

was added. After 2.5 h the reaction mixture was cooled and the diphenyl ether dissolved in petroleum ether. The residue, containing **6**, was then taken up in 2 ml of methanol and purified by preparative TLC (MeOH;  $R_F=0.21$ ). Yield: 15 mg (71 %) of **6** as blue-green needles, m.p. 216–218 °C (decomp.). MS:  $M^+=169.0637$ . Calc. for  $C_{16}H_{17}N_3$ : 169.0640.  $m/e$  (Rel. int.) 169 (100,  $M^+$ ), 143 (17.9,  $M-CN$ ), 142 (12.5,  $M-HCN$ ), 116 (6.8, 143– $H-CN$ ), 115 (10.7,  $M-2HCN$ ). UV:  $\lambda_{max}(\epsilon)$  246 (9500), 264 (12 750), 268 sh. (12 000), 365 sh. (10 500), 378 (13 600), 385 sh. (11 300), 399 (5800), 452 sh. (650), 483 (680), 503 sh. (370), 602 sh. (150), 650 nm (240). NMR ( $CDCl_3$ ):  $\delta$  4.34 (2 H, d, H-3, H-7), 4.70 (2 H, d, H-4 and H-6), 5.92 (1 H, t, H-5), 6.17 (2 H, d, H-2 and H-8);  $J_{3,4}=J_{7,8}=5.8$ ,  $J_{4,5}=J_{6,7}=8.0$  Hz.

**Preparation of 1,9-diazacycl[3.3.3]azine, 6, from 2,6-dimethylpyridine 5.** A mixture of 1 g (9.34 mmol) of **5** and 1.8 g (18.36 mmol) of ethyl *N*-cyanofornimidate, **4**, was kept at 100 °C for 45 min. It was cooled to room temperature and poured onto a column of silica gel. A blue product was eluted with EtOAc/MeOH (4:1) and further purified by preparative TLC (MeOH). Yield: < 5 % of **6**. Mass and NMR spectral data showed it to be identical with the compound obtained by decarboxylation of **6b**.

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## Synthesis of Methyl-substituted 5-Thia- and 5-Selena-1,3,6-triazacycl-[3.2.3]azines

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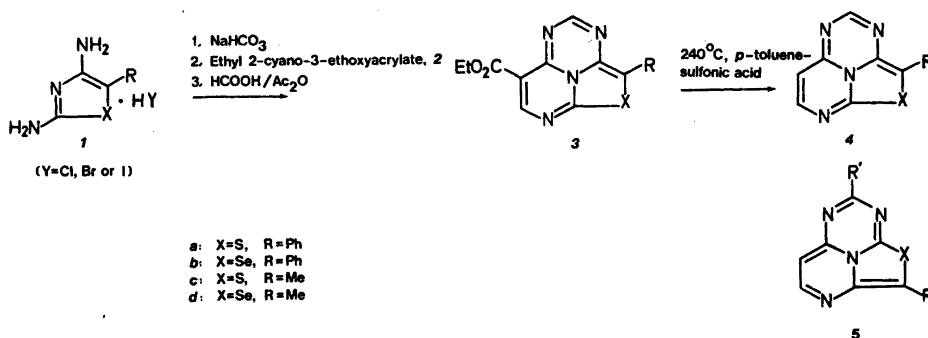
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For the study of properties of a nonbenzenoid aromatic system the parent compound is usually the most desired member. In many cases, however, available synthetic methods allow only the preparation of derivatives. Of these the phenyl analogues can be of limited value for an investigation of aromaticity.<sup>1,2</sup> The methyl-substituted systems, on the other hand, in general show properties which are very similar to those of the parent compound. Often a methyl group has a stabilizing effect on the system.<sup>3</sup>

We have recently described the synthesis of phenyl-substituted thia- and selena-1,3,6-triazacycl[3.2.3]azines <sup>4,5</sup> from 5-phenyl-2,4-diaminothia- and selenazole and ethyl 2-cyano-3-ethoxyacrylate, **2**. We did not succeed then in preparing the unsubstituted thiasystem since 2,4-diaminothiazole reacts with **2** at C-5 in preference to the amino groups,<sup>6</sup> or the methyl-substituted system since 5-methyl-2,4-diaminothiazole is unstable as the free base. Attempts to liberate it from the hydrochloride gave 4-amino-2-hydroxy-5-methylthiazole instead.<sup>7</sup>

In the synthesis of **4b**, the free base of **1b**, which could not be isolated, was instead liber-

\* For definitions and nomenclature of cyclazines, cf. Refs. 9 and 10.



ated and reacted *in situ*. The same procedure was now successfully employed for the synthesis of **4c** and **4d**.

2,4-Diamino-5-methylthiazole was liberated from its hydrochloride with sodium bicarbonate and **2** was immediately added to the solution. The condensation product was then extracted and directly formylated without isolation. Ring closure and dehydration to **3c** occurred spontaneously under the formylating conditions.

2,4-Diamino-5-methylselenazole hydrohalide, **1d**, was prepared from  $\alpha$ -chloropropionitrile and selenourea in analogy with the method used for the thiazole analogue.<sup>7</sup> Attempts to purify **1d** by recrystallization led to decomposition. Therefore the crude product was used directly and **3d** was obtained in a procedure analogous to the one described above.

Decarboxylation of **3c** and **3d** was subsequently achieved by heating in diphenyl ether containing *p*-toluenesulfonic acid.

The synthetic route we have followed could also yield the isomeric systems **5c** and **5d** (R'=H). The NMR chemical shifts for H-8 in **4a** and **5a** (R'=CH<sub>3</sub>), whose structures were proved independently, were  $\delta$  5.49 and 4.64, respectively. In the spectra of the isolated methyl analogues the same proton signals appear at  $\delta$  5.40 and 5.51. We believe this to be sufficient evidence<sup>8</sup> to assign them the structures **4c** and **4d**.

The chemical shifts for the corresponding protons in **4a**, **4b**, **4c**, and **4d** are very close and  $J_{7,8}$  is 6 Hz in all compounds. This indicates that the phenyl group has only a small effect on the electron distribution and consequently on the aromaticity of the two cyclazine systems.

**Experimental. General.** NMR spectra were recorded with a Varian Model A-60 or a Bruker Model WH-270 spectrometer using TMS as internal reference. UV and visible spectra were measured in ethanol 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<sub>254</sub> (Merck) plates with ethyl acetate:meth-

anol, 5:1, as the developing solvent, and the spots were visualized with short-wave UV light and with iodine vapour. The cyclazines were obtained in low yields. Attempts to increase the yields by variation of molar ratios, reaction temperatures and reaction times were not successful as judged from thin-layer chromatography. A detailed study of the reaction conditions could possibly lead to better yields. This has, however, not been pursued since our main object was to synthesize these compounds in amounts sufficient for spectrometric investigations.

**8-Carboxy-4-methyl-5-thia-1,3,6-triazacycl-[3.2.3]azine, 3c.** A vigorously stirred solution of 2,4-diamino-5-methylthiazole hydrochloride (2.06 g; 8.00 mmol) in 100 ml of water was neutralized with sodium bicarbonate (0.67 g; 8.00 mmol), **2** (1.35 g; 8.00 mmol) was immediately added followed by 100 ml of ethanol. The solution was stirred for 1 h at room temperature. The ethanol was then evaporated under reduced pressure and the residue extracted with 3  $\times$  100 ml of ether. The combined extracts were dried (magnesium sulfate) and the ether was evaporated. The brown residue was dissolved in 40 ml of formic acid and 15 ml of acetic anhydride was added. The solution was kept at 90 °C for 3 h, cooled, and poured into 100 ml of ice water, neutralized with aqueous saturated sodium bicarbonate solution and extracted with 3  $\times$  75 ml of methylene chloride. The combined extracts were washed with water, dried (magnesium sulfate), and evaporated to dryness. The brown residue was chromatographed on silica gel using methylene chloride-ethyl acetate as the eluent. The fractions containing **3c** ( $R_F=0.40$ ) were recrystallized from anhydrous ethanol to give 110 mg (5%) of **3c** as brown needles, m.p. 191–192 °C. UV  $\lambda_{max}(\epsilon)$ : 646 (55), 588 (300), 536 (620), 501 (780), 469 (750), 391 (9100), 292 sh (3200), 279 sh (4700), and 251 nm (12 700). NMR (CDCl<sub>3</sub>):  $\delta$  1.31 (3 H) and 4.27 (2 H) [ester group], 2.03 (3 H, Me-4), 7.10 (1 H, H-2), 8.03 (1 H, H-7). MS: M<sup>+</sup> found 262.052  $\pm$  0.002; C<sub>11</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub><sup>34</sup>S requires 262.0524. (M+2)<sup>+</sup> found 264.049  $\pm$  0.002; C<sub>11</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub><sup>34</sup>S requires 264.0482, m/e

(relative intensity): 264 (5), 263 (10), 262 (73), 217 (18), 191 (12), 190 (100), 189 (21), 162 (8), 150 (7), 149 (6), 111 (5), 104 (6), 85 (13), 77 (12), 59 (23).  $m/2e$  (relative intensity): 108.5 (5.5), 94.5 (2).

**8-Carbethoxy-4-methyl-5-selena-1,3,6-triazacycl[3.2.3]azine, 3d.** To a stirred suspension of selenourea (2.46 g; 20.0 mmol) in 10 ml of anhydrous ethanol under nitrogen was added a solution of  $\alpha$ -chloropropionitrile (1.79 g; 20.0 mmol) in 20 ml of anhydrous ethanol and then sodium iodide (3.00 g; 20.0 mmol). The mixture was kept at 70 °C for 4 h and then at room temperature for 10 h. The ethanol was evaporated and the residue was dissolved in 100 ml of water, sodium bicarbonate (1.68 g; 20.0 mmol) was added, and then immediately **2** (3.38 g; 20.0 mmol) dissolved in 50 ml of ethanol. The reaction mixture was treated as described for **3c** and 60 mg (1 %) of **3d** ( $R_F = 0.40$ ) was obtained as brown needles, m.p. 163–164 °C. UV  $\lambda_{\max}(\epsilon)$ : 650 (70), 590 (370), 542 (750), 504 (920), 467 (970), 397 (7900), 290 sh (3100), 279 sh (5000), 248 sh (13200) and 236 nm (14 300). NMR ( $\text{CDCl}_3$ ):  $\delta$  1.28 (3 H) and 4.23 (2 H) [ester group], 2.10 (3 H, Me-4), 7.05 (1 H, H-2), 7.92 (1 H, H-7). MS:  $M^+$  found  $307.996 \pm 0.003$  and  $309.996 \pm 0.003$ ;  $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$   $^{78}\text{Se}$  requires 307.9977 and  $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$   $^{80}\text{Se}$  requires 309.9969.  $m/e$  (relative intensity): 312 (7), 311 (5), 310 (40), 309 (3), 308 (19), 307 (8), 306 (8), 240 (16), 239 (12), 238 (84), 237 (20), 236 (43), 235 (21), 234 (19), 182 (33), 158 (43), 149 (21), 137 (52), 110 (29), 95 (41), 86 (63), 84 (100), 77 (55).  $m/2e$  (relative intensity): 132.5 (2), 131.5 (1), 113.5 (1).

**Decarboxylation of 3c to 4c.** A suspension of **3c** (100 mg) in 5 ml of diphenyl ether was heated to 240 °C. At that temperature *p*-toluenesulfonic acid (200 mg) was added, the solution left for 25 min and then allowed to cool to room temperature. The dark solution was passed over a column of silica gel (50 g), and the diphenyl ether was washed out with petroleum (b.p. 60–85 °C). The coloured material was eluted with ethyl acetate–methanol. From these fractions, 15 mg (21 %) of **4c** ( $R_F = 0.27$ ), brown crystals with m.p. 145–146 °C, was isolated by preparative TLC, UV  $\lambda_{\max}(\epsilon)$ : 656 (90), 590 (390), 544 (690), 505 (730), 470 sh (590), 357 (6000), 293 (3500), 282 (4900), 257 (13 000), and 250 nm (13 500). NMR ( $\text{CDCl}_3$ ):  $\delta$  1.94 (3 H, Me-4), at 6.80 (1 H, H-2), 7.30 (1 H, H-7), 5.40 (1 H, H-8);  $J_{7,8} = 6$  Hz. MS:  $M^+$  found  $190.032 \pm 0.002$ ;  $\text{C}_8\text{H}_6\text{N}_4$   $^{32}\text{S}$  requires 190.0313. ( $M+2$ ) $^+$  found  $192.027 \pm 0.002$ ;  $\text{C}_8\text{H}_6\text{N}_4$   $^{34}\text{S}$  requires 192.0271.  $m/e$  (relative intensity): 192 (5), 191 (18), 190 (100), 189 (70), 162 (20), 157 (28), 111 (17), 110 (18), 85 (40), 70 (20), 59 (20), 52 (17).  $m/2e$  (relative intensity): 95.5 (1), 94.5 (0.5), 81.5 (1).

**Decarboxylation of 3d to 4d.** Compound **3d** (20 mg) was decarboxylated in 1 ml of diphenyl ether in the presence of *p*-toluene-

sulfonic acid (40 mg) at 240 °C and purified as described for **3c** to give 3 mg (19 %) of **4d** ( $R_F = 0.27$ ) as brown crystals m.p. 172–174 °C. UV  $\lambda_{\max}(\epsilon)$ : 663 (80), 603 (400), 551 (730), 510 (780), 475 (630), 378 (7400), 366 (7200), 292 (3600), 282 (4900), 244 (15 800), and 236 nm (16 300). NMR ( $\text{CDCl}_3$ ):  $\delta$  2.02 (3 H, Me-4), 6.79 (1 H, H-2), 7.25 (1 H, H-7), 5.51 (1 H, H-8)  $J_{7,8} = 6$  Hz. MS:  $M^+$  found  $235.976 \pm 0.003$  and  $237.975 \pm 0.003$ ;  $\text{C}_8\text{H}_6\text{N}_4$   $^{78}\text{Se}$  requires 235.9765 and  $\text{C}_8\text{H}_6\text{N}_4$   $^{80}\text{Se}$  requires 237.9757.  $m/e$  (relative intensity): 240 (19), 239 (17), 238 (100), 237 (40), 236 (50), 235 (35), 234 (25), 210 (11), 185 (17), 158 (30), 157 (14), 156 (12), 133 (26), 106 (14), 79 (14), 52 (28).  $m/2e$  (relative intensity): 119.5 (0.5), 117.5 (0.5), 105.5 (0.5).

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