HALOGENO-1,2,5-THIADIAZOLOPYRIDINES AND 1,2,5-SELENADIAZOLOPYRIDINES

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Abstract -- Chloro- and bromo-1,2,5-thiadiazolopyridines and 1,2,5-selenadiazolopyridines have been synthesized by condensation of appropriate diamines with thionyl chloride or selenious acid.

The preparation of 1,2,5-thiadiazoles and 1,2,5-selenadiazoles has been the subject of considerable interest from chemical and biological points of view, many derivatives of them being used as drugs[1-4], herbicides[5,6] or radioprotectants[7,8].

The present paper, a continuation of our former study[9,10] is dealing with 1,2,5-thia- and selenadiazolopyridines; some compounds of this type exhibit biological activity[11-16].

Halogeno-1,2,5-thia- and selenadiazolopyridines 1-5 have been synthesized from the appropriate o-diaminopyridines in the condensation reactions with thionyl chloride or selenious acid, as shown in the Scheme.

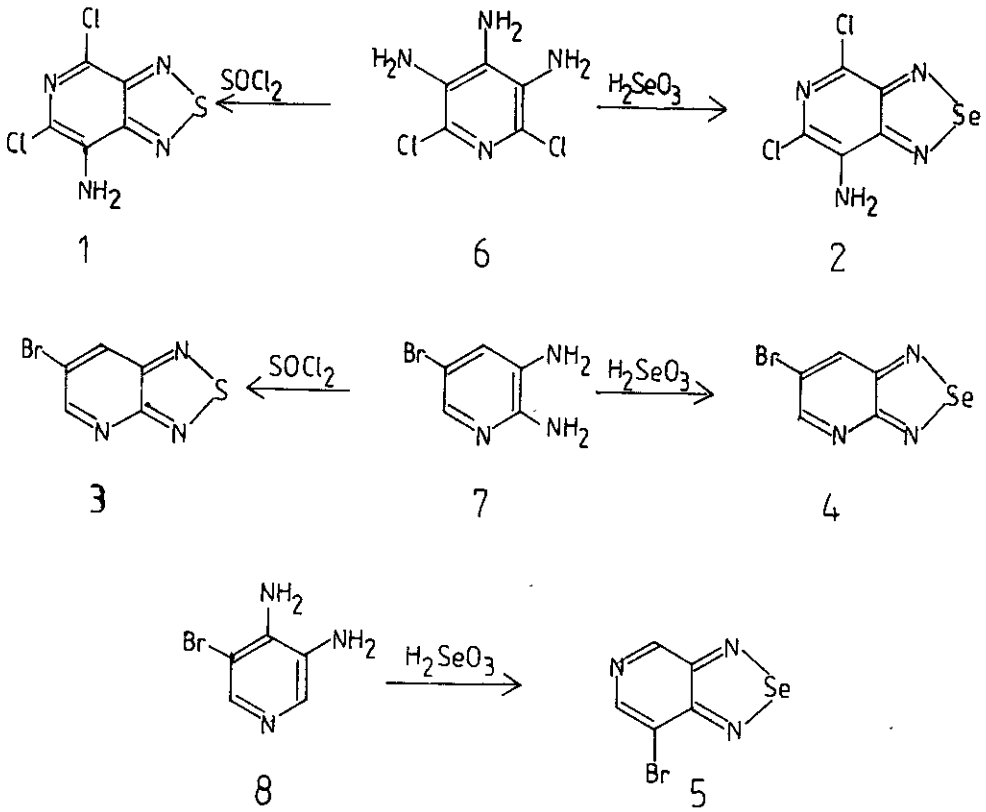
Attempts to prepare the thia analogue of 5 by the above procedure failed, only the complex mixture of products, impossible to separate, being obtained.

In ^{1}H nmr spectra, in lower field are H^5 signals of 3 and 4, for the deshielding influence of nitrogen and bromine atoms, and H^4 signals of 5; these assignements are in good agreement with the literature data[12,17].

The chlorine atoms of 1 and 2 do not undergo nucleophilic substitution, this fact being proved by the attempted hydrolysis and ammonolysis reactions, using acetic or hydrochloric acids at 100°, and ethanolic ammonia at 110°C, respectively.

Compounds 1-5 are soluble in polar (water, methanol, ethyl acetate, acetone) as well as in nonpolar (carbon tetrachloride, benzene, hexane, heptane) solvents.

The biological data of the synthesized substances will be reported elsewhere.



Scheme

The starting o-diaminopyridines 6-8 were synthesized by the following procedures: 6 was obtained from 4-aminopyridine, which was nitrated, and the formed 4-amino-3,5-dinitropyridine was reduced with stannous chloride[18].

Compound 7 was prepared from 4-aminopyridine by its bromination, followed by nitration and rearrangement of the resulting 2-bromo-5-aminopyridine, employing the procedure used for 2-amino-3-nitropyridine[19].

For the synthesis of 8, 4-aminopyridine was nitrated to give 4-nitraminopyridine[18], which was brominated under alkaline conditions; the improvement of this

procedure consists in the use of the Na salt of 4-nitraminopyridine instead of 4-nitraminopyridine[20]. The formed 3-bromo-4-nitraminopyridine was rearranged with sulfuric acid[21] to yield 3-bromo-4-amino-5-nitropyridine; its reduction with iron catalyzed by acetic acid, an application of the procedure described for 2-substituted 5-aminopyridines[22] resulted in 8.

When the above reduction was carried out with stannous chloride[21], 2-chloro-3,4-diamino-5-bromopyridine was obtained, however its reaction with selenious acid led to 4-chloro-7-bromo-1,2,5-selenadiazolo[3,4-c]pyridine, not stable enough to be purified.

EXPERIMANTAL

4,6-Dichloro-7-amino-1,2,5-thiadiazolo[3,4-c]pyridine (1) 2,6-Dichloro-3,4,5-triaminopyridine 6 (1.92g; 0.01 mole) was refluxed with thionyl chloride (88g; 0.75 mole) for five hours. The excess of thionyl chloride was removed under reduced pressure, and the residue was poured onto ice and neutralized with sodium bicarbonate. The formed precipitate was extracted with heptane and the extract condensed in vacuo.

Recrystallization from benzene or hexane gave 1.90 g (86%) of 4,6-dichloro-7-amino-1,2,5-thiadiazolo[3,4-c]pyridine (1) as red needles, mp 175-176°C; ir: 3375m, 3330m, 1600s, 1440s, 1365m, 1345w, 1210w, 1165w, 1080w, 980m, 875m, 845w, 790w, 500w; nmr: 6.90 (s, NH_2); anal. calcd for $C_5H_2N_4SCl_2$ (221.07): C, 27.16; H, 0.91; N, 25.35; Cl, 32.07; found: C, 27.05; H, 0.88; N, 25.20; Cl, 32.22[23].

4,6-Dichloro-7-amino-1,2,5-selenadiazolo[3,4-c]pyridine (2) 2,6-Dichloro-3,4,5-triaminopyridine 6 (1.92g; 0.01 mole) and selenium dioxide (2.22g; 0.02 mole) in water (100 ml) were allowed to stand under CO_2 atmosphere for seven days. The reaction mixture was neutralized with sodium bicarbonate, the crude product filtered off and recrystallized from water - diethylformamide (7:3) to give 2.32g (87%) of 4,6-dichloro-7-amino-1,2,5-selenadiazolo[3,4-c]pyridine (2) as red needles mp 188°C; ir: 3460w, 3380m, 3310m, 1600s, 1490w, 1450s, 1385w, 1355w, 1345s, 1210m, 1150w, 1085w, 960m, 795m, 765w, 740w, 445w; nmr: 6.62 (s, NH_2); anal. calcd for $C_5H_2N_4SeCl_2$ (267.97): C, 22.41; H, 0.75; N, 20.91; Cl, 26.46; found: C, 22.52; H, 0.69;

N, 20.75; Cl, 26.54.

6-Bromo-1,2,5-thiadiazolo[3,4-c]pyridine (3) 2,3-Diamino-5-bromopyridine 7 (1.88g; 0.01 mole) and thionyl chloride (88g; 0.75 mole) were worked up as for 1. As the recrystallization from chloroform afforded only tarry substances, the crude product was purified by preparative tlc, using chloroform as the eluent, and then recrystallized from hexane to yield 1.17g (54%) of 6-bromo-1,2,5-thiadiazolo[3,4-b]pyridine (3) as pale-yellow needles, mp 139.5-140°C; ir: 3030s, 1480m, 1455m, 1380w, 1340m, 1320w, 1240s, 1230m, 1045s, 1025w, 945s, 915m, 860m, 845w, 815s, 785m, 655m, 585m, 435m; nmr: 9.22 (d, J=2Hz, H^5), 8.82 (d, J=2Hz, H^7): anal. calcd for $C_5H_2N_3SBr$ (216.07): C, 27.79; H, 0.93; N, 19.45; Br, 36.98; found: C, 27.69; H, 0.85:, N, 19.46; Br, 36.72.

6-Bromo-1,2,5-selenadiazolo[3,4-b]pyridine (4) A mixture of 2,3-diamino-5-bromopyridine 7 (1.88g; 0.01 mole) and selenium dioxide (2.22g; 0.02 mole) was worked up as in the case of 2, affording the crude material, which was extracted with chloroform. The extract was concentrated to give 1.80g (68%) of 6-bromo-1,2,5-selenadiazolo[3,4-b]pyridine 4 as yellow needles, mp 180.5°C; ir: 3035w, 1475s, 1330w, 1245s, 1210m, 1045s, 935s, 910m, 830w, 780m, 750s, 730m, 575m, 480w, 385m; nmr: 9.22 (d, J=2Hz, H^5), 8.84 (d, J=2Hz, H^7); anal. calcd for $C_5H_2N_3SeBr$ (262.97): C, 22.84; H, 0.77; N, 15.98; Br, 30.39; found: C, 22.78; H, 0.82; N, 15.91; Br, 30.28.

7-Bromo-1,2,5-selenadiazolo[3,4-c]pyridine (5) A mixture of 3,4-diamino-5-bromopyridine 8 (1.88g; 0.01 mole) and selenium dioxide (2.22g; 0.02 mole) was worked up as for 2, giving the crude product, which was extracted with carbon tetrachloride, and the extract evaporated. The preparative tlc with methylene chloride as eluent, yielded 1.61g (61%) of 7-bromo-1,2,5-selenadiazolo[3,4-c]pyridine (5) as yellow needles, mp 205.5°C; ir: 1565m, 1470w, 1400w, 1320m, 1270s, 1200m, 1070w, 930s, 890m, 870s, 775m, 760m, 725s, 670w, 575m, 545s, 435s; nmr: 9.50 (s, H^4), 8.80 (s, H^6); anal. calcd for $C_5H_2N_3SeBr$ (262.97): C, 22.84; H, 0.77; N, 15.98; Br, 30.39; found: C, 22.95; H, 0.80; N, 16.04; Br, 30.31.

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23. All melting points, determined on Boetius apparatus, are uncorrected; ir spectra (ν, cm^{-1}) were recorded in KBr discs, and ^1H nmr spectra (δ, ppm) in DMSO, with HMDS as external standard. For the preparative tlc silica gel Merck plates PSC, 60F - 254 were used.

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