SYNTHESES IN THE BENZO[2,1,3]THIADIAZOLE SERIES

I. NEW SULFO DERIVATIVES OF BENZO[2,1,3]THIADIAZOLE

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The synthesis of the previously unknown 7-bromobenzo[2,1-3]thiadiazole-4-sulfonic acid, its acid chloride and amides, and the corresponding sulfinic acid, which was subsequently converted to the ethylsulfonyl derivative, is described. It is shown that the bromine in amides of 7-bromobenzo[2,1,3]thiadiazole-4-sulfonic acid and the corresponding 4-ethylsulfonyl derivative is readily replaced by an amine.

The synthesis of amides of 7-aminobenzo[2,1,3]thiadiazole-4-sulfonic acid seems of definite interest in view of their structural proximity to sulfanilamide (streptocid album). However, attempts to obtain these compounds from 4-amino(acetamido)benzo[2,1,3]thiadiazoles were unsuccessful. No reaction was observed [1] when 4-acetamidobenzo[2,1,3]thiadiazole was treated with chlorosulfonic acid under the conditions used for the chlorosulfonation of acetanilide (at 70°C for 2 h). 4-Amino-5,7-dichlorosulfonylbenzo-[2,1,3]thiadiazole was obtained in the case of the analogous reaction (140°C for 4 h) with 4-aminobenzo[2,1,3]-thiadiazole [2]. It was also found to be impossible to obtain 7-aminobenzo[2,1,3]thiadiazole-4-sulfonic acid by sulfonation with concentrated sulfuric acid at 180-190° (under the conditions of the formation of sulfanilic acid from aniline) in view of charring of the starting substances; the reaction does not proceed at lower temperatures [1]. The formation of 7-aminobenzo[2,1,3]thiadiazole-4-sulfonic acid was not observed in the reaction of the amino derivative named above with 24-26% oleum, and only a disulfonation product was obtained [2]. Considering the above, we decided to obtain 7-aminobenzo[2,1,3]thiadiazole-4-sulfonic acid derivatives by a different route starting from 4-bromobenzo[2,1,3]thiadiazole (I). It was found that 7-bromobenzo[2,1,3]thiadiazole-4-sulfonyl chloride (IV) is formed in high yield during chlorosulfonation of I with excess chlorosulfonic acid at 140° for 1.5 h. To prove the entry of the chlorosulfonyl group into the 4 position of I, we obtained 7-bromobenzo[2,1,3]thiadiazole-4-sulfonic acid (II), the structure of which was proved by replacement of the sulfo group by bromine, as a result of which we obtained the known 4,7-dibromobenzo[2,1,3]thiadiazole. Compound IV, which was identical to the sulfonyl chloride obtained in the chlorosulfonation of I, was obtained by reaction of II with excess chlorosulfonic acid.

It is necessary to note that the replacement of the sulfo group in II by bromine proceeds with considerably greater difficulty than is the case in the analogous reaction with 7-methylbenzo[2,1,3]thiadiazole-4-sulfonic acid or the isomeric 5-methylbenzo[2,1,3]thiadiazole-4-sulfonic acid. Replacement of the sulfo group by bromine during bromination of these compounds in water occurred in 15 min at 80° to give good yields of products [3]. However, in the case of bromination of II under similar conditions, only heating with excess bromine for many hours gave 4,7-dibromo derivative III in low yield.

The reduction of sulfonyl chloride IV with sodium sulfite in aqueous alkali gave 4-bromobenzo[2,1,3]-thiadiazole-7-sulfinic acid (V), from which 7-bromo-4-ethylsulfonylbenzo[2,1,3]thiadiazole (VI) was obtained by reaction with ethyl bromide in aqueous alcohol. The bromine in VI has high lability, and this made it possible to readily replace it with an amine residue (IXa, b).

Sulfonyl chloride IV was converted to 4-bromo-7-sulfonamidobenzo[2,1,3]thiadiazoles (VIIa, b) by reaction with ammonia or amines (with slight heating). Replacement of the bromine in VIIa, b by an amine

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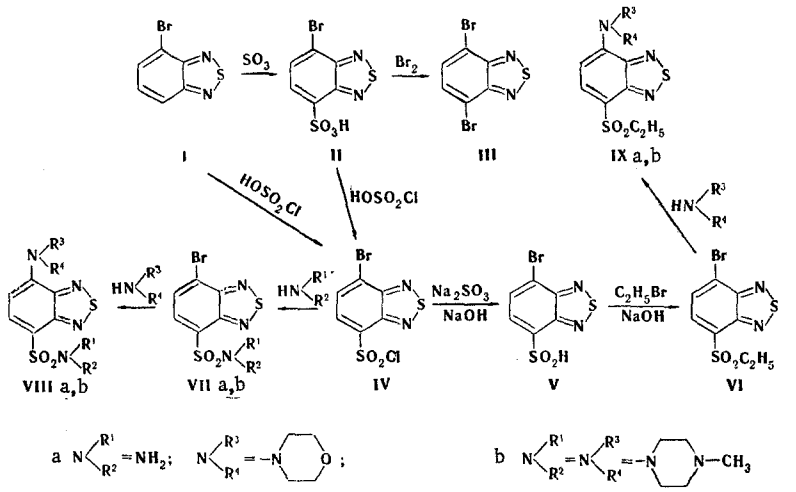
residue was accomplished at higher temperatures and with an excess of the amine; in this case, 7-amino-substituted 4-sulfonamidobenzo[2,1,3]thiadiazoles (VIIIa, b) were obtained in good yields.



The synthesized compounds did not show antimalarial and antihelminthic activity in tests on experimental animals.

EXPERIMENTAL

4-Bromobenzo[2,1,3]thiadiazole (I). This compound was obtained by bromination of benzo[2,1,3]-thiadiazole via the method in [5]. The recrystallized product (from alcohol) was used for the subsequent reactions.

7-Bromobenzo[2,1,3]thiadiazole-4-sulfonic Acid (II). A mixture of 10.75 g (0.05 mole) of I and 40 ml of 22% oleum was heated at 125-130° for 3 h. It was then cooled, and the solution was carefully poured into 60 ml of water. The aqueous mixture was cooled to 10°, and the resulting colorless crystals were separated and washed successively with glacial acetic acid–dioxane (1:1), dioxane, and ether to give 11.8 g (75%) of product. Recrystallization from acetonitrile gave a product containing 1 mole of water of crystallization. The anhydrous product (obtained by drying at 150° for 3 h) was a yellow-green substance with mp 216-218°. Found: Br 25.1; N 8.9%. $C_6H_3BrN_2O_3S_2 \cdot H_2O$. Calculated: Br 25.4; N 9.1%.

4,7-Dibromobenzo[2,1,3]thiadiazole (III). A mixture of 1.57 g (0.005 mole) of the hydrate of II and 50 ml of 3% bromine water was heated to 80° and held at this temperature for 5 h. The resulting colorless crystals were removed by filtration and washed with water to give a product with mp 183-184° (from acetone) (mp 184-185° [5]) that did not depress the melting point of III obtained according to the method in [5]. Found: Br 54.0%. $C_6H_2Br_2N_2S$. Calculated: Br 54.4%.

7-Bromo-4-chlorosulfonylbenzo[2,1,3]thiadiazole (IV). A. A mixture of 86.0 g (0.4 mole) of I and 300 ml of distilled chlorosulfonic acid was heated and stirred for 1.5 h at 140°. The cooled reaction mass was then added from a dropping funnel to stirred crushed ice (3 kg). The resulting light-colored crystalline precipitate was removed by filtration and washed with water to give 117.0 g (93.6%) of IV as colorless crystals with mp 141-142° (from acetone). Found: N 8.9; S 20.6%. $C_6H_2ClBrN_2O_2S_2$. Calculated: N 8.9; S 20.5%.

B. A mixture of 2.95 g (0.01 mole) of anhydrous sulfonic acid III and 10 ml of chlorosulfonic acid was heated at 140° for 1.5 h, and the sulfonyl chloride was isolated as described in method A to give 2.83 g (90%) of colorless crystals with mp 141-142° (from acetone); no melting-point depression was observed for a mixture of this product with a sample of IV obtained by method A.

7-Bromobenzo[2,1,3]thiadiazole-4-sulfinic Acid (V). A mixture of 31.4 g (0.1 mole) of IV, 32 g of sodium sulfite, and 300 ml of water was stirred at 65° for 1 h while maintaining an alkaline medium by the addition of a solution of 40% aqueous alkali. The resulting red solution was filtered, and the filtrate was cooled and acidified with 20% sulfuric acid. The precipitate was removed by filtration and washed with cold water to give 24.8 g (83%) of light-yellow crystals of V with mp 175-176° (from water). Found: Br 29.1; S 23.1%. $C_6H_3BrN_2O_2S_2$. Calculated: Br 28.6; S 23.0%.

7-Bromo-4-ethylsulfonylbenzo[2,1,3]thiadiazole (VI). A mixture of 27.9 g (0.1 mole) of V, 13.5 g (0.17 mole) of ethyl bromide, 150 ml of alcohol, and 30 ml of water was refluxed for 20 h while maintaining an alkaline reaction mixture by the periodic addition of 20% aqueous sodium hydroxide solution. The solution was concentrated in vacuo to half its original volume and cooled, and the resulting light-yellow shiny crystals were removed by filtration and washed with water to give 25.8 g (84%) of a product with mp 160-161° (from alcohol). Found: N 9.4; S 21.4%. $C_8H_7BrN_2O_2S_2$. Calculated: N 9.1; S 21.0%.

7-Morpholino-4-ethylsulfonylbenzo[2,1,3]thiadiazole (IXa). A mixture of 6.14 g (0.02 mole) of VI, 2.5 g (0.03 mole) of morpholine, 1.38 g (0.01 mole) of K_2CO_3, and 15 ml of dimethylformamide was refluxed for 1 h and poured into 250 ml of water. The resulting solid was removed by filtration to give 5.9 g (94.2%) of yellow-orange shiny crystals with mp 114-115° (from benzene–petroleum ether). Found: N 13.6; S 20.7%. $C_{12}H_{15}N_3O_3S_2$. Calculated: N 13.4; S 20.5%.

7-(4-Methyl-1-piperazinyl)-4-ethylsulfonylbenzo[2,1,3]thiadiazole (IXb). A mixture of 6.14 g (0.02 mole) of VI, 3.0 g (0.03 mole) of N-methylpiperazine, 1.38 g (0.01 mole) of K_2CO_3, and 15 ml of dimethylformamide was refluxed for 20 min and poured into 250 ml of water. The aqueous mixture was cooled in a refrigerator, and the resulting crystals were removed by filtration and washed with water to give 4.8 g (72.5%) of light-brown shiny crystals with mp 146-147° (aqueous dimethylformamide). Found: N 17.2; S 19.7%. $C_{13}H_{18}N_4O_2S_2$. Calculated: N 17.2, S 19.7%.

7-Bromo-4-sulfonamidobenzo[2,1,3]thiadiazole (VIIa). A total of 150 ml of 25% ammonium hydroxide was added gradually to a solution of 31.3 g (0.1 mole) of IV in 50 ml of acetone, and the mixture was refluxed for 1 h. The resulting precipitate was removed by filtration and washed with water to give 26.7 g (91%) of a colorless powder with mp 226-228° (from alcohol). Found: Br 27.1; N 14.2; S 21.6%. $C_6H_4N_3O_2S_2$. Calculated: Br 27.2; N 14.3; S 21.8%.

7-Bromo-4-(4-methyl-1-piperazinyl)sulfonylbenzo[2,1,3]thiadiazole (VIIb). A solution of 2.0 g (0.02 mole) of N-methylpiperazine in 15 ml of acetone and 20 ml of water was added to a solution of 3.13 g (0.01 mole) of IV in 15 ml of acetone, and the mixture was refluxed for 30 min. It was then diluted with 100 ml of water, and the precipitate was separated to give 3.36 g (89%) of colorless crystals with mp 192-193° (from methanol). Found: Br 21.2; N 14.7; S 17.2%. $C_{11}H_{13}BrN_4O_2S_2$. Calculated: Br 21.2; N 14.9; S 17.0%.

7-Morpholino-4-sulfonamidobenzo[2,1,3]thiadiazole (VIIIa). A mixture of 5.9 g (0.02 mole) of VII and 8 ml of morpholine was heated to 100°, after which it heated up spontaneously to the boiling point. It was then allowed to cool to 80° and poured into water (100 ml). The resulting solid was removed by filtration and washed with water to give 5.52 g (92%) of orange crystals with mp 291-220° (from methanol). Found: N 18.7; S 21.7%. $C_{10}H_{12}N_4O_3S_2$. Calculated: N 18.7; S 21.7%.

7-(4-Methyl-1-piperazinyl)-4-(4-methyl-1-piperazinyl)sulfonylbenzo[2,1,3]thiadiazole (VIIIb). This compound was obtained in analogy with the synthesis of VIIIa from 3.77 g (0.01 mole) of VIIb and 3.0 g (0.03 mole) of N-methylpiperazine. The light-brown crystals [3.63 g (93%)] had mp 207-208° (from benzene). Found: N 21.5; S 16.5%. $C_{16}H_{24}N_6O_2S_2$. Calculated: N 21.2; S 16.2%.

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