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COMPOUNDS WITH POTENTIAL ANTITUBERCULAR ACTIVITY

XII. Synthesis and Some Reactions of 6-Alkoxy-2-mercaptobenzoxazoles*

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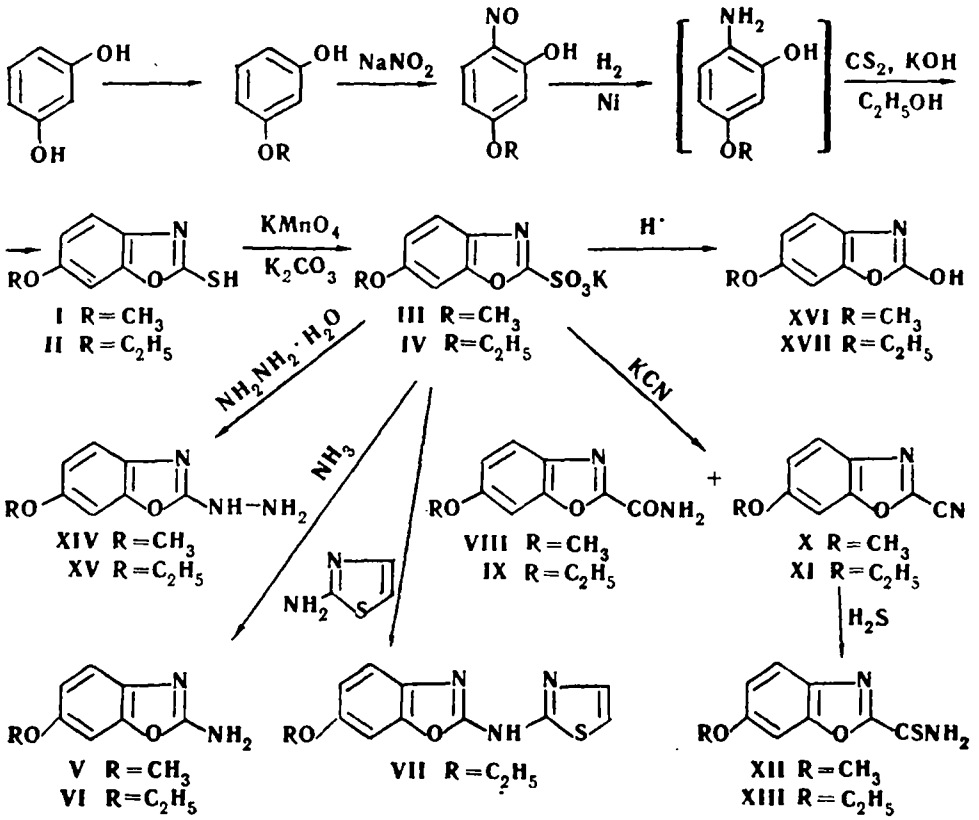
Nitrosation of resorcinol monoalkyl ethers, followed by reduction of the nitroso compounds to amines, and reaction of the latter with potassium xanthate gives 6-methoxy- and 6-ethoxy-2-mercaptobenzoxazoles. Oxidation of the latter with potassium permanganate gives the potassium salts of the corresponding 6-alkoxy-2-benzoxazole sulfonic acids. Treatment of these salts with potassium cyanide gives a mixture of amides and nitriles of the 6-alkoxy-2-benzoxazole carboxylic acids; the nitriles are converted into thioamides. Reaction of potassium 6-ethoxy-2-benzoxazole sulfonates with 2-aminothiazole gives a quite insignificant yield of 6-ethoxy-2-(thiazolyl-2'-amino) benzoxazole.

An alkoxy group in an organic molecule often enhances its biological activity (more particularly, it increases the tuberculostatic action of thiocarbanilides), so it was of interest to prepare alkoxy-substituted benzoxazoles with a view to investigating their biological action.

The aim of the present work was to synthesize hitherto undescribed 6-alkoxy-2-mercaptobenzoxazoles and to investigate some of their reaction products.

The most general method for preparing mercaptobenzoxazoles is condensation of the appropriate o-aminophenols with potassium xanthate. We have prepared the 5-alkoxy-2-aminophenols necessary for synthesizing 6-alkoxy-2-mercaptobenzoxazoles, via the mono-alkyl ethers, from resorcinol, by nitrosating the ethers and reducing the nitroso group to an amino group [1]. Resorcinol monoethyl ether was obtained in about 50% yield by treating resorcinol with ethyl bromide in the presence of alkali [2]. A similar reaction was carried out with methyl iodide, but, there, the yield of resorcinol monomethyl ether did not exceed 23-26%. A somewhat better yield (57%) of the monomethyl ether was obtained by methylating resorcinol with dimethyl sulfate [4]. Nitrosation of resorcinol monomethyl ether with sodium nitrite in acetic acid [1] gave 2-nitroso-5-ethoxyphenol. The same method also gave 2-nitroso-5-methoxyphenol. The literature method of reducing nitrosophenols (in the presence of palladium on charcoal) [1] was not followed; instead, reduction of 2-nitro-5-methoxy- and -5-ethoxyphenol was effected at atmospheric pressure in the presence of Raney



*For Part XI see [6].

nickel, and the resultant alcohol solutions of 2-amino-5-methoxy- and -5-ethoxyphenol were condensed with potassium xanthate, without isolating the amines.

This reaction gave 2-mercapto-6-methoxy-(I) and 2-mercapto-6-ethoxybenzoxazole (II), the yields of the technical materials being 85%. Oxidation of 6-alkoxy-2-mercaptobenzoxazoles with potassium permanganate in the presence of potassium carbonate [5] gave potassium 6-alkoxy-2-benzoxazole sulfonates in about 90% yield (III and IV).

Due to the high reactivity of the sulfonic acid group, these salts readily undergo nucleophilic substitution. Treatment with potassium cyanide at 60–70°C under a layer of benzene led to isolation of mixed amides (VII, IX) and nitriles (X, XI) of the corresponding 6-alkoxy-2-benzoxazole carboxylic acids. Thioamides (XII, XIII) were obtained from the nitriles X, XI. Treatment of the potassium salts of 6-alkoxy-2-benzoxazole carboxylic acids with ammonia gave 6-methoxy-(V) and 6-ethoxy-2-aminobenzoxazoles (VI). Since the previously prepared 2-(thiazolyl-2'-amino) benzoxazole [6] showed high tuberculostatic activity in vitro, it was of interest to ascertain the effect of an alkoxy group at position 6 on its tuberculostatic activity. For that purpose, potassium 6-alkoxy-2-benzoxazole sulfonates were condensed with 2-aminothiazole. It was found that reaction of 6-alkoxy derivatives proceeds less readily than with unsubstituted potassium 2-benzoxazole sulfonate.

Heating potassium 6-ethoxy-2-benzoxazole sulfonate for 31 hr with 2-aminothiazole led to the isolation of a quite insignificant yield of 6-ethoxy-2-(thiazolyl-2'-amino)benzoxazole (VII) which, like 2-(thiazolyl-2'-amino) benzoxazole, is characterized by solubility in dilute alkali. Also isolated from the reaction products were an alkali-insoluble substance of unknown structure, and the starting potassium salt.

The analogous reaction with potassium 6-methoxy-2-benzoxazole sulfonate gave only an alkali-insoluble compound, whose elementary analysis data did not correspond to 6-methoxy-2-(thiazolyl-2'-amino)-benzoxazole.

Reaction of potassium 6-alkoxy-2-benzoxazole sulfonates with hydrazine hydrates gave 6-methoxy-(XIV) and 6-ethoxy-2-hydrazinobenzoxazole (XV). The yields were considerably lower than when using the unsubstituted potassium 2-benzoxazole sulfonate. Warming potassium 6-alkoxy-2-benzoxazole sulfonates with dilute hydrochloric acid gave the corresponding 6-alkoxy-2-hydroxybenzoxazoles (XVI and XVII).

Investigation of the antitubercular action of the compounds showed* that significant tuberculostatic activity in vitro is possessed by the thioamides of 6-ethoxy-2-benzoxazole carboxylic acid (minimum tuberculostatic concentration 0.5 γ/ml without serum, $H_{37}Rv$ strain), 6-ethoxy-2-hydrazinobenzoxazole (4 γ/ml), and 6-ethoxy-2-(thiazolyl-2'-amino) benzoxazole (8 γ/ml); however, the activities of the first two of these compounds are sharply cut by serum (to 32 and 64γ/ml, respectively).

Serum does not lower the activity of 6-ethoxy-2-(thiazolyl-2'-amino) benzoxazole. Other 6-alkoxybenzoxazole derivatives had low activities.

Experimental

2-Nitroso-5-ethoxyphenol. A mixture of 25.07 g resorcinol monoethyl ether [1] and 16.5 ml glacial AcOH was cooled to 0° C, and 12.5 g $NaNO_2$ added in portions. After stirring for 30 min, cooling was removed, the reaction products diluted with water, and the precipitate filtered off. After drying, the material was extracted with benzene in a Soxhlet apparatus, and the benzene solution then evaporated. The residue consisted of 24 g dark green crystalline substance, mp 146.5–147.5° C (yield ~ 80%). For analysis it was recrystallized from EtOH, when it gave orange plates mp 149-150° C (the literature gives mp 178° C [1], 147–148° C [3]). Found: C 57.48; H 5.49; N 8.49%. Calculated for $C_8H_9NO_3$: C 57.47; H 5.42; N 8.30%.

2-Nitroso-5-methoxyphenol. Prepared similarly from resorcinol monomethyl ether [2], yield ~ 75%, mp 155–157° C. The literature gives [7] mp 157°.

6-Ethoxy-2-mercaptobenzoxazole (II). A suspension of 4.04 g technical 2-nitroso-5-ethoxyphenol in 130 ml EtOH was hydrogenated in the presence of Raney Ni, at 20° and atmospheric pressure. After absorption of hydrogen had ceased, the catalyst was quickly filtered off, 84 ml water added to the dark orange ethanolic solution of amine, and the mixture heated for 4 hr 30 min at 70–85° C with potassium ethyl xanthate prepared from 0.7 g KOH, 7 ml EtOH, and 1.8 ml CS_2. The hot solution was treated with charcoal, reheated to 70°, 25 ml water added, and a solution of 3.4 ml AcOH in 7 ml water added dropwise at the same temperature. After heating for 30 min, the reaction products

*The investigations were carried out in the chemotherapy division of VNIKhFI (Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific Research Institute) by T. N. Zykova.

were cooled in an ice mixture, the precipitate filtered off, the mother liquor evaporated to about 100 ml under vacuum, and the precipitate again filtered off. 4.03 g dark brick-colored material mp 205° C was obtained, yield ~ 85%. For analysis, it was recrystallized from 50% MeOH, when it formed colorless plates, which rapidly turned pinkish-orange in air, mp 214–215°C. Found: C 55.22; H 4.73; N 6.85; S 15.99%. Calculated for $C_9H_9NO_2S$: C 55.36; H 4.64; N 7.17; S 16.42%.

6-Methoxy-2-mercaptobenzoxazole (I). Prepared similarly, from 2-nitroso-5-methoxy-phenol, yield of technical product ~ 85%, mp 172–174°C (50% MeOH). Found: C 53.13; H 4.06; N 7.75; S 17.36%. Calculated for $C_8H_7NO_2S$: C 53.02; H 3.89; N 7.73; S 17.65%.

Potassium 6-ethoxy-2-benzoxazole sulfonate (IV). A solution of 18.7 g $KMnO_4$ in 187 ml H_2O at 60–70° C was added dropwise to a mixture of 11.07 g II, 4.78 g K_2CO_3, and 86 ml H_2O cooled with ice water, and stirring at 20° was continued until the permanganate color completely disappeared. The MnO_2 precipitate was filtered off, and thrice treated with water at 70–75°C, 200, 130, and 110 ml (total 440 ml) being used, filtration following. The bulked filtrates were salted out with KCl, using 17.1 g dry KCl or 43 ml saturated KCl solution per 100 ml of filtrate. The precipitate of potassium 6-ethoxy-2-benzoxazole sulfonate was filtered off and washed with a small amount of ice water. Drying gave 15 g (94%) technical salt, which can be used unpurified for the subsequent reactions. For analysis, the substance was twice recrystallized from water, using charcoal. Found: C 38.64; H 3.23; N 5.14%. Calculated for $C_9H_8KNO_5S$: C 38.42; H 3.58; N 4.98%.

Potassium 6-methoxy-2-benzoxazole sulfonate (III). Prepared similarly from I, yield 75%. Found: C 35.89; H 2.19; N 5.40%. Calculated for $C_8H_6KNO_5S$: C 35.70; H 2.25; N 5.20%.

Reaction of III with potassium cyanide. A suspension of 2.5 g III in 12.5 ml water was prepared, covered with a layer of benzene, cooled, and a solution of 2.2 g KCN in 10 ml H_2O dropped in, after which the mixture was stirred for about 3 hr at 65–70°C (bath temperature), the benzene being periodically decanted at 15–20 min intervals until material no longer passed into it (tested on glass). The benzene solution was evaporated to dryness, the residue (1.02 g) treated with 25 ml cold benzene. The benzene-insoluble material (0.18 g) had mp 205–206° C (ex 50% EtOH): it was 6-methoxy-2-benzoxazole carboxamide (VIII), colorless crystals, slightly soluble in cold benzene, soluble in EtOH. Found: C 56.38; H 4.33%. Calculated for $C_9H_8N_2O_3$: C 56.25; H 4.19%.

The benzene extract was again evaporated to dryness and the residue (0.84 g) recrystallized from 50% EtOH, to give 6-methoxy-2-benzoxazolecarbonitrile (X), colorless crystals, fairly soluble in EtOH and C_6H_6, mp 90–91° C. Found: C 62.14; H 3.48; N 15.86%. Calculated for $C_9H_6N_2O_2$: C 62.06; H 3.47; N 16.08%.

Reaction of IV with potassium cyanide. This was carried out as in the previous experiment. 1.4 g IV gave 0.54 g mixed amide and nitrile of 6-ethoxy-2-benzoxazole carboxylic acid. The mixture was treated with cold benzene, the benzene-insoluble residue (0.24 g) was 6-ethoxy-2-benzoxazole carboxamide (IX), recrystallized from 50% EtOH, it formed colorless needles, mp 192–194°C. Found: C 58.19; H 4.73%. Calculated for $C_{10}H_{10}N_2O_3$: C 58.25; H 4.89%.

The benzene filtrate was evaporated, the residue treated with 5% NaOH solution, and washed with water, when 0.12 g colorless crystals were obtained, mp 56–58° C (ex 50% EtOH), which was 6-ethoxy-2-benzoxazole carbonitrile (XI). Found: C 64.10; H 4.60; N 14.38%. Calculated for $C_{10}H_8N_2O_2$: C 63.82; H 4.28; N 14.88%.

Acidification of the alkali solutions gave material mp 153.5–156° C, undepressed mixed mp with 6-ethoxy-2-benzoxazole (XVII) prepared by hydrolyzing IV (see below).

6-Methoxy-2-benzoxazole carbothioamide (XII). A stream of dry H_2S was passed for 1 hr 30 min into a solution of 0.39 g nitrile X in 15 ml EtOH to which 0.1 ml Et_3N had been added. After cooling in ice-salt, the precipitate was filtered off, yield 0.24 g yellow crystalline material, mp 225–226° C (ex EtOH). Found: C 52.18; H 3.87; N 13.51; S 15.21%. Calculated for $C_9H_8N_2O_2S$: C 51.95; H 3.88; N 13.45; S 15.33%.

6-Ethoxy-2-benzoxazole carbothioamide (XIII). The reaction was carried out as in the preceding experiment. 0.4 g XI gave 0.31 g yellow crystalline compound mp 178–180° C (ex benzene). Found: C 54.26; H 4.46; S 14.44%. Calculated for $C_{10}H_{10}N_2O_2S$: C 54.04; H 4.54; S 14.43%.

6-Methoxy-2-aminobenzoxazole (V). A suspension of 2 g III in 20 ml concentrated aqueous ammonia was heated on a water-bath to 70–75°C for 1 hr 30 min. After cooling, the precipitate was filtered off and washed with water, yield 0.95 g (77.8%), colorless compound mp 178.5–181°C (ex water). Found: C 58.28; H 4.62; N 17.16%. Calculated for $C_8H_8N_2O_2$: C 58.53; H 4.91; N 17.06%.

6-Ethoxy-2-aminobenzoxazole (VI). The reaction was carried out as in the previous experiment. 3.85 g IV gave 1.56 g (64%) colorless crystalline compound mp 185–186° C (aqueous EtOH) (the literature [1] gives mp 182° C).

6-Ethoxy-2-(thiazolyl-2'-amino) benzoxazole (VII). A mixture of 1 g IV, 10 ml water, and 1 g 2-aminothiazole

was heated at 100°C for 31 hr. The resultant precipitate (0.21 g) was filtered off hot,* and treated with hot MeOH. The undissolved precipitate was filtered off, and on cooling, the MeOH solution deposited a crystalline compound mp 215° C (after 2 recrystallizations from MeOH). It was soluble in alkalies, insoluble in water and dilute acids. Found: C 55.18; H 4.31; S 12.18%. Calculated for $C_{12}H_{11}N_3O_2S$: C 55.15; H 4.24; S 12.27%.

The MeOH-insoluble part of the precipitate was washed with 5% alkali, and recrystallized from aqueous dimethylformamide. It decomposed at 240–241°C. Found: C 50.52; H 4.73; N 19.47; S 17.25%. Its nature was not established.

6-Ethoxy-2-hydrazinobenzoxazole (XV). 6 ml hydrazine hydrate was gradually added, with cooling by ice water, to a suspension of 3 g IV in 7 ml water. Then the mixture was heated at 70–75° C for 1 hr, cooled, and the precipitate filtered off. Yield 1.4 g (86%) crystalline pink compound decomposing at 155.5–157° C (ex water plus hydrosulfite). Found: C 56.08; H 5.66; N 21.54%. Calculated for $C_9H_{11}N_3O_2$: C 55.95; H 5.74; N 21.75%.

6-Methoxy-2-hydrazinobenzoxazole (XIV). The reaction was carried out as in the previous experiment. 1 g III and 2 ml hydrazine hydrate gave 0.39 g (51%) crystalline substance, decomposing at 170–171° C (ex water). Found: C 53.22; H 5.15%. Calculated for $C_8H_9N_3O_2$: C 53.62; H 5.06%.

6-Ethoxy-2-hydroxybenzoxazole (XVII). A suspension of 0.18 g IV in a few ml 0.1 N HCl was heated for a few minutes at 70–80°C. SO_2 was evolved. The colorless precipitate formed after cooling (0.1 g) was filtered off, and washed with cold water, mp 156–158°C (ex 50% EtOH). Found: C 60.26; H 4.90; N 8.15%. Calculated for $C_9H_9NO_3$: C 60.33; H 5.06; N 7.82%.

6-Methoxy-2-hydroxybenzoxazole (XVI). Prepared similarly to the above. 0.6 g III gave 0.23 g (62%) compound, mp 156–157.5°C (ex aqueous EtOH), (the literature gives [8] mp 154°C). Found: C 58.52; H 4.24; N 8.63%. Calculated for $C_8H_7NO_3$: C 58.18; H 4.27; N 8.48%.

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*On cooling, the aqueous mother liquor gave 0.25 g of the starting material IV.