STUDIES IN THE FIELD OF 2, 1, 3-THIADIAZOLE AND 2, 1, 3-SELENADIAZOLE

XLIX.* The Chloromethylation of Benzo-2, 1, 3-Thiadiazole

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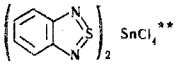
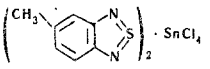
Benzo-2, 1, 3-thiadiazole (I) undergoes chloromethylation with dichlorodimethyl ether in the presence of anhydrous aluminum chloride with the predominant formation of 4, 7-di(chloromethyl) benzo-2, 1, 3-thiadiazole (II). Bases and pseudobases (paraformaldehyde, hexamethylenetetramine, dimethylformamide) exert an inhibiting influence on this reaction. In the presence of these substances, a mixture of compound II and 4-(chloromethyl) benzo-2, 1, 3-thiadiazole (III) is formed, or else no reaction takes place. The structures of compounds II and III has been shown by their reductive decomposition to o-diamines described in the literature. The high reactivity of the chlorine in the chloromethyl group has enabled various new derivatives of benzo-2, 1, 3-thiadiazole to be obtained by its replacement with hydroxy, thiocyanato, di(β-hydroxyethyl) amino, di(β-chloroethyl) amino, formyl, and carboxy groups.

The present paper gives the results of a study of the chloromethylation reaction of benzo-2, 1, 3-thiadiazole (I). When this compound is chlorinated under the conditions described for aromatic or heterocyclic compounds [1], either substances containing no chlorine are formed or no reaction takes place (the starting materials being recovered). When the reaction with dichlorodimethyl ether is carried out in the presence of anhydrous stannic chloride, a complex compound corresponding to the following formula, is formed.



(5-Methylbenzo-2, 1, 3-thiadiazole behaves analogously under these conditions, forming the complex compound



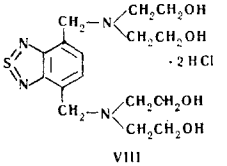
With anhydrous aluminum chloride, the main product is 4, 7-di(chloromethyl) benzo-2, 1, 3-thiadiazole (II). This compound is the main product both when the reaction is carried out with equimolecular amounts of the starting materials and when a twofold excess of I is used. Thus, the chloromethylation of I under these conditions takes place similarly to its chlorination in the presence of iron [2], where the main product is 4, 7-dichlorobenzo-2, 1, 3-thiadiazole. This can be regarded as a proof of the similarity of the mechanisms of the chloromethylation and the chlorination of the heterocycle I.

The chloromethylation reaction of I is affected by the presence of certain bases or pseudobases (hexamethylenetetramine, dimethylformamide, paraformaldehyde). In the presence of a very small amount of paraformaldehyde (contained as an impurity in the dichlorodimethyl ether obtained by the Organic Syntheses method [3]) the main product is compound II. When the amount of paraformaldehyde is large (as is the case when the dichlorodimethyl ether is obtained by the method of Bala et al. [4]), a mixture of II and 4-(chloromethyl) benzo-2, 1, 3-thiadiazole (III) is obtained. When the amount of the bases mentioned is sufficiently large, no chloromethylation takes place. Consequently, electron donating substances have an inhibiting action on this reaction. The ratio of compounds II and III in the mixture of chloromethylation products depends on the amount and strength of the base. Numerous experiments (varying the amounts of dichlorodimethyl ether, anhydrous aluminum chloride, paraformaldehyde, and hexamethylenetetramine, and also the temperature and time of the reaction) with the object of elucidating the conditions for the predominant formation of compound III proved unsuccessful. The considerable influence of the factors mentioned on the chloromethylation of certain compounds is recorded in the literature [5].

On the other hand, another reason for the lack of success is that the experiments were carried out with dichlorodimethyl ether contaminated with an unknown amount of paraformaldehyde. (We have found no information in the literature concerning the quantitative determination of paraformaldehyde as an impurity in dichlorodimethyl ether or a method of purifying the latter.)

The structure of substances II and III was shown by their reductive decomposition to 2, 3-diamino-1, 4-dimethylbenzene (IV) and 2, 3-diaminotoluene (V), respectively. The diamines IV and V were identified by chromatography on a thin layer of alumina in the presence of reference samples [6].

The chlorine in compound II is highly reactive. The reaction of II with potassium carbonate and potassium thiocyanate gave 4, 7-di(hydroxymethol)-and 4, 7-di(thiocyanatomethyl) benzo-2, 1, 3-thiadiazoles (VI and VII), respectively. With diethanolamine, 4, 7-bis[di(β-hydroxyethyl) aminomethyl]-benzo-2, 1, 3-thiadiazole was produced in the form of the dihydrochloride (VIII).

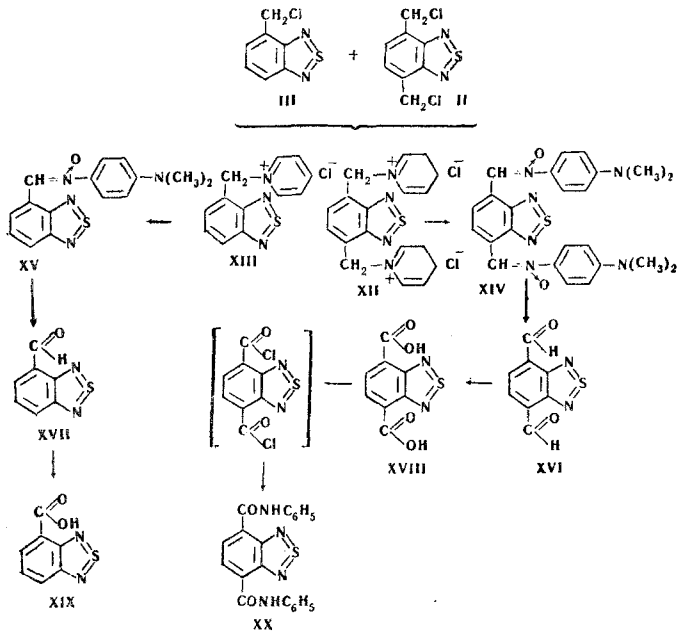


VIII

The action of thionyl chloride on VIII gave the hydrochloride of 4, 7-bis[di(β-chloroethyl) aminomethyl] benzo-2, 1, 3-thiadiazole (IX).

*For communication XLVIII, see [11].

Compound III was isolated from a mixture of II and III in the following way. The reaction of the latter with potassium carbonate gave a mixture of 4, 7-di(hydroxymethyl)- and 4-hydroxymethylbenzo-2, 1, 3-thiadiazoles (X and XI, respectively). When this mixture was extracted with chloroform, substance XI was isolated and with thionyl chloride this re-formed compound III. The separation of the mixture of compounds II and III was also effected by converting them into the di- and monopyridinium salts (XII and XIII, respectively), dissolving the mixture of salts in ethanol, and then adding acetone, whereupon the salt XII separated in the form of a precipitate while salt XIII remained in the filtrate. Using a published method [7, 8], the salts XII and XIII were converted by the action of p-nitrosodimethylaniline in the presence of piperidine or aqueous alkali into the corresponding nitrones XIV and XV, the acid hydrolysis of which gave the aldehydes XVI and XVII. The latter were oxidized by a known method to the acids XVIII and XIX respectively. The dicarboxylic acid XVIII was converted into the dianilide XX.



EXPERIMENTAL

Starting materials. The dichlorodimethyl ether was obtained by two methods: 1) by the reaction of paraformaldehyde with aluminum chloride in the presence of concentrated sulfuric acid [4], this product containing a considerable amount of paraformaldehyde as impurity; and 2) by the reaction of paraformaldehyde with hydrochloric acid in the presence of chlorosulfonic acid [3]. In this case, when the reaction was carried out at 8°–10° C the amount of paraformaldehyde in the product was very small; at 0°–5° C the paraformaldehyde content was approximately the same as in the use of method 1. It was impossible to obtain large amounts of dichlorodimethyl ether uncontaminated with paraformaldehyde by these methods.

The benzo-2, 1, 3-thiadiazole (I) was obtained by the method of Pesin et al. [9].

4, 7-Di(chloromethyl)benzo-2, 1, 3-thiadiazole (III). Twenty grams (0.15 mole) of I was added in portions to a solution of 50 g (0.38 mole) of anhydrous aluminum chloride in 50 ml of dichlorodimethyl ether [3]. The mixture was heated with stirring at 70°–75° C for 8 hr and was left overnight and poured onto ice. The precipitate that separated was filtered off and washed with water and then with ethanol. This gave 25.9 g (76%) of white needles with mp 119°–120° C from ethanol. Found, %: Cl 30.99; 31.04; S 13.69; 13.58. Calculated for $C_8H_6Cl_2N_2S$, %: Cl 30.43; S 13.75.

Mixture of 4-(chloromethyl)- and 4, 7-di(chloromethyl)benzo-2, 1, 3-thiadiazoles (III and II). Thirty grams (0.22 mole) of I was added in portions to a solution of 75 g (0.56 mole) of anhydrous aluminum chloride in 50 ml of dichlorodimethyl ether [4]. The reaction mixture was heated at 70°–75° C for 8 hr, left overnight and poured onto ice. The precipitate that separated out was filtered off and washed with water. Yield 30–45 g, mp 57°–68° C.

4-(Chloromethyl)benzo-2, 1, 3-thiadiazole (III). a) A mixture of 2 g (0.015 mole) of I, 5 g (0.038 mole) of anhydrous aluminum chloride, 4 ml of dichlorodimethyl ether [3], and 0.8 g of paraformaldehyde (or 0.5 g of hexamethylenetetramine) was heated with stirring at 100° C for 2 hr (when 1 g of paraformaldehyde or 0.8 g of hexamethylenetetramine was used or when the temperature was lowered to 75° C the reaction did not take place and the starting materials could be recovered), and then it was left overnight and poured onto ice. The precipitate that separated was filtered off and washed with water; mp 65°–67° C. After crystallization from ethanol, mp 77°–78° C. Found, %: Cl 19.31; 19.01; S 17.18; 16.95. Calculated for $C_7H_5ClN_2S$, %: Cl 19.23; S 17.34.

b) A mixture of 2.4 g (0.018 mole) of I, 6 g (0.045 mole) of anhydrous aluminum chloride, and 4.5 g of dichlorodimethyl ether [4] was heated with stirring at 60°–65° C for 3.5 hr, left overnight, and poured onto ice, and the crystals that separated out were filtered off and washed with water and then with ethanol, mp 35°–37° C. After two recrystallizations from ethanol, mp 77°–78° C.

c) 0.5 g of a mixture of compounds II and III, 0.5 g of potassium carbonate, and 50 ml of water were boiled for 4 hr. The cooled solution was extracted with benzene (or chloroform). After the extract had been dried, the solvent was distilled off. This yielded 0.22 g of a substance with mp 68°–69° C (from water), giving no depression of the melting point with 4-(hydroxymethyl)-benzo-2, 1, 3-thiadiazole (XI) [10]. A solution of 0.2 g of compound XI in 3 ml of thionyl chloride was boiled for 1 hr and then the thionyl chloride was distilled off in vacuum to dryness and the residue (0.22 g) was crystallized from ethanol, mp 77°–78° C.

Chromatography of the decomposition products of compounds II and III and mixtures of them. Twenty grams (0.09 mole) of stannic chloride was added in portions to a suspension of 3 g (0.013 mole) of 4, 7-di(chloromethyl)-benzo-2, 1, 3-thiadiazole (II) in 50 ml of hydrochloric acid (d 1.19), and the mixture was heated in the boiling water bath for 3 hr; then it was cooled and neutralized with a solution of sodium hydroxide, after which the precipitate was filtered off and the filtrate was extracted with benzene. The extract was dried with potassium carbonate and the solvent was distilled off. The residue was chromatographed on a thin layer of alumina (Brockmann activity II) in the carbon tetrachloride—ethanol (10:1) system in the presence of reference samples. The spots were revealed by means of the absorption of iodine vapor by the amines. A single spot with R_f 0.50 was formed. The R_f values of the reference samples were as follows: 0.50 for 2, 3-diamino-1, 4-dimethylbenzene; 0.43 for 3, 4-diamino-1, 2-dimethylbenzene; 0.36 for 4, 5-diamino-1, 2-dimethylbenzene; 0.41 for 2, 3-diaminotoluene; and 0.31 for 3, 4-diaminotoluene. When the product of the reduction of 4-(chloromethyl)-benzo-2, 1, 3-thiadiazole (III) was chromatographed, only one spot with R_f 0.41 was found. A chromatogram of the products of the reduction of a mixture of compounds II and III had two spots with R_f 0.50 and 0.41.

4, 7-Di(thiocyanatomethyl)benzo-2, 1, 3-thiadiazole (VII). A mixture of 1 g (4.3 mM) of 4, 7-di(chloromethyl)benzo-2, 1, 3-thiadiazole (II), 0.8 g (8.3 mM) of potassium thiocyanate, 45 ml of acetone, and 20 ml of water was boiled for 2.5 hr and was then cooled. The crystals that had deposited after three days were filtered off, mp 160°–162° C (from isobutanol). Found, % S 34.19; 33.84. Calculated for $C_{16}H_6N_4S_3$, %: S 34.55.

4, 7-Di(hydroxymethyl)benzo-2, 1, 3-thiadiazole (VI). A mixture of 0.5 g (2.1 mM) of II, 0.5 g (3.6 mM) of potassium carbonate, and

9.5 ml of water was boiled with stirring until the solid matter had dissolved completely. The crystals that separated on cooling were filtered off and washed with water. This gave 0.2 g of white needles with mp 120° C (from water). Found, %: N 14.8; 14.28; S 16.57; 1612. Calculated for $C_8H_8N_2O_2S$, %: N 14.28; S 16.31.

Dihydrochloride of 4, 7-bis[di(β-hydroxyethyl) aminomethyl] benzo-2, 1, 3-thiadiazole (VIII). A mixture of 3 g (13 mM) of II, 4 g (29 mM) of anhydrous potassium carbonate, 3.86 g (37 mM) of diethanolamine, and 95 ml of dimethylformamide was stirred at room temperature for 25–30 hr. The solid matter was filtered off and the filtrate was evaporated. The residue was dissolved in ethanol and treated with a current of dry hydrogen chloride. This gave white crystals with mp 210° C (from ethanol). Found, %: Cl 16.28; 16.24; S 7.18; 7.43. Calculated for $C_{16}H_{26}N_4O_4S \cdot 2HCl$, %: Cl 16.00; S 7.25.

4, 7-Bis[Di(β-chloroethyl) aminomethyl] benzo-2, 1, 3-thiadiazole (IX). A solution of 1.5 g of VIII in 30 ml of thionyl chloride was kept at room temperature for 24 hr and was then boiled for 2 hr. The thionyl chloride was distilled off in vacuum and the residue was washed with acetone, dissolved in hot absolute ethanol, and precipitated with dry acetone. This gave white crystals with mp 154°–156° C. Found: %: Cl 37.28; 37.55; S 6.85; 6.86. Calculated for $C_{16}H_{22}Cl_4N_4S \cdot HCl$, %: Cl 36.92; S 6.66.

Complex of benzo-2, 1, 3-thiadiazole (I) with stannic chloride. In drops, 0.5 ml of anhydrous stannic chloride was added to a solution of 1.36 g (0.01 mole) of I in 1.5 ml of dichlorodimethyl ether. The mixture was stirred at room temperature for 30 min and was then treated with ethanol and filtered, giving a yellow powder which sublimed but did not melt. Found, %: Cl 26.82; N 10.55; 10.84. Calculated for $C_{12}H_8N_4S_2 \cdot SnCl_4$, %: Cl 26.62; N 10.51.

Pyridinium salts of 4, 7-di(chloromethyl)-and 4-(chloromethyl) benzo-2, 1, 3-thiadiazoles (XII and XIII). A solution of 10 g of a mixture of compounds II and III in 150 ml of pyridine was heated in the boiling water bath for 4 hr and was cooled, and the precipitate that deposited was filtered off to give 15.4 g of a mixture of the pyridinium salts of XII and XIII. These were dissolved in 30 ml of ethanol, and 250 ml of acetone was added. The precipitate of the salt of XII was filtered off; yield 11 g, mp 218°–220° C (from isoamyl alcohol). Found, %: S 7.86; 7.77. Calculated for $C_{18}H_{16}Cl_2N_4S$, %: S 8.17.

The filtrate was evaporated to dryness in vacuum, giving 4 g of the salt of XIII, mp 238° C (from n-butanol). Found, %: N 16.03; 16.22; S 11.85; 11.37. Calculated for $C_{12}H_{10}ClN_3S$, %: N 15.94; S 12.13.

The nitrone XV. With stirring, 2.43 g of piperidine or 26 ml of 2 N NaOH was added in drops to a solution of 3.9 g (0.026 mole) of p-nitrosomethylaniline and 7 g (0.027 mole) of the pyridinium salt of XIII in ethanol. The reaction mixture was kept at room temperature for 3–4 days. This yield 5.5 g (69.3%) of lustrous brown crystals with mp 174°–175° C. Found, %: N 18.69; 18.59; S 10.34; 10.12. Calculated for $C_{15}H_{14}N_4OS$, %: N 18.75; S 10.72.

The nitrone XIV. With stirring, 4.81 g of piperidine or 60 ml of 2 N NaOH was added in drops to a solution of 8.5 g (0.057 mole) of p-nitrosomethylaniline and 11 g (0.028 mole) of the pyridinium salt of XII in ethanol. The reaction mixture was kept at room temperature for 25–30 hr. This yielded 11.8 g (91%) of lustrous dark brown crystals with mp 245° C (from aqueous pyridine). Found, %: N 17.85; 17.67; S 7.08; 7.10. Calculated for $C_{24}H_{24}N_6O_2S$, %: N 18.25; S 6.96.

4-Formylbenzo-2, 1, 3-thiadiazole (XVII). A suspension of 5.5 g (0.018 mole) of compond XV in 120 ml of hydrochloric acid (1:1) was extracted with chloroform. The extract was dried with sodium sulfate and the solvent was distilled off in vacuum to dryness. This gave 2.7 g (89%) of crystals with mp 101°–102° C (from ethanol). Found, %: N 17.36; 17.81; S 19.37; 19.36. Calculated for $C_7H_4N_2OS$, % N 17.08; S 19.50.

4, 7-Diformylbenzo-2, 1, 3-thiadiazole (XVI). Similarly, 8.6 g (0.019 mole) of compound XIV yielded 3.5 g (97.5%) of XVI with mp 165°–166° C (from acetic acid). Found, %: N 14.53; 14.60; S 16.66; 17.04. Calculated for $C_8H_4N_2O_2S$, %: N 14.56; S 16.65.

4-Carboxybenzo-2, 1, 3-thiadiazole (XIX). In drops, 7 ml of 20–25% hydrogen peroxide was added to a suspension of 0.9 g (5.5 mM) of 4-formylbenzo-2, 1, 3-thiadiazole (XVII) in 2.2 ml of 10% sodium hydroxide. The precipitate that separated out redissolved in the mixture (with a spontaneous rise in temperature to 60° C). After cooling, the precipitate of compound XVII (0.15 g) was filtered off; the acidified filtrate yielded 0.42 g (51%) of yellow crystals with mp 194°–195° C (from water). Found, %: N 15.53; 15.41; S 17.65; 17.57. Calculated for $C_7H_4N_2O_2S$, %: N 15.55; S 17.78.

4, 7-Dicarboxybenzo-2, 1, 3-thiadiazole (XVIII).

a) Similarly, 1 g (5.2 mM) of 4, 7-diformylbenzo-2, 1, 3-thiadiazole (XVI) yielded 0.3 g (25.6%) of XVIII in the form of a white powder with decomp. temp ~300° C (from glacial acetic acid).

b) A solution of 0.7 g (17.5 mM) of caustic soda in 3 ml of water was added to a solution of 1.5 g (9 mM) of silver nitrate in 3 ml of water. In portions, 0.4 g (2.1 mM) of compound XVI was added to the cooled suspension of silver oxide (−5° C). After 10 min, the reaction mixture was filtered and the residue was washed with water. On acidification, the filtrate deposited 0.25 g (53%) of an orange precipitate with decomp. temp ~300° C. Found, %: N 12.83; 12.75; S 13.92; 13.86. Calculated for $C_8H_4N_2O_4S$, %: N 12.50; S 14.28.

Dianilide of 4, 7-dicarboxybenzo-2, 1, 3-thiadiazole (XX). A mixture of 0.28 g (1.3 mM) of XVIII and 10 ml of thionyl chloride was boiled until the solid matter had dissolved completely (2 hr). The thionyl chloride was distilled off in vacuum and the residue was treated with 15 ml of dry benzene which was also distilled off. To a solution of the residue in benzene was added, in drops, with stirring, a benzene solution of 0.5 g (5.4 mM) of aniline. The mixture was stirred for 1/2 hr, and the yellow precipitate was filtered off and washed with water. This gave 0.34 g (73%) of a substance with mp 258°–260° C (from isoamyl alcohol). Found, %: N 15.27; 15.4; S 8.69; 8.75. Calculated for $C_{20}H_{14}N_4O_2S$, %: N 14.97; S 8.56.

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