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

XXXVIII. Derivatives of 5-Methyl-4-Hydroxy- And 4-Ethoxybenzo-2,1,3-Thiadiazoles*

V. G. Pesin and I. A. Belen'kaya-Lotsmanenko

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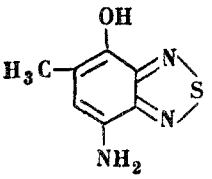
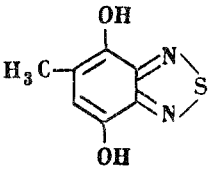
Nitration and nitrosation of 4-hydroxy-5-methyl-benzo-2,1,3-thiadiazole gives 4-hydroxy-5-methyl-7-nitro- and 4-hydroxy-5-methyl-7-nitrosobenzo-2,1,3-thiadiazoles. Oxidation of the latter, or of 4,7-diamino-5-methylbenzo-2,1,3-thiadiazole gives 5-methyl-4,7-dihydroxy-2,1,3-thiadiazole, forming derivatives with sodium bisulfite or hydroxylamine, and reduced by sodium dithionite to 5-methyl-4,7-dihydroxybenzo-2,1,3-thiadiazole. The latter is also obtained by diazotizing 5-methyl-4-hydroxy-7-aminobenzo-2,1,3-thiadiazole, and decomposing the diazonium salt. Nitration of 4-ethoxybenzo-2,1,3-thiadiazole with sodium ethoxide gives 4-ethoxy-7-aminobenzo-2,1,3-thiadiazole, acetylated to 4-ethoxy-7-acetaminobenzo-2,1,3-thiadiazole.

The present paper gives the results of an investigation of the products of nitrating 5-methyl-4-hydroxy- and 4-ethoxybenzo-2,1,3-thiadiazoles, and the properties of the amines prepared from them. These investigations are of some interest because the products, 5-methyl-4-hydroxy-7-amino-, 5-methyl-4,7-dihydroxy- and 5-methyl-4,7-dioxobenzo-2,1,3-thiadiazoles (I-III), possess structures reminiscent of 2-methyl-1-hydroxy-4-aminonaphthalene, 2-methyl-1,4-dihydroxynaphthalene, and 2-methyl-1,3-naphthoquinone respectively, named vitamins K_5, K_4, and K_3 [2]. Comparison of the biological activities of compounds I-III with those of the above-mentioned naphthalene compounds, would give some information about the connection between structure and activity. Such a comparison is worthy of attention in connection with the close resemblance between the properties of benzo-2,1,3-thiadiazole and those of naphthalene. For the same reason it appeared to be of interest to compare the biological activity of 4-ethoxy-7-acetaminobenzo-2,1,3-thiadiazole (IV) with that of 4-ethoxy-2-acetaminobenzene (phenacetin), and with this end in view, to investigate synthesis of compound IV.



I



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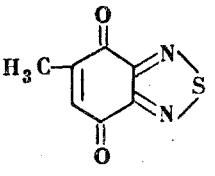


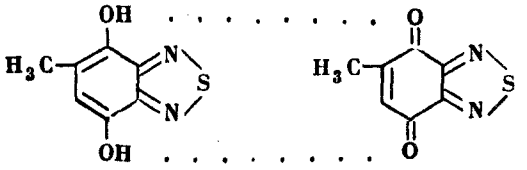
III

IV

Under the usual conditions for nitrating or nitrosating aromatic compounds, 5-methyl-4-hydroxybenzo-2,1,3-thiadiazole respectively gives 5-methyl-4-hydroxy-7-nitro- (V) and 5-methyl-4-hydroxy-7-nitrosobenzo-2,1,3-thiadiazole (VI). Reduction of nitro-derivative V with sodium hydrosulfite in aqueous medium, or of the nitroso-derivative VI with hydrogen sulfide in 25% ammonia, gives the amine I in high yield. With dry hydrogen chloride the latter gives a hydrochloride, readily hydrolyzing when dissolved in water. Treatment of amine I with potassium dichromate in weakly acid medium gives a high yield of quinone III. The structure of the latter is established by a "reverse" synthesis, potassium dichromate oxidation in weakly acid medium of 5-methyl-4,7-diamino benzo 2,1,3-thiadiazole [3].** Reaction of the quinone III with sodium bisulfite gives a bisulfite compound VII, while reaction with hydroxylamine hydrochloride gives 5-methyl-4,7-dihydroxybenzo-2,1,3-thiadiazole (VIII). Reduction of the quinone III with sodium hydrosulfite in aqueous medium gives a 70% yield of 5-methyl-4,7-dihydroxy-2,1,3-thiadiazole (II). When ethereal solutions of equimolecular amounts of phenol II and quinone III are mixed, a dark brown intermediate compound with a hydroquinone structure IX is formed.

*For Part XXXVII see [1].

**Black mixtures, from which no individual compounds can be isolated, are obtained when 5-hydroxy-4-amino- or 4-hydroxy-7-aminobenzo-2,1,3-thiadiazole are oxidized under similar conditions, or with ferric chloride in a slightly acid medium.



IX

If amine I is diazotized in sulfuric or hydrochloric acid and the diazonium salt decomposed with water, the product is a mixture of phenol II and quinone III, the latter predominating when sulfuric acid is used. After the mixture has been treated with sodium hydrosulfite, only phenol II can be isolated.

Nitration of 4-ethoxybenzo-2, 1, 3-thiadiazole (X) with sodium nitrate in concentrated sulfuric acid at room temperature or at 50-60° gives a high yield of 4-ethoxy-7-nitrobenzo-2, 1, 3-thiadiazole (XI), also obtained in 32% yield when the reactants are heated together for 10 minutes on a steam bath. The structure of XI is established by a reverse synthesis, treatment of 4-chloro-7-nitrobenzo-2, 1, 3-thiadiazole [4] with sodium nitrate in concentrated sulfuric acid at room temperature or at 50-60° gives a high yield of 4-ethoxy-7-nitrobenzo-2, 1, 3-thiadiazole (XI), also obtained in 32% yield when the reactants are heated together for 10 minutes on a steam bath. The structure of XI is established by a reverse synthesis, treatment of 4-chloro-7-nitrobenzo-2, 1, 3-thiadiazole [4] with sodium ethoxide. Sodium hydrosulfite reduced the nitro derivative XI to 4-ethoxy-7-aminobenzo-2, 1, 3-thiadiazole (XII), which is unstable, rapidly darkening in air, so that it was converted into the stable, water-soluble hydrochloride. Acetylation of the latter gives 4-ethoxy-7-acetaminobenzo-2, 1, 3-thiadiazole (IV).

The starting materials required for this research were prepared in the ways described in the literature [1, 3-5].

Experimental

4-Hydroxy-5-methyl-7-nitrobenzo-2, 1, 3-thiadiazole (V).

a) 0.35 g sodium nitrate was added to 0.5 g 4-hydroxy-5-methylbenzo 2, 1, 3-thiadiazole in 3 ml concentrated sulfuric acid, the mixture stirred for 30 min at room temperature, and then poured onto ice. The precipitate which separated was filtered off, washed with water until neutral to congo red, and then dried. Yield 0.28 g (44.2%) of a bright yellow substance mp 162-163° (decomp), soluble in organic solvents and hot water, and giving a brownish-green color with ferric chloride. After precipitating with water from alcohol, it had mp 169-170° (decomp). Found: N 19.88, 20.14; S 14.75, 14.85%. Calculated for $C_7H_5N_3O_3S$: N 19.90; S 15.15%. Similar results were obtained if the mixture of starting materials was kept for 10 min at 60-70°.

b) 0.5 g 4-Hydroxy-5-methylbenzo-2, 1, 3-thiadiazole in 7 ml sulfuric acid (d 1.84) at 0-5° was nitrated with 0.5 ml nitric acid (d 1.35) and 1.5 ml sulfuric acid (d 1.84), and after 15 min at room temperature the reaction products were poured onto ice. The precipitate was filtered off, washed with water until neutral to congo red, and dried. Yield 0.4 g substance mp 80-85°. Precipitation with water from alcohol gave a pale product, soluble in organic solvents and hot water, mp 167-169° (decomp), mixed mp with the substance prepared by method (a) undepressed.

4-Hydroxy-5-methyl-7-nitrobenzo-2, 1, 3-thiadiazole (VI). 0.8 g 4-hydroxy-5-methylbenzo-2, 1, 3 thiadiazole and 0.4 g sodium nitrate were added to a solution of 0.25 g sodium hydroxide in 15 ml water, and a solution of 1.5 ml concentrated sulfuric acid in 8 ml water added while the temperature was kept at 0-5°. Then the mixture was stirred for 20 min and filtered. The precipitate was washed with water until neutral to congo red, and then dried. Yield 0.9 g (96%) of a cream-colored material which did not melt, but swelled and darkened at 265-270°. Ferrous sulfate did not give any color or precipitate, and it did not react with sodium bisulfite.

4-Hydroxy-5-methyl-7-aminobenzo-2, 1, 3-thiadiazole (I).

a) 0.5 g VI was dissolved in 10 ml 25% ammonia, and while the solution was cooled externally with cold water, hydrogen sulfide was passed for 15 min. After keeping at room temperature for 20 min, the bright red precipitate which separated, was filtered off, washed with water, and dried. Yield 0.45 g (97%), mp 245-247° (from toluene, darkens before melting). Soluble in alcohol, dimethylformamide, dioxane, and acetone; gave a cherry-crimson red color with 10% sodium hydroxide solution, but it was not observed to give a characteristic coloration with ferric chloride. Found: N 23.54, 23.56; S 17.91, 16.68%. Calculated for $C_7H_7N_3OS$: N 23.20; S 17.67%.

b) A mixture of 0.5 g 4-hydroxy-5-methyl-7-nitrobenzo-2, 1, 3-thiadiazole and 5 g sodium hydrosulfite was

gradually poured into 35 ml boiling water. After boiling for 2 min, the reaction products were cooled, the precipitate filtered off, washed with water, and dried. Yield 0.39 g (91.1%) of red material, which after recrystallizing from toluene had mp 245-247° (darkened before melting) mixed mp with the substance prepared by method (a) undepressed.

4-Hydroxy-5-methyl-7-aminobenzo-2, 1, 3-thiadiazole hydrochloride. Hydrogen chloride was passed for 1 hr into a suspension of 0.5 g I in 50 ml acetone. Precipitation with ether then yielded 0.56 g (93%) I hydrochloride, readily soluble in water. The original amine quickly separated out from an aqueous solution (hydrolysis). Heat also readily decomposed the hydrochloride, the original amine again being formed. Found: S 14.29, 14.11; Cl 16.83, 15.71%. Calculated for $C_7H_7N_3OS \cdot HCl$: S 14.70; Cl 16.31%.

5-Methyl-4, 7-dioxobenzo-2, 1, 2-thiadiazole (III).

a) A solution of 12 g potassium dichromate in 160 ml water was added to a mixture of 4 g 5-methyl-4, 7-diaminobenzo-2, 1, 3-thiadiazole, 1.8 ml conc. H_2SO_4, and 32 ml water. The mixture was stirred for 2-3 min, and the precipitate (1.1 g) then filtered off, washed with water until neutral to congo red, and dried. Repeated extraction of the filtrate with chloroform gave a further 2.6 g III. Total yield 3.7 g (93%). After recrystallizing from alcohol the product had mp 121-122°; it was pale yellow, readily soluble in organic solvents and hot water, gave a cherry color with 10% sodium hydroxide solution, and with conc. H_2SO_4 a lemon yellow color, which in time changed to brown. Found: N 15.53, 15.14, S 17.50, 17.55%. Calculated for $C_7H_4N_2O_2S$: N 15.53; S 17.78%.

b) 3 g potassium dichromate in 40 ml water was added to a mixture of 1 g 5-methyl-4, 7-diaminobenzo-2, 1, 3-thiadiazole, 2 ml conc. H_2SO_4, and 8 ml water. After stirring for 2-3 mins, the black precipitate was filtered off, the filtrate extracted with chloroform, and the solvent evaporated off. Yield 0.87 g (87%) mp 120-122° (from alcohol), mixed mp with the substance prepared by method (a) undepressed.

5-Methyl-4, 7-dihydroxybenzo-2, 1, 3-thiadiazole (II).

a) A mixture of 1 g 5-methyl-4, 7-oxobenzo-2, 1, 3-thiadiazole and 10 g sodium hydrosulfite was added in portions to 70 ml boiling water. After boiling for 1-2 minutes, the reaction mixture was filtered hot, the filtrate extracted with ether, and the solvent distilled off. Yield 0.7 g (69.3%) of bright red material, which after recrystallizing from toluene had mp 180-181°. It was readily soluble in organic solvents and hot water, gave a violet color with 10% sodium hydroxide solution, and a brick shade of red with conc. H_2SO_4. It did not give a characteristic color with ferric chloride. Found: N 15.75, 15.79; S 17.24, 17.29%. Calculated for $C_7H_6N_2O_2S$: N 15.38; S 17.56%.

b) 1 g 4-Hydroxy-5-methyl-7-aminobenzo-2, 1, 3-thiadiazole in 20 ml conc. H_2SO_4 was diazotised with 0.4 g sodium nitrite in 6 ml H_2SO_4 (d 1.84), at 0.5°. Then the mixture was kept at room temperature for 15 min, poured into 200 ml cold water, the whole boiled for 10 min, and filtered hot. The filtrate was extracted with ether, and the ether distilled off from the extracts, giving 0.55 g dark brown material mp 95-100°, which was mixed with 5.5 sodium hydrosulfite and put into 40 ml boiling water, the whole boiled for 1 min, then filtered hot, and after cooling the filtrate was extracted with ether. The solvent was distilled off from the extracts, to give 0.45 g (45%) of a bright reddish material mp 173-174°, which after recrystallizing from toluene had mp 180-181°, undepressed on mixing with the substance prepared by method (a).

c) 1 g 4-Hydroxy-5-methyl-7-aminobenzo-2, 1, 3-thiadiazole in 20 ml conc. HCl, was diazotized at 0.5° with 0.4 g sodium nitrite in 5 ml water, then stirred for 15 min at room temperature, and the reaction products poured into 200 ml cold water, boiled for 10 min, and filtered hot. From the cold filtrate, ether extracted 0.9 g of dark brown material mp 129-135°, which was mixed with 9 g sodium hydrosulfite and treated as in method (b). Yield 0.76 g (76%) bright reddish material mp 176-177°, after recrystallization from toluene mp 180-181°, mixed mp with the substance prepared by methods (a) and (b), undepressed.

Quinhydrone from 5-methyl-4, 7-dioxobenzo-2, 1, 3-thiadiazole and 5-methyl-4, 7-dihydroxybenzo-2, 1, 3-thiazole (IX). An ethereal solution of 0.25 g 5-methyl-4, 7-dihydroxy-2, 1, 3-thiadiazole, recrystallized from toluene, was added to an ethereal solution of 0.25 g 5-methyl-4, 7-dioxobenzo-, 2, 1, 3-thiadiazole, recrystallized from alcohol, then after 3 min stirring, the ether was slowly evaporated at room temperature. Yield 0.5 g of velvety dark brown material, mp 141-143°, shrinking at 129°.

5-Methyl-4, 7-dioxobenzo-2, 1, 3-thiadiazole dioxime. A mixture of 0.5 g 5-methyl-4, 7-dioxobenzo-2, 1, 3-thiadiazole, 1 g hydroxylamine hydrochloride, and 20 ml alcohol was refluxed for 2 hr, cooled, and the precipitate (0.35 g) filtered off. A further 0.1 g material was obtained from the filtrate after concentration. Total yield 0.45 g (77.2%). The reaction product was readily soluble in dimethylformamide and dioxane, but practically insoluble in chloroform, benzene, water, and alcohols. After precipitation from small amounts of dimethylformamide or dioxane with water, it swelled up and blackened at 295-297°. Found: N 26.23, 26.49; S 15.55, 15.57%. Calculated for $C_7H_6N_4O_2S$: N 26.65; S 15.21%.

Bisulfite derivative of 5-methyl-4, 7-dioxobenzo-2, 1, 3 thiadiazole (VII). 30 ml of a solution of sodium bisulfite (d 1.24) was added to a warm solution of 0.6 g 5-methyl-4, 7-dioxobenzo-2, 1, 3-thiadiazole in 3 ml alcohol. After keeping for 1 hr 30 min at room temperature, the precipitate formed (0.27 g) was filtered off, washed with sodium bisulfite solution, and dried. In time a further 0.21 g separated from the filtrate. Total yield 0.48 g (35.5%) of material which is readily soluble in water, which did not melt but darkened at 280-300°. When dried to constant weight at 120-130°, it lost 2 molecules of water of crystallization. Found: N 6.7, 6.73; S 22.56, 23.04%. Calculated for $C_7H_4N_2O_2S \cdot 2NaHSO_3 \cdot 2H_2O$: N 6.60; S 22.65%.

4-Ethoxy-7-nitrobenzo-2, 1, 3-thiadiazole (XI).

a) 0.5 g sodium nitrite was added to 1 g 4-ethoxybenzo-2, 1, 3-thiadiazole in 10 ml conc. H_2SO_4, and the mixture stirred for 30 min at room temperature, or for 20 min at 50-60°. Then the reaction products were poured on to ice, the precipitate filtered off, washed with water until neutral to congo red, and dried. Yield 1.12 g material 104-109°, readily soluble in organic solvents; after recrystallizing from alcohol it has mp 149-151°. Found: N 19.02, 19.08; S 13.75, 13.99%. Calculated for $C_8H_7N_3O_3S$: N 18.68; S 14.22%.

b) A mixture of 1 g 4-ethoxybenzo-2, 1, 3-thiadiazole, 10 ml conc. H_2SO_4, and 0.5 g sodium nitrite was heated for 10 min on a steam bath, then cooled and poured on to ice. The black precipitate formed was filtered off, washed with water until neutral, treated with chloroform, and the chloroform evaporated. Yield 0.23 g material. Chloroform extracted a further 0.17 g material from the filtrate. Total yield 0.4 g (32%). After recrystallizing from alcohol, or precipitating from acetone with water, it had mp 149-150°, undepressed on mixing with material prepared by method (a).

c) 1 g 4-chloro-7-nitrobenzo-2, 1, 3-thiadiazole was added to an alcoholic solution of sodium ethoxide (20 ml absolute alcohol and 0.12 g sodium metal), and the whole refluxed for 2 hr, the precipitate filtered off, repeatedly washed with alcohol, and the filtrate evaporated. The residue was treated with water, filtered, and dried. Yield 0.59 g (56.6%) material, which after recrystallizing from alcohol, or precipitation from acetone with water, had mp 151-153°, undepressed on mixing with material prepared by method (a).

4-Ethoxy-7-aminobenzo-2, 1, 3-thiadiazole (XII). A mixture of 1 g 4-ethoxy 7-nitrobenzo-2, 1, 3-thiadiazole and 10 g sodium hydrosulfite was poured into 70 ml boiling water. After boiling for 1 min, the reaction products were filtered hot, and the precipitate on the filter washed with hot water. The filtrate was cooled, repeatedly extracted with ether, and the ether distilled off. Yield 0.36 g (41.6%) material, readily soluble in organic solvents, crystallized from toluene, rapidly darkening in air, especially when damp. It was difficult to determine the mp, since the reaction product darkened before melting. On passing hydrogen chloride into an ethereal solution of the amine, 4-ethoxy-7-aminobenzo-2, 1, 3-thiadiazole hydrochloride was precipitated quantitatively; it was readily soluble in water, and did not melt, but darkened and swelled at 180-190°. Found: S 13.99, 13.55; Cl 15.44, 15.13%. Calculated for $C_8H_9N_3OS \cdot HCl$: S 13.8; Cl 15.32%.

4-Ethoxy-7-acetaminobenzo 2, 1, 3-thiadiazole (IV). 0.5 g 4-ethoxy 7-aminobenzo-2, 1, 3-thiadiazole, 30 ml glacial acetic acid, 1 g anhydrous sodium acetate, and 6 ml acetic anhydride were heated together for one hr on a steam bath, the reaction products then cooled, and poured into 104 ml 25% ammonia, after which 100 ml water were added. The whole was extracted with chloroform, and the extracts concentrated to give 0.41 g (80%) material, readily soluble in hot water and organic solvents, mp 153-155° (from alcohol). Found: N 17.31, 17.46; S 13.55, 13.57%. Calculated for $C_{10}H_{11}N_3O_2S$: N 17.70; S 13.50%.

REFERENCES

1. V. G. Pesin, I; A. Belen'kaya-Lotsmanenko, and A. M. Khaletskii, ZhOKh, 34, 3763, 1964.
2. V. M. Berezovskii, Chemistry of the Vitamins [in Russian], Pishchepromizdat, Moscow, 1959.
3. V. G. Pesin, V. A. Sergeev, and A. M. Khaletskii, ZhOKh, 34, 1986, 1964.
4. V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, ZhOKh, 33, 1759, 1963.
5. V. G. Pesin, A. M. Khaletskii, and I. A. Lotsmanenko, ZhOKh, 33, 1746, 1963.

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Leningrad Chemical-Pharmaceutical Institute