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SYNTHESIS OF THE 5-SELENA-1,3,6-TRIAZACYCL[3.2.3]AZINE SYSTEM

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Abstract—The syntheses and properties of four phenyl derivatives of the 5-selena-1,3,6-triazacycl[3.2.3]azine system are described. Bromination of 4-phenyl-5-selena-1,3,6-triazacycl[3.2.3]azine, is found to occur in position 8.

In a recent publication we have presented the syntheses of the 4- and 5-thiaaza-cycl[3.2.3]azine systems **1** and **2**.[1] The present communication describes the synthesis of the analogous 5-selenaazacycl[3.2.3]azine compounds **3a-3d**, using the synthetic route employed in the synthesis of **2**, but now with 2,4-diamino-5-phenylselenazole, **4**, as starting material (Chart 1).

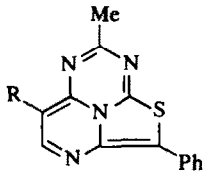
The hydrobromide of **4** was conveniently prepared from selenourea and α-bromobenzyl cyanide, following the procedure employed for 2,4-diamino-5-phenylthiazole hydrobromide.[2] The NMR spectrum of **4**·HBr contains a methine absorption at 6·85 ppm, which indicates that **4**·HBr, like 2,4-diamino-5-phenylthiazole hydrobromide, exists in a non-aromatic, tautomeric form, cf. structures **3b-3d** in Ref. 3. The free base **4** is probably very unstable, and various attempts to liberate it from the hydrobromide using different bases, low temperature, and an oxygen-free atmosphere, all resulted in precipitation of selenium within minutes. Since **4** could not be isolated, it was liberated from its hydrobromide and reacted *in situ* with **5**. A complex mixture of products then resulted and attempts to isolate **6** and/or **7** from it failed. Therefore the reaction mixture was directly formylated, and a brown crystalline compound with a molecular weight (MS), which corresponds to that of the desired selenaazacyclazine **3a**, was isolated. It is interesting to note the direct ringclosure to a cyclazine without isolation of a formylated intermediate, which was also observed for the 5-thiaazacyclazine **2a**. Decarbethoxylation of **3a** to **3b** succeeded in diphenyl ether at 250° in the presence of *p*-toluenesulphonic acid.

The two amino groups in 2,4-diamino-5-phenylselenazole are not equivalent and therefore two monocondensation products, **6** and **7**, could form, which in turn would give rise to the isomeric selenaazacyclazine systems **3** and **8** respectively. We have, however, only succeeded in preparing one of these.†

Our attempts to prove the structure of the new selenaazacyclazine system with the help of the method used for the analogous thiaazacyclazine systems **1** and **2**[1] were unsuccessful mainly because of the instability of one of the isomeric systems. Our proof of structure for **3** will therefore be based on a comparison of its properties with those of the thiaazacyclazines **1** and **2**, since it is well-known that sulphur and selenium analogues show very similar chemical, physical, and spectral properties.[4]

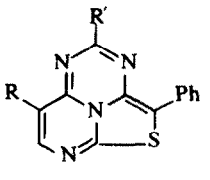
The mass spectrometric fragmentation patterns of the isomeric pairs **1a-2d** and **1b-2e** are very similar. Therefore we cannot use the mass spectra of **3a**, **3b** and **3d** to distinguish between the two isomeric structures, although they are good support for the correctness of the gross structure of **3**.

For the 4- and 5-thiaazacyclazine systems[1] it was emphasized that the presence of an S atom in the ring allows only one Kekule structure to be written. One would therefore expect more single-bond character for the C-7—C-8 bond in **1** than in **2**. The large difference in the chemical shift value for the H-8 protons in **2b** and **1b** (5·49 and 4·64 ppm respectively), is likely to be due to a certain degree of π-electron localization in the systems, since the distances between the S atom and the proton in question are at least five bonds. We therefore believe that the similarity between the chemical shifts for H-8 in **2b**



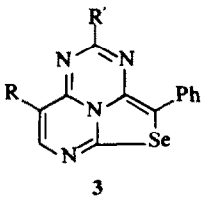
1

a: R = COOEt
b: R = H



2

a: R' = H; R = COOEt
b: R' = H; R = H
c: R' = H; R = Br
d: R' = Me; R = COOEt
e: R' = Me; R = H



3

a: R' = H; R = COOEt
b: R' = H; R = H
c: R' = H; R = Br
d: R' = Me; R = COOEt

†Heating of an acetylated mixture of the reaction products from **4** and **5** in diphenyl ether at 230° gave in addition to **3d**, a green spot on TLC which had an R_f-value and colour very similar to those of **1b** and it might therefore have structure **8**. The compound was, however, too unstable to be isolated.

and in the selenaazacyclazine prepared (5·49 and 5·66 ppm respectively), is reliable evidence for assignment of structure **3b** to it. The weakness of this arguement is, however, that only one of the two isomeric systems is available for comparison.

The UV and visible spectra of the analogous sulphur-selenium pairs **2a-3a** and **2b-3b** are very similar; the selenium compounds show a small shift to longer wave-lengths for most of the absorption bands compared with the sulphur analogues. On the other hand, the 2-methyl substituted isomeric pairs **1a-2d** and **1b-2e** show considerable differences in their spectra. Since a Me group in position 2 has little influence on the spectrum (cf. spectra of **2d-2a** and **2b-2e**), the similarity of the electronic spectral data for **3a** and **3b** with **2a** and **2b** respectively, and dissimilarity with **1a** and **1b** respectively are further arguments for the proposed selenaazacyclazine structures.

Bromine in glacial acetic acid converts **3b** to the 8-bromo derivative **3c**. Its composition follows from the exact masses of the isotope ions in the molecular ion region of the mass spectrum, and the position of substitution from the NMR spectrum, where H-7 appears as a singlet and the H-8 signal is lacking (cf. Experimental). Substitution in the 8-position is expected from arguments using resonance structures of the electrophilic substitution intermediates. This has been discussed in an earlier communication[1] (cf. structures **17** and **18** in Ref. 1).

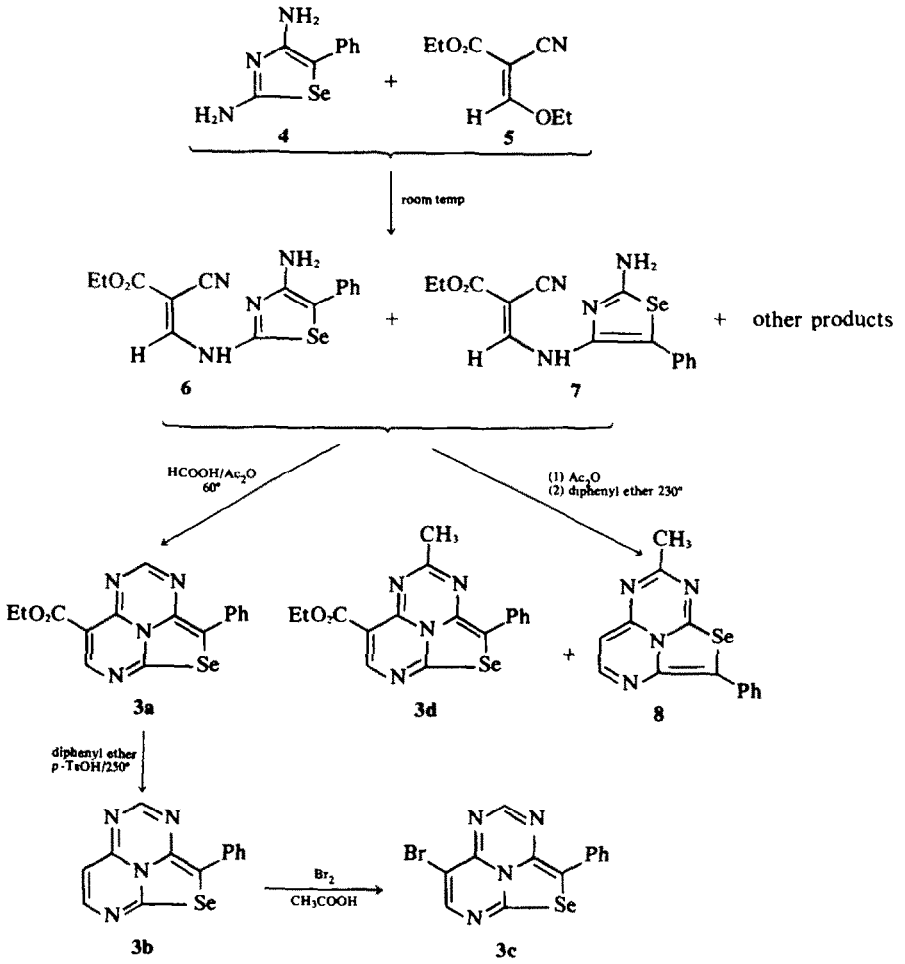


Table 1. Electronic spectral data for **1a**, **1b**, **2a**, **2b**, **2d**, **2e**, **3a** and **3b**

	nm (Rel. int.)									
2a	607(250)	550(650)	510(940)		410(14400)	334(9900)	318(9700)	304(7700)	292(6800)	233(26800)
3a	616(390)	564(910)	520(1380)		419(14900)	335(6700)	318(7850)	305(8600)	295(8150)	233(29400)
2b	606(320)	553(610)	514(730)	480(670)	381(15400)	334(12400)	318(9650)	305(6700)	281(6180)	228(23700)
3b	610(230)	556(520)	516(650)	481(600)	388(11500)	335(6600)	319(6600)	305(6450)	294(6000)	229(21500)
1a	597(400)	550(700)	510(900)		410(13300)	361(27300)	347(29200)		278(7500)	232(25700)
2d		540(850)	500(1240)		407(13800)	333(10800)	318(10100)	305(8050)		230(26000)
1b	640(250)	581(510)	541(630)		436(11600)	342(11200)	326(9800)	314(6500)	273(5959)	223(18700)
2e	600(270)	540(650)	500(800)	473(790)	379(13700)	334(12400)	319(9700)	306(6600)	297(6800)	230(21800)

EXPERIMENTAL

General. NMR spectra were recorded with a Varian Model A-60, a Jeol Model MH-60, or a Bruker Model WH-270 spectrometer using TMS as internal reference; chemical shifts are given in δ-values. UV and visible spectra were measured in EtOH with a Cary Model 15 spectrophotometer. The mass spectra, obtained from the Department of Medical Biochemistry, University of Göteborg, were recorded with a GEC-AEI 902 instrument, at an ionizing potential of 70 eV. TLC was performed on silica gel GF_{254} (Merck) plates with benzene-EtOAc 2:1 as the developing solvent when not otherwise stated, and the spots were detected with short-wave UV light and with iodine vapour. Ethyl 2-cyano-3-ethoxyacrylate and selenourea were obtained from Fluka AG, and the former was recrystallized from EtOH before use. α-Bromobenzyl cyanide[5] was distilled before use, b.p. 106–108°/1 Torr.

2,4-Diamino-5-phenylselenazole hydrobromide, 4·HBr. To a stirred suspension of selenourea (5·55 g; 45·0 mmol) in 100 ml anhyd EtOH a soln of α-bromobenzyl cyanide (8·85 g; 45·0 mmol) in 150 ml anhyd EtOH was added. The mixture was stirred for 16 hr under protection from light, filtered, and the filtrate was then evaporated to a volume of *ca.* 75 ml. Addition of 400 ml anhyd ether precipitated **4**·HBr as a pale-yellow solid, which was filtered off and washed with anhyd ether, yield: 8·37 g (58%). Recrystallization from dry acetone gave **4**·HBr as white crystals, m.p. 170° (dec). (Found: C, 32·55; H, 3·09; N, 13·09; Br, 25·84; Se, 25·17. $C_9H_{10}N_3BrSe$ requires: C, 33·88; H, 3·16; N, 13·17; Br, 25·04; Se 24·75%). The elemental analysis was carried out at the Analytical Laboratory, University of Uppsala. UV: λ_{max} at 284 (ϵ = 4500) and 235 nm (ϵ = 21500). NMR (DMSO-D_6): 5-methine proton at 6·85 (1H), phenyl protons at 7·58 (5H), and NH protons at 9·78 ppm (*ca.* 4H).

8 - Carbethoxy - 4 - phenyl - 5 - selena - 1,3,6 - triazacycl[3.2.3]azine, **3a**. A vigorously stirred soln of **4**·HBr (634 mg; 2·0 mmol) in 50 ml water was neutralized with $NaHCO_3$ (168 mg; 2·0 mmol). To the suspension of the free base **4** thus formed was added immediately **5** (338 mg; 2·0 mmol), and then 50 ml EtOH. The soln was left at room temp for 1 hr. Most of the EtOH was then removed under reduced pressure. The residue was extracted with 3 × 25 ml ether. The combined extracts were dried ($MgSO_4$) and the ether was evaporated. The remaining solid was dissolved in 20 ml formic acid and 7 ml Ac_2O was added.[6] The soln was kept at 60–70° for 1·5 hr, poured into 100 ml ice water, neutralized with 10% $NaHCO_3$ aq, and finally extracted with 3 × 100 ml CH_2Cl_2. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness. The dark-brown residue was chromatographed on silica gel (45 g ϕ < 0·0063 mm). With CH_2Cl_2–EtOAc 10:1, 70 mg (9·5%) of **3a** was obtained as brown crystals. These were homogeneous on TLC, and they were recrystallized from anhyd EtOH to give brown needles, m.p. 204–205°. NMR ($CDCl_3$): ester protons at 1·30 (3H) and 4·27 (2H), phenyl protons at 7·15–7·67 (5H), and ring protons H-2 at 7·24 (1H) and H-7 at 8·02 ppm (1H). For assignments cf. **3d** and Ref. 1, compound 1. MS: M^+ found 370·0125 ± 0·002 and 372·012 ± 0·003. $C_{16}H_{12}N_4O_2{}^{78}Se$ requires: 370·0133 and $C_{16}H_{12}N_4O_2{}^{80}Se$ requires: 372·0125. *m/e* (Rel int) 374 (8), 373 (8), 372 (38), 371 (5), 370 (19), 369 (8), 368 (8), 302 (7), 301 (7), 300 (30), 299 (9), 298 (16), 297 (9), 296 (8), 220 (6), 197 (2), 196 (3), 195 (11), 194 (8), 193 (7), 192(6), 191 (4), 171 (2), 170 (2), 169 (9), 168 (4), 167 (6), 166 (4), 165 (3), 150 (10), 149 (100), 116 (5), 115 (6), 114 (5), 89 (7), 88 (4), 77 (13). Doubly charged ions: m/2e (Rel int) 163·5 (0·6), 162·5 (0·4), 149·5 (0·4), 148·5 (0·4), 117·5 (0·4), 84·5 (0·8).

Decarbethoxylation of **3a** *to* **3b**. To a suspension of **3a** (100 mg) in 40 ml diphenyl ether kept at 250° *p*-toluenesulphonic acid (100 mg) was added. The soln was left for 50 min, and then allowed to cool to room temp. The solution was applied to a column of silica gel (20 g) and the diphenyl ether was washed out with petroleum ether (b.p. 40–60°). The coloured material was then eluted with EtOAc-MeOH 10:1. The fraction containing **3b** was purified by preparative TLC (R_f = 0·23) giving 25 mg (31%) of **3b** as a brown solid, m.p. 167–170°. NMR ($CDCl_3$); phenyl protons at 7·16–7·70 (5H), ring protons H-2 at 7·00 (1H), H-7 at 7·30 (1H), and H-8 at 5·66 ppm (1H); $J_{7,8}$ = 6 Hz MS: M$^+$ found 297·990 ± 0·003 and 299·991 ± 0·002. $C_{13}H_8N_4{}^{78}Se$ requires: 297·9922 and $C_{13}H_8N_4{}^{80}Se$ requires 299·9915. *m/e* (Rel int) 302 (20), 301 (17), 300 (100), 299 (14), 298 (52), 297 (21), 296 (20), 220 (5), 197 (9), 196 (9), 195 (53), 194 (27), 193 (28), 192 (22), 191 (13), 171 (2), 170 (3), 169 (11), 168 (11), 167 (6), 166 (6), 165 (4), 150 (6), 149 (4), 116 (20), 115 (10), 114 (13), 89 (16), 88 (10), 77 (13). Doubly charged ions: *m/2e* (Rel int) 150·5 (0·8), 149·5 (0·5), 148·5 (1·0), 137·5 (0·5), 136·5 (2·3), 135·5 (1·4), 134·5 (0·5), 123·5 (0·5), 122·5 (0·3), 121·5 (0·7), 110·5 (0·5), 109·5 (0·8), 108·5 (0·2), 83·5 (2·0).

8 - Bromo - 4 - phenyl - 5 - selena - 1,3,6 - triazacycl[3.2.3]azine, **3c**. A soln of **3b** (20 mg; 0·067 mmol) and Br_2 (30 mg; 0·19 mmol) in 5 ml glacial AcOH was heated to 70°. After 2 hr at this temp the solvent was evaporated under reduced pressure. From the residue, 18 mg (71%) of **3c** was isolated as a brown solid by preparative TLC (R_f = 0·58), m.p. 253–255°; UV: λ_{max} at 630 (ϵ = 160), 573 (ϵ = 315), 528 (ϵ = 390), 495 (ϵ = 370), 395 (ϵ = 8500), 339 (ϵ = 3150), 320 (ϵ = 3100), 308 (ϵ = 3500), 296 (ϵ = 3600) and 232 nm (ϵ = 12000). NMR (CF_3COOH): Phenyl protons at 7·56 (5H), H-2 at 7·30 (1H) and H-7 at 8·45 ppm (1H).

MS: M^+ found 375·902 ± 0·002, 377·9016 ± 0·002 and 379·8995 ± 0·002. $C_{13}H_7N_4{}^{79}Br{}^{78}Se$ requires: 375·9028, $C_{13}H_7N_4{}^{81}Br{}^{78}Se$ requires: 377·9008, $C_{13}H_7N_4{}^{79}Br{}^{80}Se$ requires 377·9020 and $C_{13}H_7N_4{}^{81}Br{}^{80}Se$ requires: 379·9000 *m/e* (Rel int) 382 (13), 381 (13), 380 (79), 379 (19), 378 (100), 377 (21), 376 (46), 375 (15), 374 (15), 300 (10), 299 (8), 298 (7), 297 (6), 273 (4), 272 (5), 271 (4), 197 (11), 196 (13), 195 (63), 194 (41), 193 (31), 192 (29), 191 (17), 190 (10), 171 (4), 170 (5), 169 (21), 168 (16), 167 (13), 166 (13), 165 (10), 150 (3), 149 (11), 116 (54), 115 (19), 114 (25), 99 (25), 97 (37), 89 (37), 85 (50), 77 (38). Doubly charged ions: *m/2e* (Rel int) 190·5 (1·3), 189·5 (1·3), 188·5 (1·3), 187·5 (1·3), 150·5 (2·5), 149·5 (11·3), 148·5 (5·0), 147·5 (2·5), 136·5 (1·3), 135·5 (1·3), 134·5 (1·3), 122·5 (1·3).

8 - Carbethoxy - 2 - methyl - 4 - phenyl - 5 - selena - 1,3,6 - triazacycl[3.2.3]azine, **3d**. One mmol each of **4**·HBr and **5** were condensed as described for **3a**. When the ether had been evaporated, 15 ml Ac_2O was added to the residue. The mixture was left at room temp for 48 hr and it was then evaporated to dryness. The residue was suspended in 10 ml diphenyl ether and the suspension was heated to and kept at 220–230° for 30 min. The dark soln formed was allowed to cool to room temp and then passed through a column of silica gel from which the diphenyl ether was washed out with benzene. CH_2Cl_2–EtOAc 3:1, eluted the coloured material. TLC showed a brown and a green spot with R_f-value (0·57 and 0·41 respectively) identical with those observed for **2d** and **1b** respectively. The green compound could not be obtained in pure form, but 7 mg of **3d**, m.p. 148–150° was isolated by preparative TLC. UV: λ_{max} at 550 (ϵ = 520), 510 (ϵ = 790), 409 (ϵ = 6170), 333 (ϵ = 6500), 317 (ϵ = 6650), 305 (ϵ = 6400) and 229 nm (ϵ = 16400). NMR ($CDCl_3$): ester protons at 1·33 (3H) and 4·28 (2H), Me protons at 2·09 (3H), phenyl protons at 7·33–7·62 (5H) and H-7 at 8·04 ppm (1H). MS: M^+ found 384·028 ± 0·003 and 386·028 ± 0·003. $C_{17}H_{14}N_4O_2{}^{78}Se$ requires: 384·0290 and $C_{17}H_{14}N_4O_2{}^{80}Se$ requires: 386·0282. *m/e* (Rel int) 388 (20), 387 (20), 386 (100), 385 (10), 384 (50), 383 (20), 382 (20), 316 (18), 315 (18), 314 (90), 313 (12), 312 (46), 311 (19), 310 (16), 234 (14), 197 (8), 196 (8), 195 (44), 194 (28), 193 (24), 192 (20), 191 (12), 190 (4), 171 (4), 170 (4), 169 (18), 168 (12), 167 (10), 166 (8), 165 (6), 149 (6), 142 (8), 116 (6), 115 (12), 114 (10), 105 (4), 103 (6), 89 (16), 88 (8), 77 (50). Doubly charged ions: *m/2e* (Rel int) 170·5 (2·0), 169·5 (1·0), 157·5 (0·8), 156·5 (2·2), 155·5 (1·2), 103·5 (2·0), 84·5 (3·0), 83·5 (1·5).

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REFERENCES

[1]O. Ceder and B. Beijer, *Tetrahedron* **30**, 3657 (1974).
[2]W. Davies, J. A. Maclaren and L. R. Wilkinson, *J. Chem. Soc.* 3491 (1950).
[3]O. Ceder and B. Beijer, *Tetrahedron* **31**, 963 (1975).
[4]D. L. Klayman and W. H. H. Günther, *Organic Selenium Compounds: Their Chemistry and Biology*, pp. 865, 903. Wiley-Interscience, New York (1973).
[5]*Org. Synth.* Coll. Vol. III, p. 347.
[6]J. C. Sheehan and D.-D. H. Yang, *J. Am. Chem. Soc.* **80**, 1154 (1958).