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

LVIII. Bromination of Derivatives of Benzo-2,1,3-thiadiazole in the Chain*

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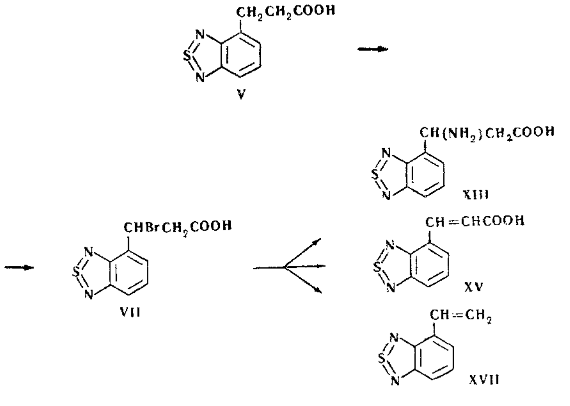
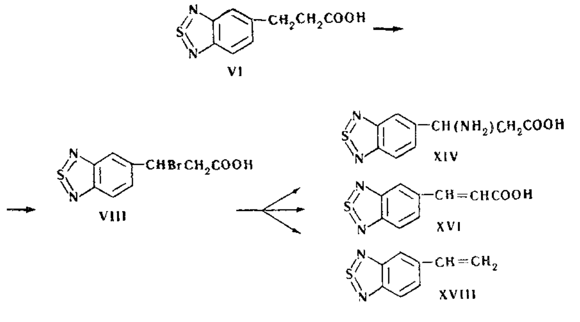
The bromination of 4- and 5-(β-carboxyethyl)benzo-2,1,3-thiadiazoles forms 4- and 5-(α-bromo-β-carboxyethyl)benzo-2,1,3-thiadiazoles. The action of 25% aqueous ammonia on these bromo derivatives forms the corresponding β-amino acids; with alcoholic alkali, derivatives of cinnamic acid are formed; and with an aqueous solution of sodium carbonate styrene derivatives are obtained. With thionyl chloride the bromine-substituted acids form the acid chlorides, which can be converted into the amides. The introduction of a nitro group into the o-position to the carboxyethyl group hinders bromination in the chain.

It has been shown previously [2] that the isomeric 4- and 5-methylbenzo-2,1,3-thiadiazoles (I and II), like the α- and β-methylnaphthalenes, brominate under the action of N-bromosuccinimide (BSI) in the absence of a catalyst to form in high yield, respectively, 4- and 5-bromomethylbenzo-2,1,3-thiadiazoles (III and IV). Toluene does not react with BSI in the absence of a catalyst [3,4]. Thus, the thiadiazole ring exerts a favorable influence on the course of the homolytic substitution reaction.

In the present work we have studied the bromination under similar conditions of 4- and 5-(β-carboxyethyl)benzo-2,1,3-thiadiazoles (V, VI) and the reactions of the bromides formed with nucleophilic reagents.

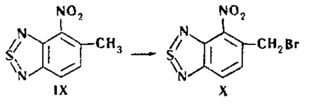




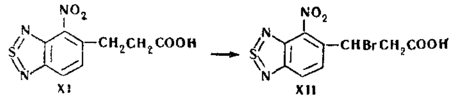
The bromination of compounds V and VI with BSI in the presence of benzoyl peroxide gave 4- and 5-(α-bromo-β-carboxyethyl)benzo-2,1,3-thiadiazoles (VII, VIII) with yields of 94 and 79%, respectively. The products of the bromination of compound VI were shown chromatographically to contain another product, besides VIII, of undetermined structure.

According to the literature [5], the bromination of phenylpropionic acid under these conditions gives a 58% yield of β-bromo-β-phenylpropionic acid. This comparison shows the greater stabilizing influence of the benzo-2,1,3-thiadiazolyl group as compared with phenyl on the intermediately formed free radicals, which is probably due to the participation of the thiadiazole ring in conjugation with the benzene nucleus. This assumption is in agreement with literature information according to which all substituents participating in conjugation with a benzene nucleus, regardless of whether the whole π-electron cloud is shifted in the direction of the substituent or in the direction of the benzene nucleus, stabilize free radicals [6].

In agreement with literature information [2, 7], the introduction of a nitro group into position 4 of compound II opposes the reaction. When 5-methyl-4-nitrobenzo-2,1,3-thiadiazole (IX) was brominated with BSI in the presence of benzoyl peroxide, the main reaction product isolated was the unchanged initial compound. In addition, 5-bromomethyl-4-nitrobenzo-2,1,3-thiadiazole (X) was detected by thin-layer chromatography*.



In the bromination of 5-(β-carboxyethyl)-4-nitrobenzo-2,1,3-thiadiazole (IX) under these conditions a very small amount of 5-(α-bromo-β-carboxyethyl)-4-nitro-benzo-2,1,3-thiadiazole (XII) is formed**.



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*For part LVII, see [1].

*This reaction confirms the assumption [2] that in the nitration of 5-bromomethyl-benzo-2,1,3-thiadiazole the nitro group enters in position 4.

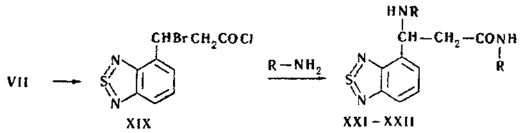
**The structure of compound XII (position of the nitro group) is provisional.

Thus, the replacement of the hydrogen of the methyl group in compound IX by a carboxymethyl group has no substantial influence on the course of bromination.

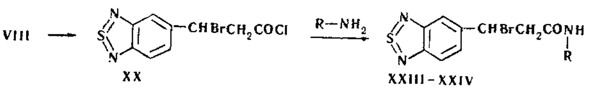
The position of the bromine in the acids VII and VIII was shown by their conversion by reaction with 25% ammonia solution into the corresponding β-amino-acids—4- and 5-(α-amino-β-carboxyethyl)benzo-2,1,3-thiadiazoles (**XIII** and **XIV**)—and by a comparison of the latter with the isomeric α-amino acids obtained by directed synthesis [8].

The action of an ethanolic solution of caustic potash on the acids VII and VIII at 20° C gives high yields of the cinnamic acid derivatives **XV** and **XVI**, respectively; with aqueous sodium carbonate, the styrene derivatives **XVII** and **XVIII** respectively, are formed.

The bromine in the chloride of the acid VII (**XIX**) is readily replaced on reaction with nucleophilic reagents; under similar conditions, the bromine in the chloride of the acid **VIII** (**XX**) does not react with the same reagents. Thus, for example, in the reaction of the acid chloride **XIX** with aniline or β-phenylisopropylamine the chlorine and the bromine are replaced (acylation and alkylation). When the reaction is carried out under similar conditions with the acid chloride **XX**, only the acylation reaction takes place.



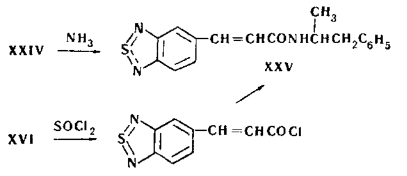
$\mathrm{XXI\ \ R = C_6H_5}$
$\mathrm{XXII\ \ R = CH(CH_3)-CH_2-C_6H_5}$



$\mathrm{XXIII\ \ R = C_6H_5}$
$\mathrm{XXIV\ \ R = CH(CH_3)-CH_2-C_6H_5}$

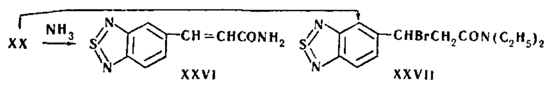
Thus, the α-carbon on the side chain in the bromide **XIX** possesses a greater electrophilicity than the α-carbon of the isomeric bromide **XX**. This can be explained by the stronger electron-accepting influence of the thiadiazole ring in the case of the bromide **XIX**.

In order to obtain the amide of the acid **XIV** and β-phenylisopropylamine we studied the reaction of the bromide **XXIV** with the amine under various conditions, but hydrogen bromide was always split out with the formation of the amide of the unsaturated acid **XVI** (**XXV**). Its structure was shown by independent synthesis from the acid **XVI** (via the chloride) and β-phenylisopropylamine.



It is interesting to compare the results of the reaction of the bromide of the acid VIII and the bromide **XXIV** with aqueous ammonia. In the first case the predominant reaction is replacement and in the second case only the elimination reaction takes place.

The reaction of the acid chloride **XX** with ammonia gives the amide of the unsaturated acid **XVI** (**XXVI**). When the reaction is carried out with a stronger nucleophilic reagent (diethylamine) the corresponding amide of the acid VIII (**XXVII**) is obtained. The action of ammonia on this under similar conditions does not split out hydrogen bromide.



The results presented agree with general ideas relating to the interrelationship of the mechanisms of substitution and elimination reactions [9–11].

The synthesis of the initial acids V and VI required for this investigation is reported in a later paper in this issue [12].

EXPERIMENTAL

4-(α-Bromo-β-carboxyethyl)benzo-2,1,3-thiadiazole (VII). A mixture of 5.5 g (0.0264 mole) of compound VI, 100 ml of carbon tet- N-bromosuccinimide, 40 ml of dry carbon tetrachloride, and 0.002 g of benzoyl peroxide was boiled for 4 hr and cooled, and the precipitate that had deposited was filtered off and washed with water until the succinimide had completely dissolved. The carbon tetrachloride was distilled off from the filtrate to dryness and the oily residue was treated with petroleum ether, giving **VII** in the form of crystals. The total yield of VII was 2.6 g (94%), mp 136–137° C (from benzene). Found, %: N 9.96, 10.29; Br 27.63, 27.95. Calculated for $C_9H_7BrN_2O_2S$, %: N 9.80; Br 27.80.

5-(α-Bromo-β-carboxyethyl)benzo-2,1,3-thiadiazole (VIII). A mixture of 5.5 g (0.264 mole) of compound **VI**, 100 ml of carbon tetrachloride, 5.2 g (0.029 mole) of N-bromosuccinimide, and 0.003 g of benzoyl peroxide was boiled for 8 hr and cooled, and the precipitate was filtered off and washed with carbon tetrachloride and then with water. This gave 6 g (79%) of a yellow substance with mp 141–142° C (from benzene). The carbon tetrachloride was distilled off in vacuum to dryness, giving 1.3 g of an oily liquid. This was chromatographed on a thin layer of alumina (Brockmann activity II) in carbon tetrachloride; two spots were found. One of them, with R_f 0.02, corresponds to the bromide **VIII** and the other, with R_f 0.48 is ascribed to a substance of undetermined structure. The spots on the chromatogram were detected in UV light and were shown up by iodine vapor. Found, %: N 9.55, 9.93; Br 27.23, 27.54. Calculated for $C_9H_7BrN_2O_2S$, %: N 9.80; Br 27.80.

4-(α-Amino-β-carboxyethyl)benzo-2,1,3-thiadiazole (XIII). With stirring, 0.5 g (0.00177 mole) of compound **VII** was added to 25 ml of of 25% aqueous ammonia; the precipitate that separated out with time was filtered off and washed with water, giving 0.85 g (64%) of a white substance with mp 188–189° C (from ethanol), R_f* 0.29. Found, %:

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*The amino acids were chromatographed on slow filter paper of the Leningrad paper mill previously purified with 0.1 N HCl in the n-butanol–propan-2-ol–0.1 N hydrochloric acid (2 : 1 : 1) system. The time of separation was 10–15 hr. The spots were detected by the action of benzidine after their treatment with gaseous chlorine [13, 14]. The R_f values of the 4- and 5-(β-amino-β-carboxyethyl)benzo-2,1,3-thiadiazoles obtained under the given conditions were 0.56 and 0.36, respectively [8].

N 18.69, 18.59; S 13.79, 14.13. Calculated for $C_9H_9N_3O_2S$, %: N 18.80; S 14.32.

5-(α-Aminocarboxyethyl)benzo-2,1,3-thiadiazole (XIV). Similarly, 0.5 g (0.00177 mole) of compound VIII yielded 0.3 g (77%) of a substance with mp 200–201° C (from ethanol), R_f* 0.67. Found, %: N 19.05, 19.05. Calculated for $C_9H_9N_3O_2S$, %: N 18.80.

Anilide of 4-(β-carboxy-α-phenylaminoethyl)benzo-2,1,3-thiadiazole (XXI). A mixture of 2 g (0.007 mole) of compound VII, 25 ml of dry benzene, and 5 ml of thionyl chloride was boiled for 2 hr, and was then heated in vacuum until the thionyl chloride had been eliminated completely; then the residue (1.5 g) was dissolved in 30 ml of dry benzene, and a solution of 0.92 g (0.01 mole)* of aniline in 10 ml of benzene was added slowly to the resulting solution with cooling. The precipitate that separated out with time was filtered off and washed with water, giving 1.44 g (78%) of a substance with mp 178–179.5° C (from ethanol). Found, %: N 14.67, 14.74; S 8.32, 8.21. Calculated for $C_{21}H_{18}N_4OS$, %: N 14.98; S 8.55.

4-(β-Carboxyvinyl)benzo-2,1,3-thiadiazole (XV). A solution of 0.5 g (0.00177 mole) of compound VII in 30 ml of 10% ethanolic caustic potash was stirred for 1 hr at 20° C and the white precipitate that deposited was washed several times with ethanol and was dissolved in water. To this solution was added, with stirring, a 0.1 N solution of hydrochloric acid to give a weakly acid reaction, and the precipitate that deposited was filtered off and washed with water, giving 0.2 g (57%) of a substance with mp 213–214° C (from 70% ethanol). Found, %: N 14.03; S 15.00, 14.99. Calculated for $C_9H_6N_2O_2S$, %: N 13.60; S 15.52.

5-(β-Carboxyvinyl)benzo-2,1,3-thiadiazole (XVI). In a similar manner, 0.5 g (0.00177 mole) of compound VIII yielded 0.32 g (91%) of a substance with mp 270–271° C (from ethanol). Found, %: N 17.00, 17.17; S 19.68, 19.76. Calculated for $C_8H_6N_2S$, %: N 17.28; S 19.75.

4-Vinylbenzo-2,1,3-thiadiazole (XVII). A mixture of 1.5 g (0.0052 mole) of compound VII, 5 g of sodium carbonate, and 25 ml of water was stirred for 2 hr and the oily layer that separated out was washed with water and left in the vacuum desiccator, giving 0.75 g (90%) of a substance with mp 109–110° C that crystallized poorly from many solvents. Found, %: N 17.00, 17.17; S 19.68, 19.76. Calculated for $C_8H_6N_2S$, %: N 17.28; S 19.75.

5-Vinylbenzo-2,1,3-thiadiazole (XVIII). Similarly, 0.5 g (0.00177 mole) of compound VIII yielded 0.28 g (99%) of a product with mp 62–63° C (from 50% ethanol). Found, %: N 17.65; S 19.22. Calculated for $C_8H_6N_2S$, %: N 17.28; S 19.75.

β-Phenylisopropylamide of 5-(α-bromo-β-carboxyethyl)benzo-2,1,3-thiadiazole (XXIV). To a benzene solution of 1.3 g (0.0045 mole) of compound VIII was added 5 ml of thionyl chloride, and the mixture was boiled for 1 hr; the benzene and the thionyl chloride were distilled off in vacuum to dryness, the residue (1 g) was dissolved in benzene (30 ml) and, at 0° C, a benzene solution of 0.9 g (0.0067 mole) of β-phenylisopropylamine was added. The precipitate that deposited was filtered off and washed with water. The benzene filtrate was evaporated in vacuum to dryness at 20° C. The residue and the residue on the filter, amounting to 0.8 g (60%) were crystallized from ethanol; white needles with mp 138.5–140° C. Found, %: N 9.75, 10.05; S 7.32, 7.69. Calculated for $C_{18}H_{18}BrN_3OS$, %: N 10.35; S 7.80.

β-Phenylisopropylamide of 5-(β-carboxyvinyl)benzo-2,1,3-thiadiazole (XXV).

A) Gaseous ammonia was passed for 30 min into a solution of 1 g (0.0025 mole) of compound XXIV in 20 ml of diethyleneglycol at 80° C, and then the mass was poured into water and the precipitate that deposited was filtered off and washed with water. This gave 0.7 g (87%) of a substance with mp 154–155° C (from ethanol). Found, %: N 13.05, 13.11; S 9.78, 9.40. Calculated for $C_{18}H_{17}N_3OS$, %: N 13.00; S 9.85.

B) When 1 g (0.0025 mole) of compound XXIV was heated with 25 ml of 25% aqueous ammonia in a sealed tube at 100° C for 4 hr, the unsaturated amide XXV was obtained.

C) Dry ammonia was passed into a solution of 1 g (0.0025 mole) of compound XXIV in glacial acetic acid at 60° C until it solidified, and then the mass was treated with water and the precipitate that separated out was filtered off. Compound XXV was obtained.

D) A mixture of 0.5 g (0.0024 mole) of compound XVI and 5 ml of thionyl chloride was boiled for 2 hr, the excess of thionyl chloride was distilled off, and the residue was washed with dry ether. The acid chloride obtained (0.45 g) was dissolved in 20 ml of dry benzene and, at 0° C, a solution of 0.6 g (0.0044 mole) of β-phenylisopropylamine in 10 ml of benzene was added. The precipitate that deposited with time was filtered off and was washed with benzene and water. This yielded 0.3 g of the amide XXV with mp 155° C (from ethanol), giving no depression of the melting point in admixture with the substances obtained by methods (A), (B), and (C).

Anilide of 5-(α-bromo-β-carboxyethyl)benzo-2,1,3-thiadiazole (XXIII). A mixture of 0.3 g (0.001 mole) of compound VIII, 10 ml of dry benzene, and 3 ml of thionyl chloride was heated for 1 hr, and the excess of thionyl chloride and the benzene were distilled off in vacuum to dryness. The residue (0.25 g) was dissolved in 15 ml of benzene and the solution was treated slowly dropwise with 0.2 g of aniline in 10 ml of dry benzene. The precipitate that deposited was filtered off and washed with water and the benzene was distilled off to dryness. The residue on the filter and the residue from the distillation of the solvent were recrystallized from ethanol, giving 0.15 g of a substance with mp 192–193° C. Found, %: N 11.70, 12.06; Br 21.99, 22.57. Calculated for $C_{15}H_{12}BrN_3S$, %: N 11.60; Br 22.10.

β-Phenylisopropylamide of 4-[β-carboxy-α-(β-phenylisopropylamino)ethyl]-benzo-2,1,3-thiadiazole (XXII). A mixture of 0.5 g (0.00177 mole) of compound VII and 3 ml of thionyl chloride was boiled for 2 hr and the excess of thionyl chloride was distilled off in vacuum. To the dry residue (0.5 g) in 20 ml of dry benzene was slowly added, with cooling to 0° C, 0.9 g (0.0067 mole) of β-phenylisopropylamine in 15 ml of dry benzene. The solvent was distilled off in vacuum. The residue (an oily mass) was washed with 5% hydrochloric acid solution and with water, giving 0.2 g of a substance with mp 174–175° C (the product began to soften at 150° C). Found, %: N 12.04, 12.07. Calculated for $C_{27}H_{30}N_4OS$, %: N 12.20.

Amide of 5-(β-carboxyvinyl)benzo-2,1,3-thiadiazole (XXVI). Dry ammonia was passed into a solution of 0.5 g of acid chloride (from 0.6 g of VIII and 3 ml of thionyl in 20 ml of dry ether for 20 min. The precipitate that separated out was filtered off, giving 0.2 g of a substance with mp 209–210° C (from ethanol). Found, %: N 21.00; S 15.83, 15.72. Calculated for $C_9H_7N_3OS$, %: N 20.50; S 15.60.

Diethylamide of 5-(α-bromo-β-carboxyethyl)benzo-2,1,3-thiadiazole (XXVII). A mixture of 1.3 g (0.0045 mole) of compound VIII, 5 ml of thionyl chloride, and 20 ml of dry benzene was boiled for 1 hr and the solvent was evaporated off in vacuum to dryness. The residue (1 g) was dissolved in benzene and, with cooling to 0° C, a solution of 0.48 g (0.0066 mole) of diethylamine in 10 ml of benzene was added dropwise. The mixture was stirred at 20° C for 10 hr and the precipitate that deposited (diethylamine hydrochloride) was filtered off. The benzene filtrate was chromatographed on a column of alumina (Brockmann activity III) 15 cm long and 1.5 cm in diameter, the product being eluted with benzene. This gave 0.2 g of a pink substance with mp 105–106° C (from 50% ethanol). Found, %: N 12.29, 12.23. Calculated for $C_{13}H_{16}BrN_3OS$, %: N 12.30.

5-Bromomethyl-4-nitrobenzo-2,1,3-thiadiazole (X). A mixture of 1 g of compound IX, 0.9 g of N-bromosuccinimide, 0.005 g of benzoyl peroxide, and 50 ml of carbon tetrachloride was boiled for 18 hr and cooled, the precipitate that had deposited was filtered off, the carbon tetrachloride was distilled off to dryness, and the residue was washed with ethanol, giving 0.85 g of the initial IX. The ethanolic filtrate was evaporated to dryness in vacuum and the residue (an oily mass) was chromatographed on a thin layer of alumina (Brockmann activity II) in the carbon tetrachloride–benzene (1 : 10) system. Two spots with close R_f values were found differing in the intensity of their fluorescence in UV light. The R_f values of reference samples

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*The anilide XXI was also obtained when the reaction was carried out with equimolecular amounts of the starting materials.

(compounds IX and X) were also close (0.74 and 0.73). After crystallization of the oily mass from 30% ethanol, mp 121–122° C [2].

5-(α-Bromo-β-carboxyethyl)-4-nitrobenzo-2,1,3-thiadiazole (XII). A mixture of 1 g of compound XI, 0.8 g of N-bromosuccinimide, 0.002 g of benzoyl peroxide, and 50 ml of dry carbon tetrachloride was boiled for 25 hr and cooled, and the precipitate (the starting material, succinimide, and N-bromo-succinimide) was filtered off and washed with water, giving 0.8 g of unchanged compound XI. The carbon tetrachloride was distilled off from the filtrate, and the residue (an oily mass) crystallized on treatment with ethanol, giving 0.1 g of a substance with mp 109–110° C (from ethanol). Found, %: N 14.23, 14.51; S 10.41, 10.85. Calculated for $C_9H_6BrN_3O_4S$, %: N 14.00; S 10.70.

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