Novel Heterocyclic Systems. Part 21.[1] Synthesis of 3-Hydroxypyridine-2(1*H*)-selone and its Application in the Synthesis of 1-Azaphenoxaselenine and its Substituted Derivatives

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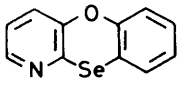
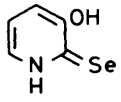
3-Hydroxypyridine-2(1*H*)-selone (**2**) is produced by the reaction of sodium hydrogen selenide, prepared *in situ*, with 2-chloro-3-hydroxypyridine. Reaction of the dianion of selone (**2**) with 1-chloro-2-nitrobenzene produces a new heterocyclic system, 1-azaphenoxaselenine (**1**). The same procedure is also applied in the synthesis of a range of substituted 1-azaphenoxaselenines *via* reactions of the dianion of (**2**) with various substituted *ortho*-chloronitrobenzenes.

Several substituted 1-azaphenoxathiines† are known to exhibit central nervous system depressant activity.[2,3] The general structural similarity of these heterocycles to the clinically important phenothiazines has encouraged us to undertake a survey of the synthesis and structural parameters of a range of related heterocyclic systems.[4] As part of this survey we were interested in obtaining 1-azaphenoxaselenine (**1**) and substituted examples of this new heterocyclic system. The simplest approach to such compounds, by analogy with the known syntheses of 1-azaphenoxathiines, would appear to be *via* the reactions of the dianion of 3-hydroxypyridine-2(1*H*)-selone (**2**) with *ortho*-chloronitrobenzenes. Thus, as the first stage in the syntheses of 1-azaphenoxaselenines it was necessary to develop a synthesis of selone (**2**).



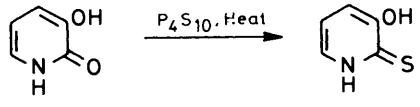
(**1**)



(**2**)

We now report the successful synthesis of compound (**2**) by the reaction of sodium hydrogen selenide with 2-chloro-3-hydroxypyridine, and its successful application in the synthesis of compound (**1**) and its substituted counterparts.

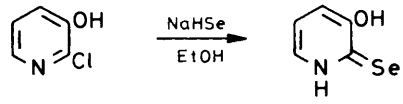
Synthesis of 3-*Hydroxypyridine*-2(1H)-*selone* (**2**).—Following our previous success in preparing 3-hydroxypyridine-2(1*H*)-thione (**4**) *via* the fusion of 3-hydroxy-2-pyridone (**3**) with phosphorus(v) sulphide [equation (1)][5] our initial attempts at



(**3**) (**4**) (1)

the synthesis of selone (**2**) involved the analogous fusion of phosphorus(v) selenide with compound (**3**). Indeed, small quantities of selone (**2**) (*ca.* 10% yield) were obtained by this approach, but several variations of the experimental procedure failed to provide significant improvements in the yield. Thus, an alternative procedure was sought.

A successful synthesis of compound (**2**) (77% yield) was obtained by the reaction of ethanolic sodium hydrogen selenide with 2-chloro-3-hydroxypyridine (**5**) [equation (2)], the sodium



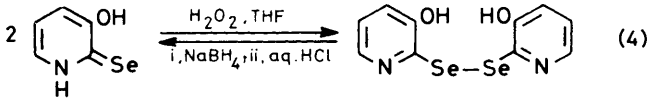
(**5**) (**2**) (2)

hydrogen selenide being prepared *in situ* by reduction of selenium with sodium tetrahydroborate (sodium borohydride) in ethanol [equation (3)]. A similar procedure had previously been used to prepare pyridine-2(1*H*)-selone in 60% yield from 2-chloropyridine.[6]

$$Se + NaBH_4 + 3EtOH \longrightarrow NaSeH + B(OEt)_3 + 3H_2 \quad (3)$$

Properties and Redox Reactions of 3-*Hydroxypyridine*-2(1H)-*selone* (**2**).—Compound (**2**) was obtained as bright yellow fluorescent crystals, which were readily soluble in methanol and moderately soluble in dichloromethane. It is a sensitive compound which produces a red deposit of selenium on being kept in acidic media. This process accounts, at least in part, for the low yield isolable from the phosphorus(v) selenide reaction.

On prolonged contact with air, particularly in solution, selone (**2**) is slowly oxidized to bis-(3-hydroxypyridin-2-yl) diselenide (**6**). This oxidation process is much more rapid in solvents, such as unpurified tetrahydrofuran (THF), which are contaminated by peroxides, and can be made quantitative by use of hydrogen peroxide [equation (4)].



(**2**) (**6**) (4)

Fortunately, the diselenide (**6**) is readily reconverted into selone (**2**) by reduction with alkaline sodium tetrahydroborate followed by a rapid work-up with dil. hydrochloric acid [equation (4)]. Good samples of selone (**2**) can be obtained by use of an inert atmosphere for the reaction and work-up stages.

Preparation of 1-*Azaphenoxaselenines* (**1**) *and* (**7**).—The procedure [equation (5)] adopted for the synthesis of 1-

† The use of a final 'e' in the names of several heterocyclic systems referred to in this paper is in accordance with recommendations in the most recent revision of the I.U.P.A.C. rules for nomenclature of such compounds – see *Pure Appl. Chem.*, 1983, **55**, 413.

Table 1. Syntheses of 1-azaphenoxaselenines (7)

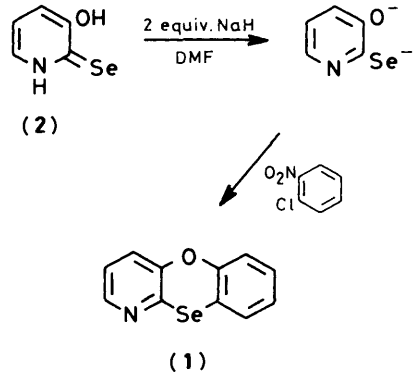
Compound	R^1	R^2	Scale (mmol)[a]	Volume of DMF (ml)[b]	Reflux period (h)	Yield (%)[c]	M.p. (°C)[d]	M.p. of corresponding 1-azaphenoxathiine
(1)	H	H	7.20	80	3	59	67.5—68.5	66—68[e]
(7a)	NO_2	H	4.89	75	7	63	165—167	166—167[f]
(7b)	CF_3	H	5.40	60	5	62	87—88	87—88[g]
(7c)	Cl	H	8.20	65	5	74	109—110	122—124[e]
(7d)[i]	Br	H	4.17	60	3	61	116—117	155—156[g]
(7e)	OMe	H	5.89	60	3	52	65—66	75—76[g]
(7f)	H	NO_2	3.60	60	5	69	147—148	142—143[h]

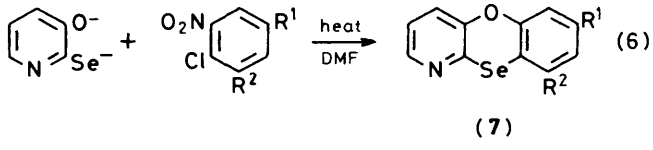
[a] Refers to amount of selone (2) and amount of substituted chloronitrobenzene utilized in the reaction. [b] Total volume of DMF employed; this was added in three stages (see Experimental section) in approx equal amounts. [c] Yield of isolated material after purification by column chromatography. [d] Determined on samples supported between microscope slides on a hot-stage block, and reported uncorrected. [e] See ref. 4*a*. [f] See ref. 3. [g] See ref. 2. [h] See ref. 4*b*. [i] In this case the starting material was 2,5-dibromonitrobenzene rather than 5-bromo-2-chloronitrobenzene because of the readier availability of the former compound.

Table 2. ^{13}C N.m.r. chemical shifts[a] of 1-azaphenoxaselenines (corresponding 1-azaphenoxathiines in parentheses where known)[b]

Carbon atom	Compound (1)	(7a)	(7b)	(7c)	(7d)	(7e)	(7f)
2	145.5 (144.7)	146.4 (145.6)	146.1	145.9 (145.2)	145.9	145.5	146.2 (145.5)
3	122.6 (122.2)	123.4 (123.1)	123.1	122.7 (122.4)	122.8*	122.4*	123.4* (122.4)
4	125.3 (124.7)	124.7 (124.2)	124.5	124.4* (123.7)	124.5	124.3*	124.0* (123.4)*
6	118.4 (117.4)	113.2 (112.5)	115.3 (q, *J* 4 Hz)	118.8 (117.8)*	121.7*	104.8	123.4* (123.1)*
7	128.2 (126.9)	147.8 (147.2)	130.7 (q, *J* 33 Hz)	133.6 (133.2)	121.0	160.2	127.5 (126.7)
8	124.3 (123.6)	119.8 (119.6)	121.8 (q, *J* 4 Hz)	125.4* (124.9)	128.3	111.6	121.9* (121.4)*
9	129.6 (127.7)	129.7 (126.9)	130.0	130.4 (127.5)	130.4	129.7	146.2 (145.2)
4a	149.0 (147.9)	147.8 (146.7)	148.4	148.5 (147.5)	148.5	148.9	148.7 (147.2)
5a	151.1 (150.0)	151.0 (149.7)	151.0	151.5 (150.6)	151.6	151.9	151.9 (150.8)
9a	115.3 (119.0)	125.5 (128.6)	120.7	113.7 (118.0)*	114.5	105.0	118.0 (121.2)
10a	141.5 (143.5)	139.3 (141.0)	140.2	140.9 (143.3)	140.9	141.9	141.5 (142.3)
Other			123.5 (q, *J* 272 Hz, CF_3)			55.4 (OMe)	

[a] Recorded in $CDCl_3$; possibly permutable sets of assignments within any given spectrum are indicated *. [b] See refs. 3, 4*a*, and 4*b*.





azaphenoxaselenine (**1**) was adapted from that used previously for the synthesis of 1-azaphenoxathiine and its analogues.[3,4] Thus, selone (**2**) was converted into its disodium salt by means of sodium hydride in dimethylformamide (DMF). The disodium salt was stirred at room temperature overnight with 2-chloronitrobenzene, whereupon t.l.c. [silica; developed by ethyl acetate–cyclohexane (3:7)] indicated that no 2-chloronitrobenzene remained, and the mixture was then refluxed for 3 h. At this point the reaction mixture was quenched by being poured into distilled water, and the product was extracted and purified. Pure compound (**1**) was isolated in 59% yield, which compares favourably with the yield (28%) reported in the analogous preparation of 1-azaphenoxathiine.[4a]

The method proved to be entirely applicable to the synthesis of substituted 1-azaphenoxaselenines (**7**) [equation (6)]. The period of reflux necessary varied somewhat but otherwise few changes were necessary. The substituted 1-azaphenoxaselenines (**7**) were obtained in yields of 52—74% (Table 1). In some cases small amounts of substituted 1-(dimethylamino)-2-nitrobenzenes were isolated as by-products.

The mass-spectral fragmentation patterns, i.r. spectra, ^1H and ^{13}C n.m.r. spectra, and even the m.p.s (Table 1) of compounds (**7**) are very similar to those of the corresponding 1-azaphenoxathiines, suggesting a very close structural similarity. We hope to be able to confirm this in due course with *X*-ray crystal-structure determinations. Meanwhile, detailed analyses of the ^{13}C n.m.r. spectra allow maximum structural insight.

^{13}C N.M.R. Spectra of Substituted 1-Azaphenoxaseleniines (**7**).—The ^{13}C n.m.r. chemical shifts of compounds (**1**) and (**7a**—**f**) are listed in Table 2, along with the values of the corresponding 1-azaphenoxathiines. The numbering scheme is as indicated in the Figure.

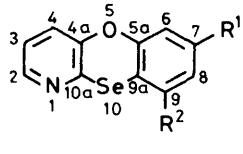


Figure. Numbering scheme for 1-azaphenoxaselenines

In order to aid the assignments a two-dimensional proton–carbon chemical-shift-correlation spectrum and a fully proton-coupled 75.5 MHz ^{13}C n.m.r. spectrum were run on one of the compounds, specifically 7-nitro-1-azaphenoxaselenine (**7a**). Only ten signals were observed in the proton-noise-decoupled spectrum, whereas eleven were expected. The proton-coupled spectrum, however, revealed that the intense signal at δ_C 147.8 was not a resonance of a protonated carbon atom, since there was no large C–H coupling constant. Furthermore the detailed fine structure of this resonance, as revealed by an expanded spectrum, indicated that it almost certainly subsumed two quaternary carbon atom signals.

The protonated-carbon resonances were readily identified from the coupled spectrum as those at δ_C 113.2, 119.8, 123.4, 124.7, 129.7, and 146.4. This was further confirmed by the two-dimensional spectrum, which also allowed ready assignment of these resonances by inspection of the chemical shifts and coupling patterns of the proton signals with which the carbon signals were coupled. Of the quaternary carbon resonances, only the resonance for C-9a could be readily assigned because of its lack of strongly deshielding factors. Nevertheless, this detailed analysis, which allowed unequivocal assignment of seven of the ^{13}C resonances of 7-nitro-1-azaphenoxaselenine, showed clearly that the chemical shifts observed were very similar to those observed for the corresponding 1-azaphenoxathiine (see Table 2). Thus, this fact could be used, together with calculations based on substituent-shift effects,[7] to assign most of the resonances of the other 1-azaphenoxaselenines studied, and this is the basis of the assignments recorded in Table 2.

It has previously been suggested, on the basis of a number of *X*-ray crystal-structure determinations,[8–10] that nitro groups *ortho* to a sulphur or selenium atom exhibit an oxygen–sulphur or oxygen–selenium bonding interaction. More recently, ^{13}C n.m.r. and u.v. studies of 9-nitro-1-azaphenoxathiine[4b] suggested that a similar type of interaction occurs in this compound. This has subsequently been confirmed by an *X*-ray crystal structure.[11] It was therefore of interest to discover whether the same type of interaction would occur in 9-nitro-1-azaphenoxaselenine (**7f**).

The ^{13}C n.m.r. spectrum of compound (**7f**) (see Table 2) does indeed show great similarity to that observed for 9-nitro-1-azaphenoxathiine.[4b] The differences observed between these two compounds are comparable in magnitude with the differences observed between other analogous 1-azaphenoxathiine–1-azaphenoxaselenine pairs. Thus, if the ^{13}C n.m.r. chemical shifts in 9-nitro-1-azaphenoxathiine are indeed a reflection of nitro group–sulphur interaction,[4b] then it would appear that a similar interaction also occurs between the nitro group and the selenium atom in 9-nitro-1-azaphenoxaselenine (**7f**).

Further support for this hypothesis comes from a comparison of the u.v. spectra of compounds (**7a**) and (**7f**). The latter shows a bathochromic shift of 44 nm with respect to the former for the longest wavelength absorption maximum. This is even greater than the 30 nm shift observed previously for the corresponding 1-azaphenoxathiines.[3,4b] Final confirmation of the interaction must await an *X*-ray crystal-structure determination.

Conclusions.—3-Hydroxypyridine-2(1*H*)-selone can be prepared in high yield by the reaction of sodium hydrogen selenide with 2-chloro-3-hydroxypyridine. The reactions of its dianion with various *ortho*-chloronitrobenzenes produce 1-azaphenoxaselenines in yields (52—74%) better than those reported for the analogous syntheses of the corresponding 1-azaphenoxathiines (19—54%).[2,3,4a] The properties and spectra of the 1-azaphenoxaselenines are very similar to those of the corresponding 1-azaphenoxathiines.

Experimental

2-Chloro-3-nitropyridine, selenium, and sodium tetrahydroborate were purchased from Aldrich and used without further purification. Solvents were purified and dried, where necessary, by standard literature procedures.[12] Sodium hydride was purchased as an 80% dispersion in oil; the solid was washed with pentane under nitrogen to remove the oil prior to use, and aliquots of a batch of such material were weighed out for individual reactions.

M.p.s were determined using a Gallenkamp hot-stage apparatus and are uncorrected. ^1H N.m.r. spectra were generally recorded using a Varian HA-100 spectrometer. ^{13}C N.m.r. spectra were generally recorded using a Varian XL-100 spectrometer operating at 25.2 MHz for ^{13}C use, but in the case of the spectra determined in greater detail for 7-nitro-1-azaphenoxaselenine, including the fully proton-coupled spectrum and the 2D spectrum, a Nicolet NT-300 wide-bore spectrometer operating at 75.5 MHz for ^{13}C spectra was utilized. All chemical shifts are reported in p.p.m. (δ) downfield from tetramethylsilane. U.v. spectra were recorded on a Perkin-Elmer UV402 spectrophotometer, and i.r. spectra (KBr discs) on a Pye Unicam SP1050 instrument. Mass spectra were run on a modified KRATOS MS9 mass spectrometer, and elemental analyses were obtained using a Perkin-Elmer 185 C,H,N analyser.

Preparation of 3-*Hydroxypyridine*-2(1H)-*selone* (**2**).—Absolute ethanol (230 ml) was carefully added to a magnetically stirred mixture of selenium (9.14 g, 0.116 mol) and sodium tetrahydroborate (4.85 g, 0.128 mol) in a 500 ml round-bottomed flask cooled in ice–water.* Once the initial vigorous reaction had subsided the neck of the flask was closed with a rubber septum, and the pressure build-up was released *via* a needle connected to a sodium hypochlorite bubbler. The flask was then flushed with nitrogen *via* a second needle through the septum, and was maintained under a slight positive pressure of nitrogen thereafter. The reaction mixture was stirred at 0 °C for a further 15 min, and then at ambient temperature overnight (*ca.* 15 h). 2-Chloro-3-hydroxypyridine (**5**) (15.02 g, 0.116 mol) was added to the red solution, a reflux condenser was inserted between the flask and the septum, the apparatus was again flushed with nitrogen, and the mixture was then refluxed under a slight positive pressure of nitrogen for 22 h.

The mixture was cooled and the greyish solid remaining was removed by filtration. The filtrate was evaporated to leave a bright yellow solid which was rapidly partitioned between dichloromethane (100 ml) and dil. hydrochloric acid (100 ml). The acid layer was extracted as rapidly as possible with further dichloromethane (10 × 50 ml), the combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to leave crude selone (**2**) (15.50 g, 77%). Recrystallization from dichloromethane gave bright yellow fluorescent crystals of *compound* (**2**), m.p. 142—146 °C, which were soluble in methanol, moderately soluble in dichloromethane, and essentially insoluble in pentane; $\nu_{max.}$ 3 100br (with fine structure) 1 580, 1 515, 1 395, 1 290, 1 255, 1 120, 1 045, and 770 cm^{-1}; $\lambda_{max.}$ (0.129mM in distilled water) 215 (ε 9 400 $dm^3\ mol^{-1}\ cm^{-1}$), 245sh, 270sh, and 362 nm (5 900); δ_H ($CDCl_3$) 7.44 (1 H, dd, *J* 1.5 and 6.0 Hz, 6-H), 7.19 (1 H, dd, *J* 1.4 and 7.6 Hz, 4-H), and 6.96 (1 H, dd, *J* 5.9 and 7.7 Hz, 5-H); δ_C ($CDCl_3$) 160.4 (singlet in the off-resonance decoupled spectrum), 157.1 (s), 129.7 (d), 117.9 (d), and 117.0 (d); *m/z* 177 (rel. intensity 18%), 175 (100), 173 (52), 172 (17), 171 (19), 95 (30), 94 (18), 67 (49), and 39 (51) (Found: M^+, 174.9541. $C_5H_5NO^{80}Se$ requires *M*, 174.9536)

* **Caution**! Addition of acid to this solution will generate gaseous H_2Se, which is both noxious and highly toxic.

(Found: C, 34.5; H, 2.95; N, 8.1. C_5H_5NOSe requires C, 34.49; H, 2.87; N, 8.05%).

Preparation of Bis-(3-hydroxypyridin-2-yl) Diselenide (**6**).—To a solution of selone (**2**) (0.377 g, 2.17 mmol) in THF (15 ml), stirred magnetically in a 50 ml conical flask, was added 30% hydrogen peroxide solution (0.2 ml). The mixture, which turned cloudy after a few min, was stirred at 20 °C for 1 h, by which time a substantial pale yellow precipitate had formed. The supernatant solution was decanted and added to distilled water (15 ml). This mixture was then extracted with dichloromethane (3 × 15 ml), and the extracts were dried ($MgSO_4$) and evaporated to yield crude diselenide (**6**) (0.189 g), which was combined with the precipitate formed in the original reaction mixture (0.127 g), providing a total yield of crude compound (**6**) of 85%. Recrystallization from methanol gave *pale yellow needles*, m.p. 226—227 °C (a phase change occurs at *ca.* 180—190 °C). The pure compound is moderately soluble in hot methanol, but only very sparingly soluble in dichloromethane, and essentially insoluble in pentane; $\nu_{max.}$ 2 750br (with fine structure), 1 570, 1 455, 1 330, 1 295, 1 195, 1 120, 1 080, 1 055, 795, 785, and 670 cm^{-1}; $\lambda_{max.}$ (0.0860mM in methanol) 215 (ε 17 400), 235sh, and 300 nm (10 900); δ_H [$(CD_3)_2SO$] 10.98 (2 H, s, exch., OH), 7.95 (2 H, app. t, *J* 3 Hz), and 7.14 (4 H, app. d, *J* 3 Hz); δ_C [$(CD_3)_2SO$] 151.9 (singlet in the off-resonance decoupled spectrum), 140.6 (d), 140.3 (s), 123.2 (d), and 120.7 (d); *m/z* 348 (5%), 346 (5), 268 (6), 267 (5), 251(5), 188 (29), 187 (20), 177 (17), 175 (89), 173 (47), 172 (16), 171 (20), 146 (8), 127 (6), 95 (56), 94 (24), 67 (38), 66 (18), and 39 (100) (Found: M^+, 347.8914. $C_{10}H_8N_2O_2{}^{80}Se_2$ requires *M*, 347.8916) (Found: C, 34.5; H, 2.2; N, 7.7. $C_{10}H_8N_2O_2Se_2$ requires C, 34.68; H, 2.31; N, 8.09%).

Conversion of Diselenide (**6**) *into Selone* (**2**).—The diselenide (**6**) (0.331 g, 0.96 mmol) was placed in a dry, two-necked, 100 ml, round-bottomed flask fitted with a 50 ml pressure-equalizing dropping funnel and a magnetic follower. The dropping funnel was charged with alkaline aqueous sodium tetrahydroborate [NaBH4 (0.091 g, 2.4 mmol) in 2.5M-NaOH (30 ml)] and the system was then flushed with argon and maintained under a slight positive pressure of argon. The tetrahydroborate solution was added dropwise to stirred compound (**6**) over a period of 10 min, whereupon the diselenide dissolved to give a bright yellow solution. This solution was immediately concentrated under reduced pressure, and the solid obtained was redissolved in dil. hydrochloric acid (3M; 30 ml). The aqueous solution was rapidly extracted with dichloromethane (4 × 15 ml), and the combined extracts were dried ($MgSO_4$), and then evaporated under reduced pressure to give selone (**2**) (0.278 g, 83%), identical with that prepared as reported above.

Preparation of 1-Azaphenoxaselenine (**1**).—A 100 ml, two-necked, round-bottomed flask fitted with a magnetic follower was rapidly charged with oil-free sodium hydride (0.39 g, 16.3 mmol). The flask was fitted with a septum on the side arm and a septum-capped reflux condenser, then cooled in an ice-bath, and flushed with argon *via* needles through the septa, and maintained under a static pressure of argon. Dry DMF (30 ml) was added *via* a double-ended needle and the suspension was stirred during the addition of a solution of selone (**2**) (1.26 g, 7.2 mmol) in dry DMF (30 ml), also added *via* a double-ended needle. The mixture was stirred for 30 min at 0 °C, and then for 1 h at 20 °C, and was then recooled to 0 °C. A solution of 2-chloronitrobenzene (1.14 g, 7.2 mmol) in dry DMF (20 ml) was added dropwise to the stirred solution over a period of 15 min, during which the reaction mixture darkened. The mixture was stirred at 20 °C overnight and then refluxed for 3 h, after which it was cooled and poured into distilled water (100 ml). The aqueous mixture was extracted with ethyl acetate (5 × 80 ml). The combined extracts were washed successively with 1M-aqueous Na_2CO_3 (2 × 80 ml) and distilled water (2 × 80 ml), dried (Na_2SO_4), and then evaporated under reduced pressure to yield a brown oil consisting primarily of the required heterocycle (**1**) according to t.l.c. Flash-column chromatography on silica, with ethyl acetate–cyclohexane (3:7) as eluant, gave the *title compound* (**1**) (1.07 g, 59%) as an off-white solid, which after recrystallization from diethyl ether–hexane was analytically pure, m.p. 67.5—68.5 °C. The compound is soluble in chloroform, ethyl acetate, and diethyl ether, and has some solubility in light petroleum; $\nu_{max.}$ 3 060, 1 570, 1 470, 1 410, 1 270, 1 220, 1 080, 940, 810, 755, and 725 cm^{-1}; $\lambda_{max.}$ (0.0815mM in methanol) 235 (ε 16 100) and 315 nm (4 400); δ_H ($CDCl_3$) 8.17 (1 H, dd, *J* 2 and 5 Hz, 2-H) and 7.3—6.8 (6 H, m); *m/z* 249 (46%), 247 (22), 170 (13), 169 (100), 140 (11), and 39 (18) (Found: M^+, 248.9691. $C_{11}H_7NO^{80}Se$ requires *M*, 248.9693) (Found: C, 53.4; H, 2.8; N, 5.7. $C_{11}H_7NOSe$ requires C, 53.22; H, 2.82; N, 5.65%). The ^{13}C n.m.r. spectrum is recorded in Table 2.

Preparation of Substituted 1-Azaphenoxaselenines (**7**).—The method of preparation of the substituted 1-azaphenoxaselenines (**7a**—**f**) was almost identical with that described for the preparation of the parent compound (**1**). The proportions of the main reactants were identical but the scale differed somewhat and the amount of excess of NaH varied slightly because of the need for rapid weighing of this compound. Also, the amount of solvent (DMF) varied somewhat, as did the period of reflux. Details of the actual conditions used are given in Table 1, along with details of the product yields and m.p.s. ^{13}C N.m.r. chemical shifts are listed in Table 2. Other spectral and analytical data are given individually below.

All the compounds were soluble in solvents such as chloroform and ethyl acetate, but sparingly soluble in light petroleum. In their electron-impact mass spectra all compounds displayed a substantial molecular-ion cluster with a characteristic Se isotope pattern, and a major ion corresponding to loss of either the substituent (particularly NO_2) or Se.

7-Nitro-1-azaphenoxaselenine (**7a**). Orange crystals (from absolute ethanol); $\lambda_{max.}$ (0.0710mM in methanol) 212 (ε 21 400), 230sh, 264sh, 311 (6 200), and 361 nm (5 100); δ_H ($CDCl_3$) 8.23 (1 H, dd, *J* 2 and 5 Hz, 2-H), 7.95—7.75 (2 H, m), and 7.5—7.0 (3 H, m) (Found: M^+, 293.9543. $C_{11}H_6N_2O_3{}^{80}Se$ requires *M*, 293.9543) (Found: C, 44.9; H, 2.0; N, 9.2. $C_{11}H_6N_2O_3Se$ requires C, 45.05; H, 2.05; N, 9.56%).

7-(Trifluoromethyl)-1-azaphenoxaselenine (**7b**). Needles (from ethanol–water); $\lambda_{max.}$ (0.0464mM in methanol) 220sh, 235 (ε 15 500), 247 (13 800), and 308 nm (6 250); δ_H ($CDCl_3$) 8.19 (1 H, dd, *J* 2 and 5 Hz, 2-H) and 7.4—6.9 (6 H, m) (Found: M^+, 316.9565. $C_{12}H_6F_3NO^{80}Se$ requires *M*, 316.9566) (Found: C, 45.6; H, 1.7; N, 4.2. $C_{12}H_6F_3NOSe$ requires C, 45.57; H, 1.90; N, 4.43%).

7-Chloro-1-azaphenoxaselenine (**7c**). Needles (from absolute ethanol); $\lambda_{max.}$ (0.0557mM in methanol) 225sh, 240 (ε 19 600, with fine structure), and 305 nm (6 500); δ_H ($CDCl_3$) 8.17 (1 H, dd, *J* 2 and 5 Hz, 2-H) and 7.3—6.8 (5 H, m) (Found: M^+, 282.9302. $C_{11}H_6{}^{35}ClNO^{80}Se$ requires *M*, 282.9303) (Found: C, 46.9; H, 1.8; N, 5.0. $C_{11}H_6ClNOSe$ requires C, 46.73; H, 2.12; N, 4.96%).

7-Bromo-1-azaphenoxaselenine (**7d**). Pale orange crystals (from ethanol–water); $\lambda_{max.}$ (0.0593mM in methanol) 216 (ε 15 500), 242 (16 200, with fine structure), and 305 nm (5 400); δ_H ($CDCl_3$) 8.15 (1 H, dd, *J* 2 and 5 Hz, 2-H) and 7.3—6.9 (5 H, m) (Found: M^+, 326.8798. $C_{11}H_6{}^{79}BrNO^{80}Se$ requires *M*, 326.8797) (Found: C, 40.4; H, 1.6; N, 4.2. $C_{11}H_6BrNOSe$ requires C, 40.37; H, 1.83; N, 4.28%).

7-Methoxy-1-azaphenoxaselenine (**7e**). Fawn crystals (from diethyl ether–hexane); $\lambda_{max.}$ (0.0727mM in methanol) 216 (ε

24 500), 235sh,, 296 (6 600), and 325sh nm; δ_H ($CDCl_3$) 8.1 (1 H, dd, *J* 2 and 5 Hz, 2-H), 7.3—6.9 (3 H, m), and 6.7—6.5 (2 H, m) (Found: M^+, 278.9797. $C_{12}H_9NO_2{}^{80}Se$ requires *M*, 278.9798) (Found: C, 51.9; H, 2.9; N, 4.8. $C_{12}H_9NO_2Se$ requires C, 51.80; H, 3.24; N, 5.04%).

9-*Nitro*-1-*azaphenoxaselenine* (**7f**). Bright orange crystals (from chloroform–hexane); $\lambda_{max.}$ (0.0820mM in methanol) 225 (ε 23 650), 305 (8 200), and 415 nm (2 800); δ_H ($CDCl_3$) 8.15 (1 H, br, unresolved, 2-H), 8.0 (1 H, dd, *J* 4 and 5 Hz, 8-H), and 7.4–-6.9 (4 H, m) (Found: M^+, 293.9542. $C_{11}H_6N_2O_3{}^{80}Se$ requires *M*, 293.9543) (Found: C, 44.9; H, 1.8; N, 9.2. $C_{11}H_6N_2O_3Se$ requires C, 45.05; H, 2.05; N, 9.56%).

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References

1 For Part 20 see C. M. Lindsay, K. Smith, W. W. Lam, M. J. Musmar, G. E. Martin, A. F. Hoffschwelle, V. M. Lynch, and S. H. Simonsen, 'Synthesis, N.M.R. Spectroscopy, and Structural Parameters of a Number of Benzoquinoxalinodiheterins (Dithiins, Oxathiins, Thiazines, etc.),' in preparation. The present paper also represents Part 33 in the series 'Chemistry of Phenoxathiins and Isosterically Related Heterocycles.'

2 A. J. Elliott, N. Eisenstein, and L. C. Iorio, *J. Med. Chem.*, 1980, **23**, 333.

3 G. E. Martin, J. C. Turley, L. Williams, M. L. Steenberg, and J. P. Buckley, *J. Heterocycl. Chem.*, 1977, **14**, 1067.

4 (*a*) G. E. Martin, J. C. Turley, and L. Williams, *J. Heterocycl. Chem.*, 1977, **14**, 1249; (*b*) G. E. Martin and J. C. Turley, *ibid.*, 1978, **15**, 609; (*c*) G. E. Martin, J. D. Korp, J. C. Turley, and I. Bernal, *ibid.*, p. 721; S. R. Caldwell and G. E. Martin, *ibid.*, 1980, **17**, 989; S. R. Caldwell, G. E. Martin, S. H. Simonsen, R. R. Inners, and M. R. Willcott, *ibid.*, 1981, **18**, 479; S. Puig-Torres, G. E. Martin, K. Smith, P. Cacioli, and J. A. Reiss, *ibid.*, 1982, **19**, 879; J. S. Davies, K. Smith, J. R. Turner, and G. Gymer, *Tetrahedron Lett.*, 1979, 5035; V. M. Lynch, S. H. Simonsen, G. E. Martin, S. Puig-Torres, and K. Smith, *Acta Crystallogr., Sect. C*, 1984, **40**, 1483; S. P. Torres, G. E. Martin, J. J. Ford, M. R. Willcott, and K. Smith, *J. Heterocycl. Chem.*, 1982, **19**, 1441; S. B. Larson, S. H. Simonsen, G. E. Martin, K. Smith, and S. Puig-Torres, *Acta Crystallogr., Sect. C*, 1984, **40**, 103; S. Puig-Torres, C. H. Womack, G. E. Martin, and K. Smith, *J. Heterocycl. Chem.*, 1982, **19**, 1561; S. Puig-Torres, R. T. Gampe, G. E. Martin, M. R. Willcott, and K. Smith, *ibid.*, 1983, **20**, 253.

5 J. S. Davies, K. Smith, and J. R. Turner, *Tetrahedron Lett.*, 1980, **21**, 2191.

6 B. L. Townsend and R. S. Tipson, 'Nucleic Acid Chemistry,' Wiley-Interscience, New York, 1978, vol. 2, p. 869.

7 G. C. Levy and G. N. Nelson, 'Carbon-13 N.M.R. for Organic Chemists,' Wiley-Interscience, New York, 1972, p. 81; F. W. Wehrli and T. Wirthlin, 'Interpretation of Carbon-13 N.M.R. Spectra,' Heyden, London, 1976, p. 47.

8 J. S. Ricci and I. Bernal, *J. Chem. Soc. B*, 1970, 806.

9 R. Eriksen and S. Hauge, *Acta Chem. Scand.*, 1972, **26**, 3153.

10 R. Eriksen, *Acta Chem. Scand., Sect. A*, 1975, **29**, 517.

11 M. B. Hossain, C. A. Dwiggins, D. van der Helm, P. K. Sen Gupta, J. C. Turley, and G. E. Martin, *Acta Crystallogr., Sect. B*, 1982, **38**, 881.

12 D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, 'Purification of Laboratory Chemicals,' Pergamon, Oxford, 1966.

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