found: C, 38.29; H, 3.09; N, 9.00.

**N-Methyl-2-selenopyridine.**—A solution of 1.2 g. (0.052 g.-atom) of metallic sodium in 50 ml. of absolute ethyl alcohol was chilled in an ice bath; hydrogen selenide was bub-

(11) R. Rothstein, *J. Chem. Soc.*, 1556 (1940).
(12) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946).
(13) For instance, A. W. Baker and G. H. Harris, *ibid.*, **82**, 1923 (1960).
(14) E. Shaw, *et al.*, *J. Am. Chem. Soc.*, **72**, 4362 (1950).
(15) Melting points are uncorrected.
(16) Analyses were carried out by: Midwest Microlab, Inc., Indianapolis, Indiana, and by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York.

bled through the solution for 2 hr. To the mixture 3.0 g. (0.01 mole) of 1-methyl-2-bromopyridinium iodide were added and the mixture was refluxed for 4 hr., then left to stand at room temperature overnight. Colloidal selenium was removed by filtration and the filtrate evaporated to dryness under vacuum. The residue was dissolved in 30 ml. of water and 5 ml. of glacial acetic acid was added. The resultant red precipitate was filtered off and washed with the aid of Celite, water, and methanol. The clear orange filtrate was evaporated under vacuum until light orange needles began to form and then cooled. The solid which separated was washed with cold water and dried over phosphorus pentoxide under vacuum. It was recrystallized from benzene and petroleum ether to give 1.0 g. (yield: 58%); m.p. 68–78°.

*Anal.* Calcd. for $C_6H_7NSe$: C, 41.87; H, 4.10; N, 8.14; Found: C, 42.12; H, 4.38; N, 8.33.

**2-Methylselenopyridine.**—A solution of 2.0 g. (0.0126 mole) of 2- selenopyridine in 12.6 ml. of 1 *N* sodium hydroxide solution was treated with 1.7 g. (0.0126 mole) of methyl iodide. Stirring was continued at room temperature for 2 hr. The solution was then extracted with benzene and the extract distilled. A yield of 1.2 g. (55%) was obtained. 2-Methylselenopyridine is a light yellow liquid of unpleasant odor, boiling at 43–44° (0.25 mm), $n^{22}D$ 1.6190.

*Anal.* Calcd. for $C_6H_6NSe$: C, 41.87; H, 4.10; N, 8.14; Found: C, 41.74; H, 4.00; N, 8.26.

**2-Carboxymethylselenopyridine.**—A solution of 0.2 g. (0.00136 mole) of 2-selenopyridine in 20 ml. of water, 0.2 g. (0.0024 mole) of sodium bicarbonate, and 0.13 g. (0.0014 mole) of chloroacetic acid was refluxed for 30 min. and then neutralized with 1 *N* sodium hydroxide solution. The mixture was acidified with glacial acetic acid and filtered immediately. The white crystalline product was recrystallized from ethanol and petroleum ether to give 0.1 g. (yield: 36.6%) m.p. 121–124°.

*Anal.* Calcd. for $C_7H_7NO_2Se$: C, 38.90; H, 3.25; N, 6.44; Found: C, 38.88; H, 3.29; N, 6.52.

**2,2′-Dipyridyl Diselenide.**—To a solution of 1.58 g. (0.01 mole) of 2-selenopyridine in 60 ml. of water 0.2 ml. of 30% hydrogen peroxide was added with stirring. The product separated immediately as a yellow oil which solidified on standing. The diselenide was removed by filtration, washed with a small amount of water, and dried. A yield of 1.2 g. (75.8%) was obtained. One recrystallization from petroleum ether (b.p. 37–56°) yielded analytically pure yellow needles melting at 47.5–48.0°.

*Anal.* Calcd. for $C_{10}H_8N_2Se_2$: C, 38.21; H, 2.56; N, 8.91. Found: C, 38.34; H, 2.58; N, 9.03.

**Ultraviolet Spectrum.**—Water (pH 5.4) $\lambda_{max}$ 241, 282 mμ; $\epsilon_{max}$ 12,900, 7,000.

**Molecular Weight Determinations.**—A molecular weight determination for 2-selenopyridine, based on freezing point depression in naphthalene, yielded a value of 321 (theor. for monomer, 158; theor. for dimer 316).

In view of the observation that 2-selenopyridine is partially oxidized to 2,2′-dipyridyl diselenide on being left to stand in aromatic solvents at room temperature, it was deemed necessary to measure molecular weights using a very rapid method. Thermoelectric measurements[17] using the Mechrolab Osmometer[18] were, therefore, carried out. This procedure is very fast (*ca.* 10 min.); oxidation during this period is negligible. The molecular weight determination for selenopyridine was carried out under nitrogen. The following results were obtained at 37.0°.

| | Ethanol | | Benzene | |
|---|---|---|---|---|
| | Mol. wt. (theor.), monomer | Mol. wt. found | Mol. wt. (theor.) dimer | Mol. wt. found |
| 2-Pyridone | 95 | 102 | 190 | 186 |
| 2-Thiopyridine | 111 | 116 | 222 | 235 |
| 2-Selenopyridine | 158 | 187 | 316 | 323 |
| 2,2′-Dipyridyl diselenide | 314 | 336 | ... | ... |

**Dissociation Constants.**—Measurements of acid dissociation constants were carried out titrimetrically using a Leeds & Northrop Model 7764 pH indicator. For the basic dissociation constants a spectrophotometric method[19] based on the ultraviolet absorption of compound dissolved in sulfuric acid solution with known $H°$ values[20], was employed. "Titration curves" were obtained when the differences between molar extinction values at 310 and 350 mμ were plotted against $H°$. At the former wave length the extinction of the diprotonated form of selenopyridine exceeds that of the neutral molecule, while at the latter wave length the converse is true. $pK'_a$ values were obtained from the above "titration curves."

Lack of decomposition of 2-selenopyridine in sulfuric acid was established by neutralizing the ice-cold acid solutions with solid potassium hydroxide. The original spectrum for neutral 2-selenopyridine was then obtained. We are indebted to Dr. Henry Harbury for the use of his Cary Model 11 spectrophotometer for these determinations.

(17) C. Tomlinson, *Mikrochim. Acta*, 457 (1961).

(18) Measurements were carried out at the Schwarzkopf Analytical Laboratory, Woodside, New York.

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(20) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).