Tetrahedron Vol. 36, pp. 2681 to 2683
(' Pergamon Press Ltd., 1980. Printed in Great Britain

0040-4020/80/0915-2681 $02.00/0

THE PREPARATION AND PROPERTIES OF 1,4-DIAZAPHENOSELENAZINE

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(*Received UK 8 November* 1979)

Abstract—The preparation and properties of 1,4-diazaphenoselenazine are described and compared with those of 1,4-diazaphenothiazine. Experiments leading to nitro and chloro derivatives and also ring-cleavage products of both the selenium and sulphur-containing heterocycles are also described.

Much attention has been given in recent years to the study of aza analogues of phenothiazines.[1] Interest in these compounds stems from their potential use as drugs, antioxidants and dyestuffs. In clinical applications the aza drugs often display enhanced activity over their simple phenothiazine analogues.

Phenoselenazines have also attracted attention as possible tranquillizing and antihistamine drugs. For example, the selenium analogue **1** of promazine has been found to have tranquillizing activity of the same order of magnitude as promazine but greater antihistamine activity. To date, no aza analogues of phenoselenazine have been reported. Following our interest[2] in 1,4-diazaphenothiazine {pyrazino[2,3-b]benzothiazine) (**2**)} we have prepared its selenium analogue (**4**) and explored some aspects of its chemistry.

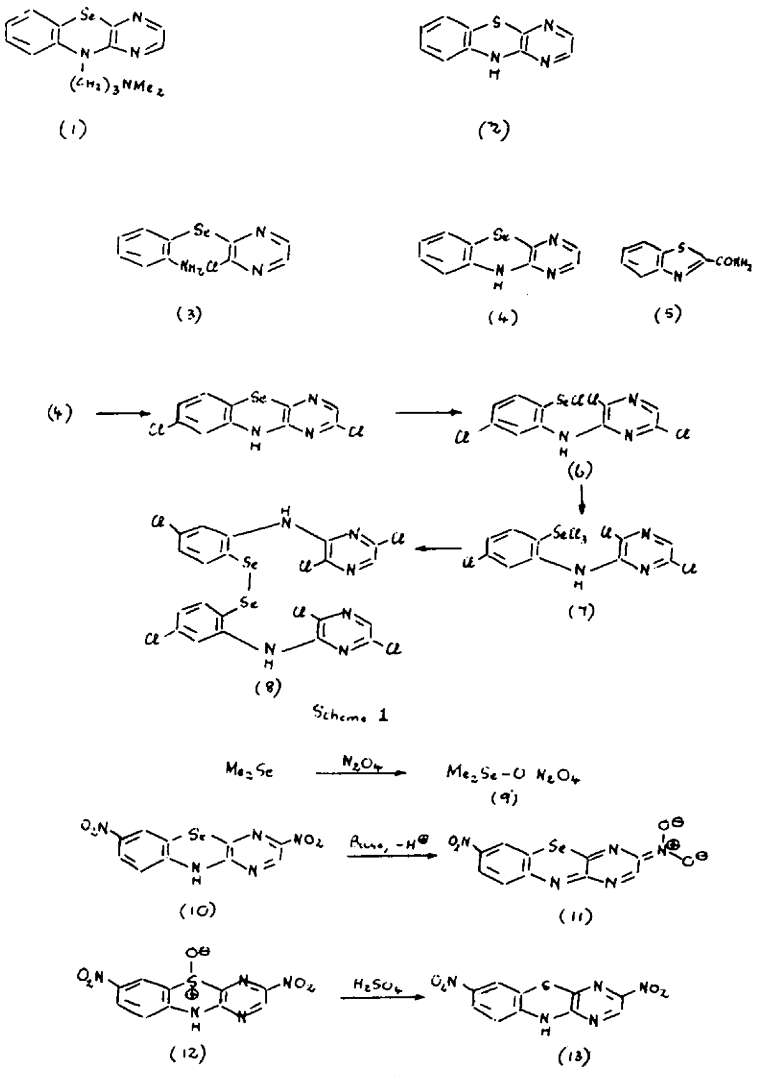
RESULTS

1,4-Diazaphenoselenazine (**4**) was prepared by the acid-catalysed condensation of the Zn salt of 2-aminoselenophenol with 2,3-dichloropyrazine. Reaction was complete in boiling ethanol in 20 min. If the reaction was interrupted after a few min, the intermediate selenide (**3**) was obtained. The ^{1}H NMR spectrum of the selenide showed a pair of doublets at 8.28 and 8.45 δ (J = 3 Hz) attributable to the two pyrazinyl protons. On heating, the selenide cyclised to 1,4-diazaphenoselenazine (**4**), the ^{1}H NMR spectrum of which showed a two-proton singlet for the pyrazinyl protons at δ 7.88. 1,4-Diazaphenoselenazine is a relatively stable yellow compound, although on prolonged storage and exposure to light it turned red, possibly due to the extrusion of elemental selenium. It had an UV max at 248 nm (ε = 23,500). An UV max in the region of 250 nm is characteristic of both phenothiazines and azaphenothiazines.

The ^{1}H NMR spectra of 1,4-diazaphenoselenazine and 1,4-diazaphenothiazine are virtually superimposable. Comparison of the ^{13}C NMR spectra of the two compounds shows that the carbons linked to the group 6 elements absorb at different frequencies, selenium causing an upfield shift of *ca* 4 ppm (δ 117 → δ 113). A similar upfield shift is observable when the chemical shifts of the carbons bound to selenium and sulphur in bis-2-aminophenyldiselenide and bis-2-aminophenyldisulphide are compared.

We have previously found that when 1,4-diazaphenothiazine (**2**) is treated with iodobenzene dichloride, ring contraction occurs and benzothiazole-2-carboxamide (**5**) is formed.[2] This transformation is more conveniently carried out by bubbling chlorine gas through a solution of compound **2** in aqueous acetonitrile. Similar treatment of 1,4-diazaphenoselenazine (**4**) did not produce the expected benzoselenazole but merely caused extensive decomposition. However, treatment of **4** with excess of chlorine in *dry* acetonitrile gave an orange solid, tentatively identified as the selenium trichloride (**7**). The mass spectrum of this compound showed a cluster of ions of composition $C_{10}H_5Cl_5N_2Se$ which could arise from the molecular ions by loss of chlorine, rearrangement, and loss of NH. The selenium trichloride (**7**) could possibly be formed by the reaction sequence shown in Scheme 1. The selenium trichloride decomposed in DMSO solution (evolution of chloromethylmethyl sulphide[3-5]) and on addition of water a yellow solid was precipitated. This had an elemental composition and spectroscopic properties consistent with its formulation as the diselenide (**8**). A complex series of changes is clearly involved in this transformation; the initial step is probably the formation of the selenium monochloride (**6**). A similar loss of chlorine occurs when α-anthraquinoyl selenium trichloride is dissolved in acetone.[6,7] It is also known that diphenyldiselenide is formed by the action of water on phenylselenium bromide.[8]

1,4-Diazaphenothiazine (**2**) was oxidised with 30% aqueous hydrogen peroxide to either a sulphoxide or a sulphone but similar treatment of 1,4-diazaphenoselenazine (**4**) gave only brown oily material. There is a report in the literature[9] that reaction of dimethyl selenide with dinitrogen tetroxide gives the selenoxide adduct (**9**). Reaction of the selenazine with dinitrogen tetroxide did not, however, yield a selenoxide. Instead the 3,7-dinitro derivative (**10**) was formed. In the case of the thiazine (**2**), the corresponding 3,7-dinitro compound (**13**) was also obtained but with excess of reagent the major product was the 3,7-dinitro-S-oxide (**12**). On dissolution in conc sulphuric acid, deoxygenation of the S-oxide occurred and 1,4-diaza-3,7-dinitrophenothiazine (**13**) was formed.[10] As expected,[2] compounds **10** and **13** have indicator properties; they both give bright blue anions (e.g. **11**) on treatment with aqueous base.



Scheme 1

EXPERIMENTAL

M.ps are uncorrected and were determined using a Gallenkamp apparatus or Koffler microscope hotstage. Preparative tlc was carried out using Merck silica gel $^{60}F_{254}$ chromatography plates. IR spectra were recorded on a Unicam SP 200 spectrometer. UV spectra were taken in 96% EtOH soln on a Unicam SP 800A spectrometer. ^{1}H NMR spectra were taken on a Perkin–Elmer R12B spectrometer using TMS or DDS as an internal standard; chemical shifts are reported in δ units. ^{13}C NMR spectra were obtained on a Bruker WP 60 spectrometer and mass spectra were obtained using an AEI MS 9 or MS 30 operating at 70 eV.

1,4-Diazaphenoselenazine (4). Conc HCl (12 drops) was added to a mixture of the Zn salt of 2-aminoselenophenol (10.00 g)[11] and 2,3-dichloropyrazine (8.00 g) in EtOH (100 ml). After heating under reflux for 20 min, the resulting red soln was cooled. Yellow crystals of 1,4-diazaphenoselenazine (5.30 g, 87%) separated, which on recrystallization from benzene gave a sample of m.p. 158–160°; IR (cm^{-1}, Nujol): 3200 (NH); UV (λ_{max} nm) 248 (ε = 23,500); ^{1}H NMR (DMSO-d_6): 6.7–7.3 (4 H, m, 6, 7, 8, 9-H); 7.8 (2 H, s, 2 and 3-H) 9.5–9.6 broad (1 H, s, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): 112.8 (5a-C), 118.0, 124.8, 129.7, 130.3, 130.9 (4a-C), 139.0, 140.6 (9a-C), 141.6, 150.9, (10a-C); MS (m/e): 251, 249, 247, 246, 245 (M^+); 170, 169 (M^+-Se). (Found: C, 48.24, H, 2.91; N, 16.36. $C_{10}H_7N_3Se$ requires: C, 48.19; H, 2.81, N, 16.87%).

2-(2-Aminophenylseleno)-3-chloropyrazine (3). Conc HCl was added to a mixture of the Zn salt of 2-aminoselenophenol (3.00 g), 2,3-dichloropyrazine (2.50 g) and EtOH (30 ml) in order to adjust the pH to 3. The mixture was boiled for a few min and the resulting clear yellow solution cooled and neutralised with aqueous NaOAc soln. The resulting white ppt of 3 was filtered off and dried. IR (cm^{-1}, Nujol): 3450 and 3380 (NH_2); ^{1}H NMR (DMSO-d_6): 5.5 broad (2 H, s, NH_2), 6.5–7.5 (4 H, m, Ar–H); 8.28 (1 H, dd, J = 3 Hz, 6 (or 5)-H), 8.45 (1 H, d, J = 3 Hz, 5 (or 6)-H).

Reaction of 1,4-diazaphenothiazine with aqueous chlorine. Cl_2 gas was bubbled through a suspension of the thiazine (1.00 g) in aqueous acetonitrile (14, 50 ml) until the solid dissolved and the soln became yellow. The soln was evaporated to dryness and the residue sublimed to give pure 5 (0.56 g, 63%), m.p. 228–230° (lit.[2] 228–230°). The IR and UV of the product were identical with that of an authentic specimen.

Reaction of 1,4-diazaphenoselenazine with chlorine. Cl_2 gas was bubbled through a suspension of 1,4-diazaphenoselenazine (0.25 g) in dry acetonitrile (20 ml) until a clear golden-yellow soln was obtained. On leaving the soln in a stoppered flask, in an atmosphere of Cl_2, an orange crystalline solid precipitated. This was filtered off and found to be virtually insoluble in CCl_2 and to melt with decomposition at 148–154.° MS (*m/e*): 412.8976, 411.9022, 410.9011, 409.9056, 408.9025, 408.2986, 407.9154, 406.9079, 405.9174.

The product (0.30 g) obtained as described above was dissolved in DMSO. A foul odour was immediately detectable and after 15 min at room temp, the soln was diluted with water. The yellow crystalline diselenide (**8**) precipitated and was recrystallised from CCl_4·UV (λ_{max} nm) 272.5 (ε = 32,800), 362 (ε = 11,650); ^{1}H NMR (CCl_4)†: 7.4 (1 H, dd, $J_{3,5}$ = 2 Hz, $J_{5,6}$ = 7 Hz, benzenoid ring H-5), 7.7 (1 H, d, $J_{3,5}$ = 2 Hz, benzenoid ring H-3); 8.1 (1 H, s, pyrazine H), 8.43 (1 H, d, $J_{5,6}$ = 7 Hz, benzenoid ring H-6): MS (*m/e*): 705, 703 (M^+); 626 (M^+-Se); 590 (M^+-Se-Cl); 355, 354, 353, 352, 351 and 350 (M^+/2). (Found: C, 34.11; H, 1.43, N, 11.79; $C_{20}H_{10}Cl_6N_6Se_2$ requires: C, 34.04, H, 1.42, N, 11.85%.)

1,4-*Diazaphenothiazine 5-oxide.* 1,4-Diazaphenothiazine (1.00 g) was dissolved in glacial AcOH (40 ml). H_2O (1.5 ml, 30% w/v) was added and the orange soln was heated at 50° until it went yellow (*ca* 20 min). The volume of the mixture was reduced to about 15 ml by distillation under reduced pressure and water (60 ml) was added. The pale yellow crystals (0.80 g, 74%) were filtered off and gave on recrystallisation from EtOH the S-oxide, m.p. 250–251° (dec); IR (cm^{-1} Nujol) 3200 (NH), 1660 (C=N), 1010 (S=O); ^{1}H NMR (CF_3COOD); 7.5–8.3 (4 H, m, 6,7,8 and 9-H), 8.87 (2 H, s, 2 and 3-H). Found: C, 54.81; H, 3.13; N, 18.97. $C_{10}H_7N_3OS$ requires C, 55.30; H, 2.76; N, 19.35%.

1,4-*Diazaphenothiazine 5,5-dioxide.* 1,4-Diazaphenothiazine (1.00 g) was dissolved in glacial AcOH (50 ml). H_2O_2 (3.6 ml, 30% w/v) was added and the mixture was heated at 70° overnight. The SS-dioxide separated as a pale yellow solid and was purified by dissolution in AcOH and addition of EtOH. It had m.p. 306–309° (dec.); IR (cm^{-1} Nujol) 1300–1250 and 1140 (asymmetric and symmetric SO_2 stretch); MS (m/e) 223 (M^+), 185 (M^+-SO), 169 (M^+-SO_2). (Found: C, 51.04; H, 2.78; N, 18.00. $C_{10}H_7N_3O_2S$ requires: C, 51.50, H, 2.58, N, 18.03%.)

1,4-*Diaza*-3,7-*dinitrophenoselenazine* (**10**). When nitrogen dioxide was bubbled through a stirred suspension of 1,4-diazaphenoselenazine (2.00 g) in freshly distilled acetonitrile (40 ml) at −12°, a red crystalline product formed. This was filtered off, dried, and recrystallised from DMF to give the dinitro compound (1.5 g, 55%) m.p. 250–251°. UV (λ_{max} nm) 211 (ε = 15,300), 295 (ε = 16,800), 363 (ε = 4,100), 465 (ε = 10,450); ^{1}H NMR (DMSO-d_6): 7.05 (1 H, d, $J_{8,9}$ = 9 Hz, H-9), 7.98 (1 H, dd, $J_{6,8}$ = 3 Hz, $J_{8,9}$ = 9 Hz, H-8), 8.27 (1 H, d, $J_{6,8}$ = 3 Hz, H-6), 8.66 (1 H, s, H-2) and 11.18 (1 H, s, broad, H-10, D_2O exchangeable). (Found: (for sample dried in vacuum for 30 hr at 100°): C, 35.59; H, 1.50, N, 20.70. $C_{10}H_4N_4O_4Se$ requires: C, 35.50, H, 1.49; N, 20.72%.)

1,4-*Diaza*-3,7-*dinitrophenothiazine*-5-*oxide* (**12**). A cold soln of dinitrogen tetroxide in $CHCl_3$ was added to a stirred soln of 1,4-diazaphenothiazine (5.00 g) in $CHCl_3$ (50 ml). Addition was continued until the mixture changed from red to orange in colour. The *S*-oxide (7.50 g, 98%) precipitated and after recrystallisation from AcOH: water (8:2) had m.p. 198° dec.; UV (λ_{max} nm): 209 (ε = 23,500) 240 (ε = 12,000), 265 (ε = 11,700), 282 (ε = 10,950), 347 (ε = 9,720), 380 (ε = 12,700), 463 (ε = 8,300); ^{1}H NMR (DMSO-d_6) 7.77 (1 H, d, $J_{8,9}$ = 8 Hz, H-9), 8.6 (1 H, dd, $J_{6,8}$ = 3 Hz, $J_{8,9}$ = 8 Hz, H-8), 9.14 (1 H, d, $J_{6,8}$ = 3 Hz, H-6), 9.7 (1 H, s, H-2), 13.5 broad (1 H, s, NH, D_2O exchangeable) MS (*m/e*)† 307 (M^+), 291 (M^+-O). (Found: C, 39.40; H, 1.75; N, 22.12. $C_{10}H_5N_5O_5S$ requires: C, 39.08; H, 1.63; N, 22.80%).

1,4-*Diaza*-3,7-*dinitrophenothiazine* (**13**). (a) 1,4-Diazaphenothiazine (0.10 g), was added to a stirred soln of dinitrogen tetroxide (0.2 ml) in $CHCl_3$ (10 ml) at 0°. A red colour developed immediately and after removal of solvent a red solid was obtained. This was shown by tlc (petrol 60–80°: EtOAc 9:1) to be a mixture of two compounds. Preparative tlc gave 20 mg of the more mobile red dinitro compound **13** and 50 mg of the orange dinitro-S-oxide (**12**). The dinitro compound had m.p. 208–210° dec after crystallisation from AcOH, UV (λ_{max} nm): 215 (ε = 16,100), 291 (ε = 17,100), 366 (ε = 5,810), 463 (ε = 9,240), 607 (ε = 1,140); MS (*m/e*) 291 (M^+), 218 (M^+-NO_2-HCN), 172 (M^+-2NO_2 HCN). (Found: C, 41.46; H, 1.75; N, 23.63. $C_{10}H_5N_5O_5S$ requires: C, 41.24; H, 1.73; N, 24.05%.)

(b) 1,4-Diaza-3,7-dinitrophenothiazine-5-oxide (0.30 g) was dissolved in conc H_2SO_4 (2 ml) to give an intensely purple-red soln. Water was added dropwise until a red solid (0.12 g, 42%) precipitated out. This was found to be identical with a sample of the dinitro compound prepared as described above.

Acknowledgements—The authors wish to thank S.R.C. for a research studentship (to G.R.) and Mr W. G. Gunn and Mr A. Cakebread for the measurement of the mass spectra.

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†In $CDCl_3$ the N–H absorption was observed at δ 8.2.

†The mass spectrum of the crude material showed a peak at 336 m.u. presumably due to the presence of a trinitro derivative in the product as impurity.