RESEARCHES ON 2,1,3-THIA-AND SELENADIAZOLES

XLIV. Chloromethylation of 4-and 5-Chlorobenzo-2,1,3-Thia-and Selenadiazoles*

V. G. Pesin and E. K. D'yachenko

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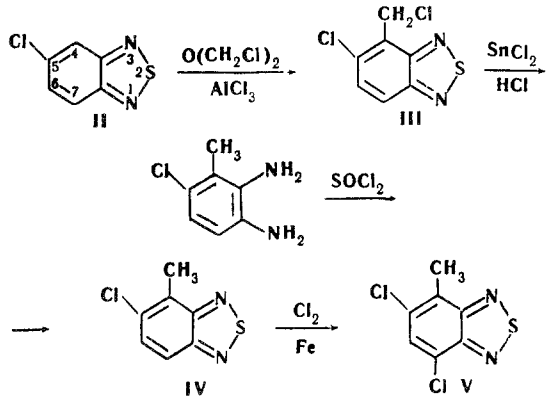
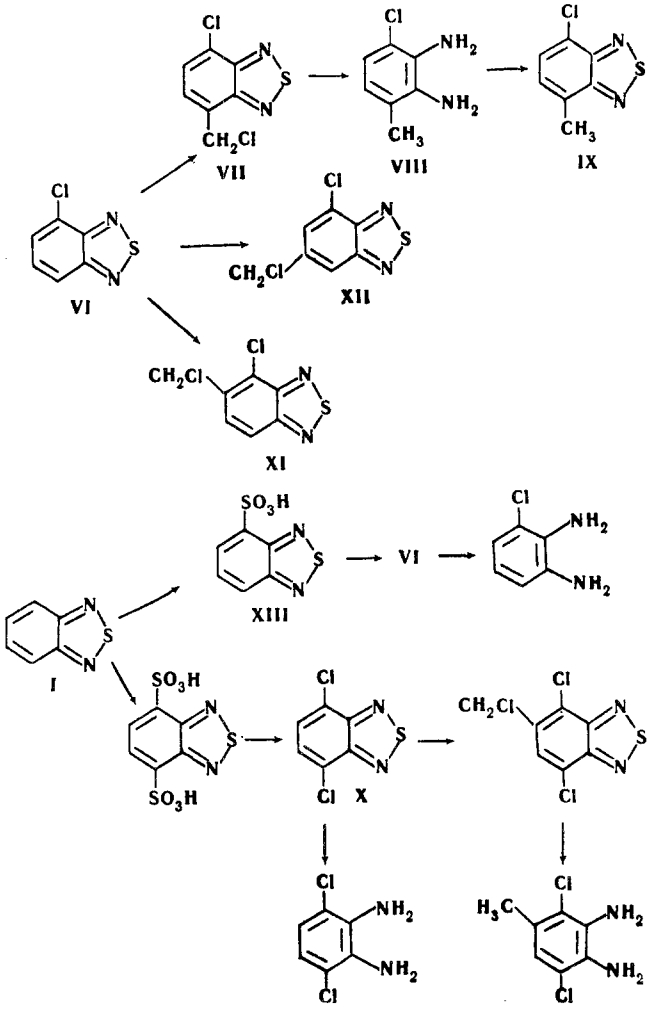
Chloromethylation of 4- and 5-chlorobenzo-2, 1, 3-thiadiazoles with dichlorodimethyl ether in the presence of anhydrous aluminum chloride gives 4-chloro-7-chloromethyl- and 5-chloro-4-chloromethylbenzo-2, 1, 3-thiadiazoles respectively. Reductive scission followed by treatment with thionyl chloride converts them to 4-chloro-7-methyl- and 5-chloro-4-methylbenzo-2, 1, 3-thiadiazoles; Chlorination of the latter gives 4-methyl-5, 7-dichlorobenzo-2, 1, 3-thiadiazole. Replacement of the chlorine in the chloromethyl groups gives 4-chloro-7-hydrosymethyl-, 5-chloro-4-hydroxymethyl-, 4-chloro-7-cyanomethyl-, 4-chloro-7-carboxymethyl-, 5-chloro-4-carboxymethylbenzo-2, 1, 3-thiadiazoles. Reductive scission of 4-chlorobenzo-2, 1, 3-thidiazole followed by treatment with sodium selenite gives 4-chlorobenzo-2, 1, 3-selenadiazole.

It was previously shown [2,3] that benzo-2,1,3-thiadiazole (I) and its 4-and 5-methyl derivatives are chloromethylated by dichlorodimethyl ether in the presence of chlorosulfonic acid or anhydrous aluminum chloride at 70°–80°. The present paper gives the results of an investigation of that reaction as applied to 4-and 5-chlorobenzo-2,1,3-thia-and selenadiazoles. The latter do not give chloromethyl derivatives when treated with dichlorodimethyl ether in the presence of chlorosulfonic acid under the conditions investigated by us [2, 3].

Heating 5-chlorobenzo-2,1,3-thiadiazole (II) with dichlorodimethyl ether at 100° in the presence of anhydrous aluminum chloride gives 5-chloro-4-chloromethylbenzo-2,1,3-thiadiazole (III). Its structure is shown by reductive scission, followed by treatment of the resultant o-diamine with thionyl chloride, to give 5-chloro-4-methylbenzo-2,1,3-thiadiazole (IV). Chlorination of the latter converts it to 4-methyl-5,7-dichlorobenzo-2,1,3-thiadiazole (V) [4].



Under like conditions 4-chlorobenzo-2,1,3-thiadiazole (VI) gives 4-chloro-7-chloromethylbenzo-2,1,3-thiadiazole (VIII). The structure of the latter is shown by its product reductive scission followed by treatment of the resultant 4-chloro-2,3 diaminotoluene (VIII) with thionyl chloride: 4-chloro-7-methylbenzo-2,1,3-thiadiazole (IX) [4,5].

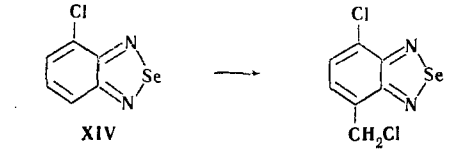


Chromatography of the products of reductive scission of VII showed that in addition to VIII there are formed 3-chloro-1,2-diaminobenzene, corresponding to the starting VI; 1,4-dichloro-2,3-

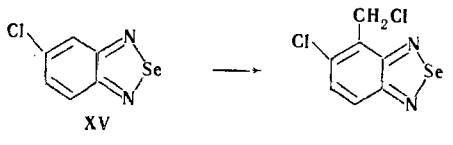
*Part XLIII see [1].

diaminobenzene, corresponding to 4,7-dichlorobenzo-2,1,3-thiadiazole (X), and a further substance (*a*) whose structure has not been established. Substance *a* is not a product of reductive scission of two other isomers: 4-chloro-5-chloromethyl- (XI) and 4-chloro-6-chloromethylbenzo-2,1,3-thiadiazole* (XII) which might arise by chloromethylation of VI. Moreover substance *a* is not identical with 2,5-dichloro-3,4-diaminotoluene, which might arise by reductive scission of 5-chloromethyl-4,7-dichlorobenzo-2,1,3-thiadiazole. The formation of the latter might have been expected by chloromethylation of 4,7-dichlorobenzo-2,1,3-thiadiazole (X), detected among the products of chloromethylation of VI. The dichloride X is probably a mixture with starting VI. The latter can be synthesized by chlorinating 4-sulfobenz-2,1,3-thiadiazole (XIII) [6], prepared by sulfonating I [7]. Hence it follows that when I is sulfonated, the XIII formed is accompanied by the side reaction product 4,7-disulfobenzo-2,1,3-thiadiazole.

4-and 5-chlorobenzo-2,1,3-selenadiazoles (XIV, XV) are not so readily chloromethylated as their thio analogs under identical conditions, side reaction predominating, and giving inorganic compounds or substances insoluble in water, mixtures which it is difficult to separate. Consequently the chloromethylation products XIV and XV were submitted to reductive scission, and the resultant mixtures of o-diamines investigated chromatographically. Comparison of the chromatograms of the o-diamines formed by reductive scission of chloromethylation products XIV and XV with those of the thio analogs, shows that chloromethylation proceeds in a qualitatively identical way in both cases.



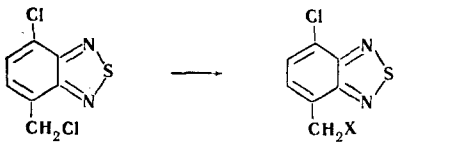
XIV



XV

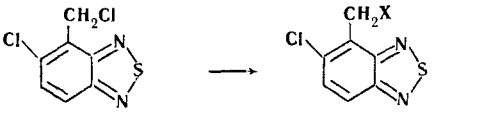
The chlorine of the chloromethyl groups in III and VII is readily replaced by other groups, making it possible to prepare 4-chloro-7-hydroxymethyl- (XVI), 5-chloro-4-hydroxymethyl-(XVII), 4-chloro-7-cyanomethyl-(XVIII), 4-chloro-7-carboxymethyl-(XIX), and 5-chloro-4-carboxy-methylbenzo-2,1,3-thiadiazole (XX).

*The assumption that the products of reductive scission do not contain the o-diamine corresponding to XII, is a consequence of the more probable isomer XI not being found in the chloromethylation products of VI.



VII

XVI : X = OH
XVIII : X = CN
XIX : X = COOH



III

XVII : X = OH
XX : X = COOH

EXPERIMENTAL

5-Chlorobenzo-2, 1, 3-thiadiazole (II) was prepared as described in [8], and 5-chlorobenzo-2, 1, 3-selenadiazole (XV) as described in [9].

4-Chloro-7-chloromethylbenzo-2, 1, 3-thiadiazole (VII). 3.4 g (0.02 mole) 4-chlorobenzo-2, 1, 3-thiadiazole [6] was added to a solution of 10.6 g (0.08 mole) anhydrous $AlCl_3$ in 4.3 g (0.04 mole) dichlorodimethyl ether [11], the mixture heated for 1 hr at 100°, with stirring, a condenser set for downward distillation being used. About 3 ml liquid distilled off (temperature of vapors 33–34°),* the residue cooled, and poured into water, after which the precipitate was filtered off. Yield 4.17 g (95%), mp 104–105° (ex EtOH). Found: Cl 32.29; 32.40; S 14.13; 14.55%. Calculated for $C_7H_4Cl_2N_2S$: Cl 32.4; S 14.6%.

The liquid which came off from the reaction mixture was insoluble in water, but after some time it decomposed, the hydrolysis product was acid to Congo Red, and gave the silver mirror reaction.

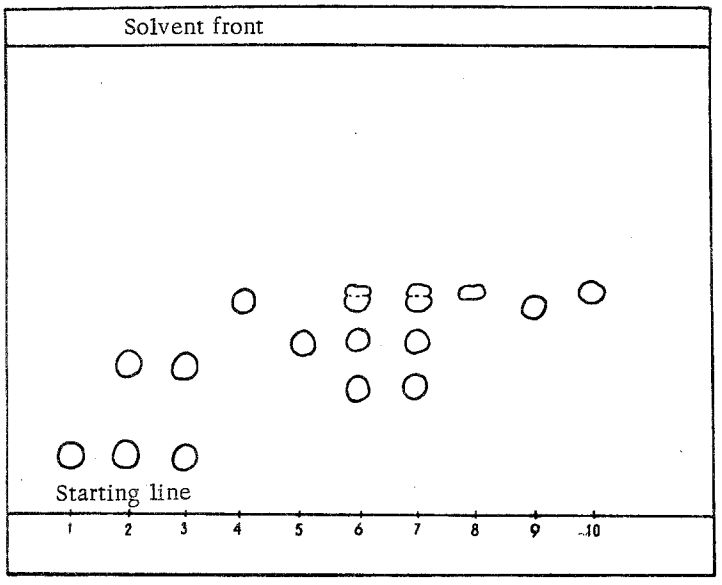
5-Chloro-4-chloromethylbenzo-2, 1, 3-thiadiazole (III). 3.4 g (0.02 mole) 5-chlorobenzo-2, 1, 3-thiadiazole [8] gave, similarly to VII, 4.05 g (92%) crystals, mp 109–110° (ex dilute AcOH). Found: Cl 32.02; 32.29; S 14.13; 14.14%. Calculated for $C_7H_4Cl_2N_2S$: Cl 32.4; S 14.6%.

Reactions of 4- and 5-chlorobenzo-2, 1, 3-selenadiazole with dichlorodimethyl ether a) 1.07 g (0.005 mole) 4-chlorobenzo-2, 1, 3-selenadiazole (XIV) was added in portions to a solution of 2.67 g (0.02 mole) anhydrous $AlCl_3$ in 1.15 g (0.01 mole) dichlorodimethyl ether. The mixture was heated and stirred for 1 hr at 120°, using a downward sloping condenser. About 1 ml liquid distilled over. After cooling the reaction products were diluted with water, and filtered. The solid was suspended in 20 ml HCl (d 1.19), 6 g $SnCl_2$ added, and the whole refluxed for 2 hr. The products were cooled, treated with excess 25% NaOH solution, extracted with benzene, the solvent removed and the residue chromatographed.

A mixture 1.09 g 5-chlorobenzo-2, 13-selenadiazole, 1.15 g dichlorodimethyl ether, and 2.67 g anhydrous $AlCl_3$ was heated and stirred at 120°, then worked up as described above. The diamine isolated was chromatographed.

4-Chloro-7-methylbenzo-2, 1, 3-thiadiazole (IX). 5 g 4-chloro-7-chloromethylbenzo-2, 1, 3-thiadiazole (VII), 50 g $SnCl_2$, and 150 ml concentrated HCl were refluxed together for 3 hr, the products cooled, poured into excess 25% NaOH, with cooling, and the mixture extracted with benzene. Removal of the solvent gave 0.7 g (19.6%) of an oily liquid, which was dissolved in 30 ml dry pyridine, and 1 ml $SOCl_2$ added with stirring, after which the mixture was held at 50° for 1 hr, the products cooled, neutralized with HCl, diluted with water, and the precipitate filtered off,

*Under investigation.



1) 4-Chloro-1, 2-diaminobenzene, R_f 0.12; 2) products of reductive scission after chloromethylating 5-chlorobenzo-2,13-selenadiazole, R_f 0.12; 0.31; 3) reductive scission products after chloromethylation of 5-chlorobenzo-2,1,3-thiadiazole, R_f 0.12; 0.31; 4) 4-chloro-2,3-diaminotoluene, R_f 0.44; 5) 3-chloro-1,2-diaminobenzene, R_f 0.44; 5) 3-chloro-1,2-diaminobenzene, R_f 0.35; 6) reductive scission products after chloromethylation of 4-chlorobenzo-2, 1, 3-selenadiazole, R_f 0.26; 0.35; 0.44; 0.45; 7) products of reductive scission after chloromethylating 4-chlorobenz-2, 1, 3-thiadiazole, R_f 0.26; 0.35; 0.44; 0.45; 8) 1, 4-dichloro-2, 3-diaminobenzene, R_f 0.45 (bright spot in UV ligh.); 9) 2-chloro-3, 4-diaminotoluene, R_f 0.45 (dark spot in UV light).

Note. Spots 6 and 7, R_f 0.44 and 0.45, are sharply separated in a 2-dimensional chromatogram using the same system.

white needles, mp 135.5-137° (ex MeOH). Undepressed mixed mp with IX prepared as described in [4, 5].

5-Chloro-4-methylbenzo-2, 1, 3-thiadiazole (IV). 90 g $SnCl_2$ was added in portions to a suspension of 9 g III in 250 ml concentrated HCl, the mixture refluxed for 3 hr, cooled, poured with cooling into excess 25% NaOH, and the products extracted with benzene, or $CHCl_3$. Removal of the solvent gave 3.1 g oily liquid, which was dissolved in 50 ml dry pyridine, 4.1 ml $SOCl_2$ added, the whole stirred for 1 hr at 40°, the products neutralized with HCl, diluted with water, and the precipitate filtered off. Yield 2.5 g (68.3%), compound mp 74-75° (ex aqueous EtOH). Found: Cl 19.01; 19.22; S 17.36; 17.63%. Calculated for $C_7H_5ClN_2S$: Cl 19.2; S 17.6%.

4-Methyl-5, 7-dichlorobenzo-2, 1, 3-thiadiazole (V). 0.1 g reduced Fe was added to a melt of 1 g IV (100°), the whole well stirred, and dry chlorine passed in for 20 min; the products were cooled, and white crystals isolated, mp 113-115°. Undepressed mixed mp with 4-methyl-5, 7-dichlorobenzo-2, 1, 3-thiadiazole [4, 5].

4-Chloro-7-carboxymethylbenzo-2, 1, 3-thiadiazole (XVI). A mixture of 0.5 g VII, 0.5 g K_2CO_3, and 17 ml water was refluxed for 4 hr, the products cooled, the precipitate filtered off, when 0.1 g (37%) white needles mp 130° (ex water) were obtained. Found: Cl 18.08; 18.16; S 15.75; 15.68%. Calculated for $C_7H_5ClN_2OS$: Cl 17.7; S 15.95%.

5-Chloro-4-hydroxymethylbenzo-2, 1, 3-thiadiazole (XVII). A mixture of 2 g III, 2 g K_2CO_3, and 25 ml water was refluxed for 8 hr, cooled, the precipitate filtered off, when 0.1 g (5.5%) white needles, mp 100-101° (ex water) was obtained. Found: Cl 18.00; 18.01; S 16.29; 16.07%. Calculated for $C_7H_5ClN_2OS$; Cl 17.7; S 15.95%.

5-Chloro-4-carboxymethylbenzo-2, 1, 3-thiadiazole (XX). A mixture of 1.75 g III, 0.8 g KCN, 25 ml EtOH, and 5 ml water was refluxed and stirred for 7 hr filtered hot, cooled, the black precipitate (0.58 g) filtered off, dissolved in 20 ml AcOH + 10 ml EtOH, and 5 ml water was refluxed and stirred for 7 hr filtered hot, cooled, the black precipitate (0.58 g) filtered off, dissolved in 20 ml AcOH + 10 ml HCl, refluxed for 4 hr, cooled, and the crystals filtered off, yield 0.47 g (21%), mp 176-178° (ex EtOH). Found: Cl 15.58; 15.67; S 14.10; 13.82%. Calculated for $C_8H_5ClN_2SO_2$: Cl 15.55; S 13.95%.

4-Chloro-7-cyanomethylbenzo-2, 1, 3-thiadiazole (XVIII). A mixture of 0.55 g VII, 0.2 g KCN, 1.5 ml water, and 1.5 ml EtOH was refluxed for 2 hr, cooled, the precipitate filtered off, giving 0.4 g compound mp 146° (ex dilute AcOH, then from aqueous EtOH). Found: Cl 16.95; 17.16; S 15.29; 15,13%. Calculated for $C_8H_4ClN_3S$: Cl 16.92; S 15.30%.

4-Chloro-7-carboxymethylbenzo-2, 1, 3-thiadiazole (XIX). A mixture of 0.85 g XVIII, 20 ml AcOH, and 10 ml HCl (d 1.19) was refluxed for 5 hr, cooled, the precipitate filtered off. Yield 0.69 g (74%), mp 190° (ex EtOH). Found: Cl 15.53; 16.01; S 13.53; 14.00%. Calculated for $C_8H_5ClN_2O_2S$: Cl 15.53; S 13.95%.

4-Chlorobenzo-2, 1, 3-selenaidiazole (XIV). 60 g $SnCl_2$ was added in portions to a suspension of 10 g VI in 120 ml HCl (d 1.19), and the mixture refluxed for 3 hr. The products were cooled, poured into excess 30% NaOH, the mixture extracted with ether, and the solvent then removed, leaving an oil, which was treated with HCl, to give a precipitate (6.8 g) which was dissolved in hot water. 5.5 g Na selenite dissolved in water was added to this solution, and the whole cooled, to give a compound mp 158-160°.

Chromatography of the o-diamines obtained by reductive scission of chloromethyl derivatives II, VI, XIV, and XV was carried out, using TLC on alumina (Brockman grade II activity) and a CCl_4-EtOH 10:1 system, the visualizer being iodine vapor.

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Leningrad Chemical and Pharmaceutical Institute