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REACTION OF 2-ACYLPHENYLSELENOCYANATES WITH HYDROXYLAMINE AND PHENYLHYDRAZINE

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Abstract—2-Selenocyanatobenzophenone reacts with hydroxylamine to give 3 - phenyl - 1,2 - benzisoselenazole N-oxide, the structure of which is indicated by polarographic reduction studies. The corresponding methyl and ethyl ketones react similarly but 3 - methyl - 2 - selenocyanato acetophenone yields 4,8 - dimethyl - 2 - imino - 2H - 1,3 - benzoselenazine 3-oxide. Benzoselenopheno[3,2-b]indole is formed under mild conditions by action of phenylhydrazine on 2-selenocyanatoacetophenone. 12H - Quinoxalino[2,3-b][1,4]benzoselenazine is obtained by condensation of 2,3-dichloroquinoxaline with the Zn salt of 2-aminobenzeneselenol.

2-Acylphenylselenocyanates (1) have been prepared[1,2] from 2-aminophenyl ketones by diazotisation followed by treatment with potassium selenocyanate. The objective of this work was to prepare Se–N heterocycles from these ketones.

Reaction of 2-selenocyanatobenzophenone (1a) with hydroxylamine hydrochloride in pyridine gave a crystalline product (31%). Analytical data and mass spectrum were consistent with structure 2 or 3a. These products would be formed by attack of O or N respectively of the intermediate oxime to effect nucleophilic displacement of cyanide ion from Se, with subsequent deprotonation, as in Scheme 1. Comparable intermolecular attack by oxime or hydrazone on benzeneseleninic anhydride has been reported by Barton *et al.*[3] The product gave triphenylphosphine oxide on heating with triphenylphosphine but no other product could be isolated. Spectroscopic data did not distinguish between structures 2 and 3a but the mass spectrum showed a peak at 259 (M-16; 11%) corresponding to loss of oxygen probably from N-oxide (3a).

In the hope of obtaining further evidence to distinguish between 2 and 3a, polarographic reduction of the product was compared with those of the oxime–ether and imine-oxide systems of noxiptylene (4) and chlordiazepoxide (5) respectively. Franklyn Smyth *et al.*[4] have shown that the $C=N^{+}-O^{-}$ and C=N groups in compounds such as 5 are reduced at different potentials. In acid media, the polarogram of 5 shows three peaks corresponding to reductions of the N-oxide (a) followed by C=N (b), both 2-electron processes (at $E_{1/2}$ − 0.6 v and − 0.75 v respectively). The N–C=N system (c) reduces at the most negative potential by a 4-electron process. In alkaline medium (pH 12), however, a single peak is observed corresponding to reduction of $C=N^{+}-O$ by a 2-electron process (to CH–N–OH). In contrast, the C=N–O system of 4 exhibits a single peak (at $E_{1/2}$ − 0.82 v in pH 3 buffer solution).

Differential pulse polarography of the product was

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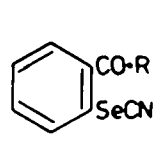
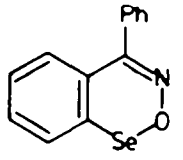
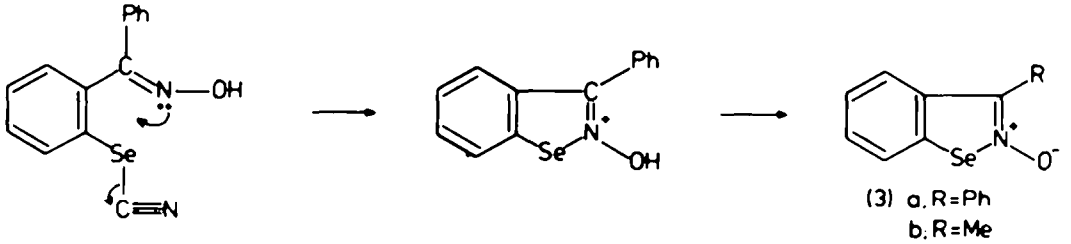


(1) a; R=Ph
b; R=Me
c; R=Et



(2)



(3) a, R=Ph
b; R=Me
c; R=Et

Scheme 1.

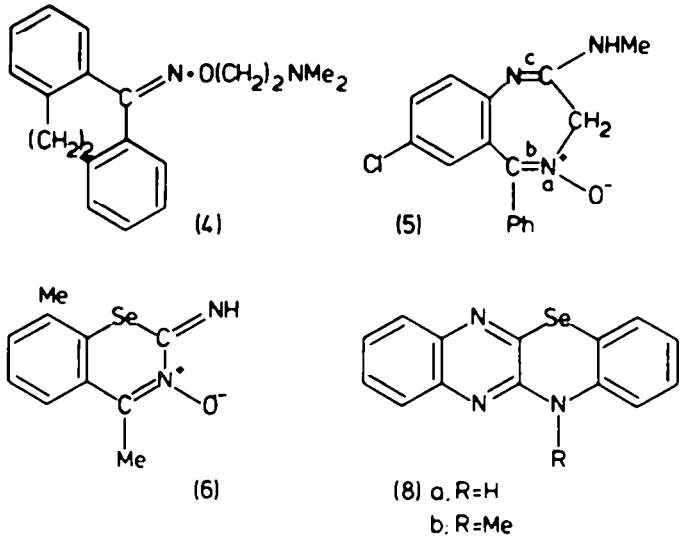
Table 1. Polarograms for compound (3a)

pH		1	2	3	4	5	6	7	8	9	10
Wave 1	$E_{1/2}$ (V)	−0.47	−0.50	−0.60	−0.65	−0.71	−0.76	−0.82	−0.81	−0.86	−0.86
	i_p (μA)	1.53	1.20	1.15	1.23	1.34	1.38	1.50	0.81	0.38	0.31
Wave 2	$E_{1/2}$ (V)	−0.60	−0.62	−0.72	−0.78	−0.82	−0.86	−0.92	−0.96	−1.04	—
	i_p (μA)	1.96	1.53	1.33	1.28	1.34	1.49	1.80	1.04	0.20	—

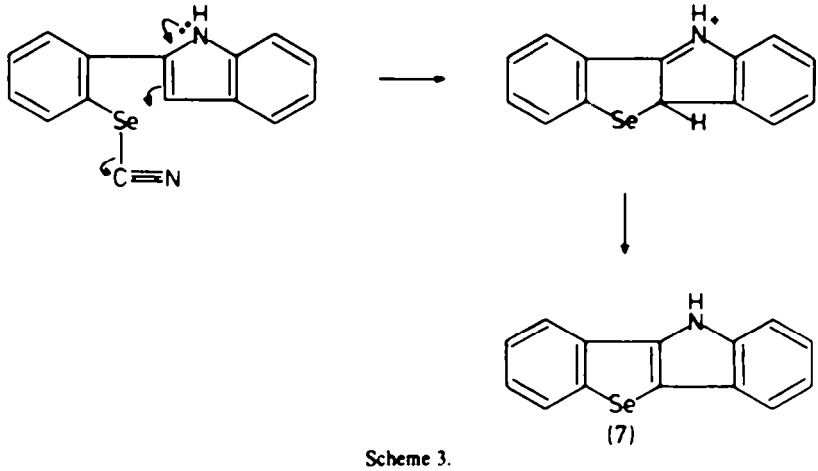
carried out in buffer solutions containing a little dimethyl sulphoxide. The results obtained are given in Table 1 and show the two waves corresponding to two reducible groups in acidic media. In alkaline media, the first wave is found at much reduced intensity and the second wave disappears. These results correspond closely with those given by the N-oxide structure (5) and strongly suggest that the hydroxylamine reaction product is the N-oxide (3a).

The 2-selenocyanatoketones (1b and 1c) gave analogous products (3b and 3c). These structures were indicated by the close similarity of the UV spectra (Experimental). In contrast, 3 - methyl - 2 - selenocyanato acetophenone yielded a product without elimination of hydrogen cyanide. No cyanide peak was present in the IR spectrum but a broad band at 3300 cm^{-1} was attributed to an NH group and suggested structure 6.

When the methyl ketone (1b) was heated with ethanolic phenylhydrazine and a little acetic acid, the known benzoselenopheno[3,2-b]indole[5] (7) was obtained, presumably by Fischer indole synthesis from 1b followed by displacement of cyanide ion from Se (Scheme 2). When 4,5 - dimethoxy - 2 - selenocyanatoacetophenone was treated similarly the only product isolated was bis - (2 - acetyl - 4,5 - dimethoxyphenyl) diselenide. Treatment of the selenocyanate with hydrochloric acid and acetic acid did give a very small yield of the dimethoxy-analogue of 7.



Scheme 2.



Scheme 3.

In another approach to Se,N-heterocycles, the Zn salt of 2-aminophenylselenol[6] was condensed with 2,3-dichloroquinoxaline in ethanol–trimethylamine. 2 - (*o* - Aminophenylseleno) - 3 - chloroquinoxaline could be isolated and then cyclised in hot ethanol to form 12H - quinoxalino[2,3-b][1,4]benzoselenazine (**8a**). Methylation gave a mixture of two products, as shown by the N-Me peaks in the PMR spectrum, but only one, believed to be the 12 - methyl - isomer (**8b**), could be isolated (*cf.* the analogous methylation of quinoxalino[2,3-b][1,4]benzothiazine described by Carter and Cheeseman[7]).

EXPERIMENTAL

Perkin–Elmer spectrometers used were: IR 297, UV 402 (for ethanol solutions), and PMR R32 at 90 MHz (with TMS as internal standard in $CDCl_3$ or $(CD_3)_2SO$). Evaporations were carried out below 35° on a rotary evaporator; petrol refers to the fraction (b.p. 60–80°).

2-Selenocyanatophenyl ketones. The methyl ketone was prepared from 2-aminoacetophenone[2] and the following were prepared similarly:

2-Selenocyanatopropiophenone (47%), m.p. 106–107° from petrol (Found: C, 50.3; H, 3.8; N, 6.0. $C_{10}H_9NOSe$ requires: C, 50.4; H, 3.8; N, 5.9%), ν_{max} 2150 (C≡N) and 1657 (C=O) cm^{-1}; *4,5 - dimethoxy - 2 - selenocyanatoacetophenone* (10%), m.p. 161–162°, from ethanol (Found: C, 46.4; H, 4.0; N, 4.9. $C_{11}H_{11}NO_3Se$ requires C, 46.5; H, 3.9; N, 4.9%), ν_{max} 2140 and 1640 cm^{-1}; and *3 - methyl - 2 - selenocyanatoacetophenone* (41%), m.p. 85–86°, from petrol (Found: C, 50.4; H, 3.8; N, 5.9%), ν_{max} 2145 and 1660 cm^{-1}.

3 - Phenyl - 1,2 - benzisoselenazole - N - oxide. 2-Selenocyanatobenzophenone (2 g) and hydroxylamine hydrochloride (1.04 g) were dissolved in pyridine (24 ml) and kept at room temp for 24 days. Evaporation, addition of water, and isolation with EtOAc gave **3a** (0.6 g; 31%), m.p. 205–206° (Found: C, 57.0; H, 3.3; N, 5.3. $C_{14}H_9NOSe$ requires C, 57.0; H, 3.3; 5.1%), *m/e* 275 (M^+, 5%), 259 (M-16, 11%).

Similarly prepared were *3 - methyl - 1,2 - benzisoselenazole - N - oxide* (12%), m.p. 203–204°, from EtOH (Found: C, 45.2; H, 3.3; N, 6.6. C_8H_7NOSe requires C, 45.3; H, 3.3; N, 6.6%), δ 2.33 (3H, s, Me), 7.3–8.1 (4H, m, ArH); and *3 - ethyl - 1,2 - benzisoselenazole - N - oxide* (22%), m.p. 195–196° from EtOAc (Found: C, 47.6; H, 4.0; N, 6.2. C_9H_9NOSe requires C, 47.8; H, 4.0; N, 6.2%). The UV spectra were very similar: **3a**, λ_{max} 232, 309 (ε, 26,000, 10,700); (3b), 238, 296 (19,300, 12,500); and **3c**, 238 295 nm (23,100, 15,100).

Polarography. Differential pulse polarograms were recorded on a PAR 174A Polarographic Analyser with 3-electrode system (*cf.* Ref. 4). A little DMSO was added to the buffer solns (phosphate, acetate, borate) as **3a** was insoluble in water. The results are given in Table 1.

4,8 - Dimethyl - 2 - imino - 2H - 1,3 - benzoselenazine - N(3) - oxide. 3 - Methyl - 2 - selenocyanatoacetophenone (1.24 g), hydroxylamine hydrochloride (0.9 g) and pyridine (20 ml) were shaken and left for 5 days. Yellow crystals were filtered off and a further crop was obtained by adding water (250 ml) to the filtrate. The combined crops were recrystallised from EtOH to give the *product* (25%), m.p. 211–214° (Found: C, 47.9; H, 4.2; N, 10.6. $C_{10}H_{10}N_2OSe$ requires, C, 47.4; H, 4.0; N, 11.1%), ν_{max} 3160 cm^{-1} (NH, br), λ_{max} 258 and 390 nm (ε, 27,800 and 17,100), δ 2.32 (3H, s, 8-Me), 2.63 (3H, s, 4-Me), 7.18–8.0 (3H, m, ArH).

Benzoselenopheno[3,2-b]indole. 2 - Selenocyanatoacetophenone (1.4 g), phenylhydrazine (880 mg) and AcOH (100 mg) in EtOH (40 ml) were heated under reflux for 8 hr. Evaporation and crystallisation from benzene gave product (0.7 g; 41%), m.p. 231–232° (lit.[3] 233°) (Found: C, 61.9; H, 3.4; N, 5.3. Calc. for $C_{14}H_9NSe$: C, 62.2; H, 3.4; N, 5.2%), ν_{max} 3380 cm^{-1} (NH), δ 7.08–8.0 (8H, m, ArH) and 8.57 (br, 1H, NH).

7,8 - Dimethoxybenzoselenopheno[3,2-b]indole. 4,5 - Dimethoxy - 2 - selenocyanatoacetophenone (400 mg), phenylhydrazine (290 mg), AcOH (20 ml) and 2M HCl (20 ml) were refluxed for 6 hr and poured into water (200 ml). The ppt was collected and extracted with boiling EtOH (3 × 40 ml). The hot extracts were filtered (charcoal) and cooled to give *bis - (2 - acetyl - 4,5 - dimethoxyphenyl)diselenide* (50 mg), m.p. 201–202° (Found: C, 46.8; H, 4.4. $C_{20}H_{22}O_6Se_2$ requires: C, 46.5; H, 4.3%), ν_{max} 1640 cm^{-1} (C=O). Evaporation of the ethanolic filtrate and chromatography on silica in EtOAc–petrol (2:3) gave the *indole* (25 mg), m.p. 215–217° (Found: C, 58.0; H, 3.9; N, 3.9. $C_{16}H_{13}NO_2Se$ requires: C, 58.2; H, 4.0; N, 4.2%), ν_{max} 3400 cm^{-1} (NH), δ 3.94 (3H, s, 8-OMe), 3.95 (3H, s, 7-OMe), 7.0–7.7 (6H, m, ArH), 8.51 (1H, s, NH).

2 - (2 - Aminophenylseleno) - 3 - chloroquinoxaline. 2,3 - Dichloroquinoxaline (3 g) and the Zn salt of 2-aminophenylselenol[6] (2.45 g) in Et_3N (25 ml) and EtOH (95 ml) were refluxed for 5.5 hr. A yellow solid was collected, washed with water (400 ml), and extracted with cold EtOAc (500 ml), insoluble material being filtered off. The filtrate was concentrated (below 30°) to give the yellow *amino-compound*, m.p. 227–228°. By mixing the mixture and washings, more product was obtained (total 2.74 g; 68%) (Found: C, 49.9; H, 3.1; Cl, 10.8; N, 12.6; Se, 23.5. $C_{14}H_{10}ClN_3Se$ requires: C, 50.2; H, 3.0; Cl, 10.6; N, 12.6; Se, 23.6%), ν_{max} 3410,3300 cm^{-1} (NH_2), δ 4.23 (2H, s, NH_2 exchanges with D_2O), 6.6–8.1 (8H, m, ArH).

12H - Quinoxalino[2,3-b][1,4]benzoselenazine. The amino-compound (0.25 g) was heated with EtOH (10 ml) for 2 min. On cooling the soln, the orange *product* (0.16 g; 72%), m.p. 232–234°, separated. After recrystallisation from EtOH, it had m.p. 236–237° (Found: C, 56.4; H, 3.2; N, 14.0; Se, 26.4. $C_{14}H_9N_3Se$ requires: C, 56.4; H, 3.0; N, 14.1; Se, 26.5%), ν_{max} 3270 cm^{-1} (NH), λ_{max} 222, 254, 426 nm (ε, 33,200, 82,400, 12,800), m/e 299 (M^+ for ^{80}Se, 83%), 219 (M^+-^{80}Se, 100%).

Methylation of 12H - quinoxalino[2,3-b][1,4]benzoselenazine. NaH (0.5 g; 80% dispersion) was added to NN-dimethylacetamide (30 ml) under N_2 and the mixture was heated to 100° and allowed to cool. Addition to the quinoxalino-compound (0.82 g) gave a deep red soln which was again heated to 100° and allowed to cool. The mixture turned yellow on addition of MeI (7 ml). It was left at room temp for 5 hr poured into water, and extracted with EtOAc. Evaporation and chromatography on silica in $CHCl_3$ gave orange crystals, m.p. 115–117°. The PMR spectrum indicated that this was a mixture of two products (presumably the 12- and 11-Me derivatives): δ 3.46 (s, 11-Me) and 3.57 (s, 12-Me) in 1:4 ratio. Preparative TLC on silica in benzene gave *12 - methyl - 12H - quinoxalino[2,3-b][1,4]benzoselenazine* (20 mg), m.p. 116–120° (Found: C, 57.6; H, 3.6; N, 13.4. $C_{15}H_{11}N_3Se$ requires: C, 57.7; H, 3.6; N, 13.5%), δ 3.57 (3H, s, 12-Me), 6.8–7.9 (8H, m, ArH).

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