REACTIVITY OF sym-TRIAZOLO[3,4-b]BENZOTHIAZOLE

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The reactivity of sym-triazolo[3,4-b]benzothiazole (I) has been studied. Compound I is stable under the conditions of acid hydrolysis; when it is heated with acetic anhydride in the presence of sodium acetate or with an aqueous solution of alkali, the triazole ring opens with the formation of 2-acetylamino- and 2-aminobenzothiazoles, respectively. Compound I has been brominated in position 3 and has been subjected to the Vilsmeier and Mannich reactions. The thiosemicarbazone and oxime of sym-triazolo[3,4-b]benzothiazole-3-carbaldehyde have been obtained, and the oxime has been converted into the corresponding nitrile. The thioamide, ester, and hydrazide of sym-triazolo[3,4-b]benzothiazole-3-carboxylic acid have also been obtained.

Although the synthesis of sym-triazolo[3,4-b]benzothiazole (I) and some of its derivatives has been described in the literature [1-4], there is no information on the reactivity of this tricyclic system.

In order to obtain unsubstituted I, we used the method of the ring closure of 2-hydrazinobenzothiazole with orthoformic ester [2, 4]. The initial 2-hydrazinobenzothiazole was obtained by the reaction of potassium benzothiazole-2-sulfonate with hydrazine hydrate [5, 6]. The stability of I under conditions of acid and alkaline hydrolysis was studied. When compound I was boiled in 20% hydrochloric acid, only the hydrochloride of the initial compound was obtained, and this was readily hydrolyzed by water. When compound I was boiled with 20% aqueous caustic soda solution for 6 h, the opening of the triazole ring took place partially and 2-aminobenzothiazole was isolated, as well as the unchanged tricyclic compound.

We observed a similar phenomenon in attempts to acetylate I. When it was heated with acetic anhydride in the presence of sodium acetate, a high yield of 2-acetylaminobenzothiazole was obtained. Under milder conditions, when it was heated in acetic acid with two moles of acetic anhydride, no cleavage took place and compound I was recovered unchanged.

Since in the tricyclic system under consideration the carbon atom in position 3 has an excess of π electrons,* it could be expected that electrophilic substitution reactions – in particular, the Mannich and Vilsmeier reactions, bromination, etc. – would take place at this position.

However, the bromination of I was possible only by using bromosuccinimide; this gave about a 50% yield of a monobromo derivative which was shown by its PMR spectrum to be 3-bromotriazolo[3,4-b]-benzothiazole (II). In the PMR spectrum of II, the signal of the proton in position 3 of the unsubstituted I (9.03 ppm) had disappeared; the signals of the protons of the benzene ring remained unchanged.

In attempts to perform the bromination of I with molecular bromine in chloroform, the initial compound was recovered unchanged. The bromine atom in compound II is fairly mobile and undergoes nucleophilic substitution reactions which will be described in another paper.

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*The calculations of the π electron densities in the molecule of triazolo[3,4-b]benzothiazole were carried out by the molecular orbital method in the laboratory of physical chemistry of VNIKhFI [Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry] by G. G. Dvoryantseva and T. N. Ul'yanova. These results will be published in a separate paper.

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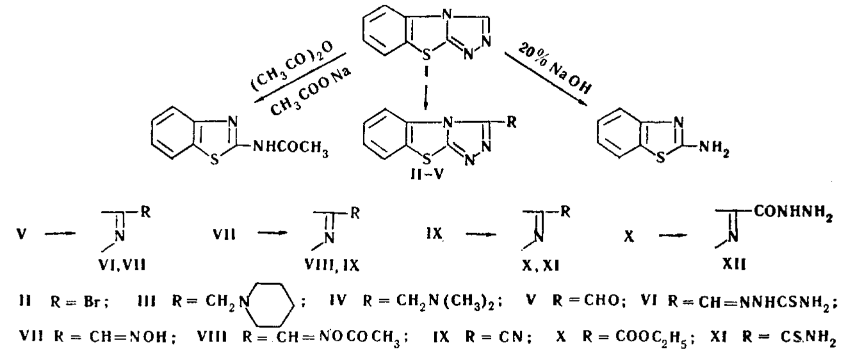

II $R = Br$; III $R = CH_2N$; IV $R = CH_2N(CH_3)_2$; V $R = CHO$; VI $R = CH{=}NNHCSNH_2$; VII $R = CH{=}NOH$; VIII $R = CH{=}NOCOCH_3$; IX $R = CN$; X $R = COOC_2H_5$; XI $R = CSNH_2$

The Mannich and Vilsmeier reactions have not previously been described for triazolo heterocycles condensed at a nitrogen atom.

It was found that I is capable of taking part in the Mannich reaction with hydrochlorides of secondary amines (dimethylamine and piperidine); however, the process does not go to completion, and even on prolonged heating of the components a certain amount of the starting material does not react. The Mannich bases (III and IV) formed readily give quaternary salts.

The Vilsmeier reaction led to the formation of sym-triazolo[3,4-b]benzothiazole-3-carbaldehyde (V) only when the reactants were heated briefly at 70°C. At a higher temperature and with longer times of heating, pronounced resinification of the reaction mixture took place and it was impossible to isolate an individual compound. From V the thiosemicarbazone (VI) and the oxime (VII) were prepared.

The action on VII of acetic anhydride in the presence of sodium acetate forms the nitrile (IX) together with a small amount of the acetyl derivative of the oxime (VIII). The thioamide XI was formed from IX in the usual way. Boiling the nitrile with an ethanolic solution of hydrogen chloride and subsequent treatment with water led to the formation of ethyl sym-triazolo[3,4-b]benzothiazole-3-carboxylate (X); the reaction of X with hydrazine hydrate gave the hydrazide XII.

All the 3-substituted sym-triazolo[3,4-b]benzothiazoles were sent for the study of their bacteriostatic activities* ; these compounds did not possess appreciable antibacterial activity.

EXPERIMENTAL

Action of 20% Hydrochloric Acid on sym-Triazolo[3,4-b]benzothiazole. A suspension of 0.5 g (2.84 mmoles) of I in 10 ml of 20% hydrochloric acid was boiled for 1 h. On cooling, the solution deposited a precipitate of the hydrochloride of I, which was filtered off and washed with hydrochloric acid and then with absolute ethanol. Yield 0.24 g. Colorless crystals, decomp. temperature 237°C (absolute ethanol). Found %: Cl 16.82. $C_8H_5N_3S \cdot HCl$. Calculated %: Cl 16.75. When the hydrochloride was triturated with water, a substance with mp 176°C was obtained, a mixture of which with I gave no depression of the melting point. The acid mother liquors were neutralized with dry sodium carbonate, giving a precipitate (0.21 g) identical with I.

Action of 20% Caustic Soda Solution on sym-Triazolo[3,4-b]benzothiazole. A suspension of 2 g (11.36 mmoles) of I in 15 ml of 20% aqueous sodium carbonate solution was boiled for 6 h. After cooling, the precipitate was filtered off, washed with water, dried (weight 1.55 g), and treated with ether; the substance insoluble in ether (0.71 g) gave no depression of the melting point in admixture with I. After evaporation of the ethereal solution, the residue (0.44 g; yield 25%) was recrystallized from water, giving 0.14 g of colorless plates with mp 128-130°C. Found %: C 56.22; H 4.23. $C_7H_6N_2S$. Calculated %: C 55.97; H 4.03. A mixture of the substance with the 2-aminobenzothiazole (mp 128°C [6]) obtained by the reaction of benzothiazole-2-sulfonic acid with ammonia gave no depression of the melting point.

Acetylation of sym-Triazolo[3,4-b]benzothiazole. A mixture of 0.5 g (2.84 mmoles) of I, 0.5 g of anhydrous sodium acetate, and 5 ml of acetic anhydride was boiled for 2 h and was then cooled and poured into water. The precipitate was filtered off, washed with water, and crystallized from 50% ethanol. This

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*The investigations were carried out in the Department of Chemotherapeutics of VNIKhFI by T. N. Zykova and S. N. Milovanova.

gave 0.38 g (69%) of 2-acetylaminobenzothiazole, mp 187-189°C (compare mp 186-187°C [7], 189°C [8]). Found %: C 56.08; H 4.37; N 14.50; S 16.50. $C_9H_8N_2OS$. Calculated %: C 56.10; H 4.17; N 14.51; S 16.65.

3-Bromo-sym-triazolo[3,4-b]benzothiazole (II). A suspension of 5 g (28.4 mmoles) of I, 5.1 g of bromosuccinimide, and 200 ml of carbon tetrachloride was boiled for 5 h. Then it was filtered in the hot state from the red precipitate that had formed, and the precipitate was washed with 50 ml of carbon tetrachloride. The filtrates were combined and cooled, and the faintly colored precipitate was filtered off, washed with carbon tetrachloride, and recrystallized from methanol. This gave 2.23 g of almost colorless crystals with mp 170.5-172°C. Found %: C 37.76; H 1.57; Br 31.26. $C_8H_4N_3SBr$. Calculated %: C 37.81; H 1.58; Br 31.45.

3-Dimethylaminomethyl-sym-triazolo[3,4-b]benzothiazole (III). A mixture of 1.07 g (6.07 mmoles) of I, 0.36 g of paraformaldehyde, 0.64 g of dimethylamine hydrochloride, and 16.5 ml of isoamyl alcohol was boiled for 7 h, by which time the solid matter had dissolved completely. The crystalline precipitate that deposited when the solution was cooled to 20°C was filtered off, washed with ether, and triturated with a small amount of aqueous ammonia. This gave 0.44 g (31%) of III; mp 114-115°C [rhombs from petroleum ether (bp 100-120°C)]. Found %: C 57.19; H 5.21; N 23.81. $C_{11}H_{12}N_4S$. Calculated %: C 56.87; H 5.20; N 24.12. When the ethanolic filtrate was cooled with a freezing mixture, 0.24 g of needles with mp 173-175°C (water) deposited; a mixture of these with I gave no depression of the melting point.

3-Dimethylaminomethyl-sym-triazolo[3,4-b]benzothiazole Methiodide. This was obtained by the action of methyl iodide on a solution of III in benzene at room temperature. Colorless crystals with mp 215-216.5°C (ethanol). Found %: C 38.71; H 4.06; I 34.30. $C_{12}H_{15}N_4SI$. Calculated %: C 38.54; H 4.04; I 33.91.

3-Piperidinomethyl-sym-triazolo[3,4-b]benzothiazole (IV). A suspension of 1 g (5.68 mmoles) of I, 0.32 g of paraformaldehyde, and 1.14 g of piperidine hydrochloride in 15.4 ml of isoamyl alcohol was boiled for 10 h. After cooling, the precipitate was filtered off and was washed with isoamyl alcohol and then with ether and was treated with ammonia. This gave 0.59 g of IV (63%, calculated on the I that had reacted), mp 194-197°C (methanol). Found %: C 62.02; H 5.86; N 20.84; S 11.91. $C_{14}H_{16}N_4S$. Calculated %: C 61.73; H 5.92; N 20.57; S 11.74. The mother solution was evaporated. The residue was treated with ammonia, and the oily substance so formed was triturated with ether, after which 0.4 g of a crystalline precipitate was filtered off. mp 169-170°C (water). A mixture with I gave no depression of the melting point.

3-Formyl-sym-triazolo[3,4-b]benzothiazole (V). In drops, 20.2 ml of redistilled phosphorus oxychloride was added to 80 ml of redistilled dimethylformamide cooled to −5°C and, at the same temperature, a suspension of 15 g (85.2 mmoles) of I in 80 ml of dimethylformamide was added. The solution was stirred at room temperature for 1 h. A voluminous precipitate gradually formed. The reaction mixture was heated at 78°C for 15 min, whereupon the precipitate redissolved. The substance that deposited after cooling was filtered off, washed with dimethylformamide and then with ether, and carefully triturated with saturated sodium acetate solution. This gave 9.46 g of V; the mother liquor after standing gave an additional 2.74 g of V. The total yield was 12.2 g (70%); mp 191-192.5°C (acetone). Found %: C 52.97; H 2.20; S 15.52. $C_9H_5N_3OS$. Calculated %: C 53.19; H 2.48; S 15.78.

3-Formyl-sym-triazolo[3,4-b]benzothiazole Thiosemicarbazone (VI). Two drops of glacial acetic acid and a hot solution of 0.05 g of thiosemicarbazide in 3 ml of water were added to a suspension of 0.1 g (0.49 mmole) of V in 3 ml of ethanol. The mixture was boiled for 1 h, and cooled, and the precipitate was filtered off and washed with 50% ethanol. Yield 0.12 g (88%), mp 247-248°C. Found %: C 43.34; H 2.96; S 23.37. $C_{10}H_8N_6S_2$. Calculated %: C 43.46; H 2.91; S 23.21.

3-Formyl-sym-triazolo[3,4-b]benzothiazole Oxime (VII). A mixture of 1 g (4.9 mmoles) of V, 0.33 g of hydroxylamine hydrochloride, 11 ml of absolute ethanol, and 11 ml of dry pyridine were boiled for 2 h, and the precipitate was filtered off, washed with cooled ethanol and with water and again with ethanol. Yield 1 g (93.5%), decomp. temperature 261-263°C (butanol). Found %: C 49.40; H 2.80; S 14.63. $C_9H_9N_4S$. Calculated %: C 49.53; H 2.77; S 14.69.

sym-Triazolo[3,4-b]benzothiazole-3-carbonitrile (IX). A suspension of 6.74 g (30.9 mmoles) of VII and 3.5 g of fused sodium acetate in 105.5 ml of acetic anhydride was boiled for 4 h and cooled to 20°C. The precipitate that deposited was filtered off and was washed with acetic anhydride and with water. Yield 4.59 g of IX (74.2%), mp 195-198°C (ethanol). Found %: C 54.01; H 2.43; S 16.14. $C_9H_4N_4S$. Calculated %: C 53.99; H 2.09; S 16.01. On deep cooling, the mother liquor deposited 0.15 g of the acetyl derivative of the oxime, VIII, mp 225-230°C (ethanol). Found %: N 21.46; S 12.30. $C_{11}H_8N_4SO_2$. Calculated %: N 21.53; S 12.32.

sym-Triazolo[3,4-b]benzothiazole-3-carbothioamide (XI). A solution of 1 g (5 mmoles) of VIII in 50 ml of absolute ethanol was treated with 4 ml of triethylamine, and a current of dry hydrogen sulfide was passed through the mixture at 20°C for 1 h. The precipitate immediately deposited. The reaction mixture was cooled and the precipitate was filtered off and washed with ethanol and then with water. This gave 1 g of XI, decomp. temperature 218-220°C (ethanol). Yield 85.5%. Found %: C 46.33; H 3.20; S 27.39. $C_9H_6N_4S_2$. Calculated %: C 46.13; H 2.58; S 27.37.

Ethyl sym-Triazolo[3,4-b]benzothiazole-3-carboxylate (X). A current of hydrogen chloride was passed into a solution of 1 g (5 mmoles) of IX in 65 ml of absolute ethanol at the boil. The small amount of ammonium chloride that precipitated was filtered from the hot solution. The ethanolic mother liquor was evaporated to half its volume, and then an equal volume of water was added and the mixture was neutralized with saturated aqueous sodium acetate solution. The precipitate was filtered off and washed with water. Yield 0.78 g (63%); colorless crystals, mp 176.5-178°C (ethanol). Found %: C 53.19; H 3.60; N 16.66; S 12.89. $C_{11}H_9N_3SO_2$. Calculated %: C 53.43; H 3.67; N 16.99; S 12.96.

sym-Triazolo[3,4-b]benzothiazole-3-carbohydrazide (XII). A solution of 0.54 g (2.19 mmoles) of XI and 0.15 ml of hydrazine hydrate in 15 ml of absolute ethanol was boiled for 4 h. After cooling, the precipitate was filtered off. Yield 0.45 g (88.1%). Colorless crystals, mp 252-255°C (butanol). Found %: C 46.40; H 3.12; S 13.49. $C_9H_7N_5SO$. Calculated %: C 46.26; H 3.02; S 13.75.

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