UDC 547.787.3

COMPOUNDS WITH POTENTIAL ANTITUBERCULAR ACTIVITY

XI. Synthesis of Some Derivatives of 2-Aminobenzoxazole*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 2, pp. 205–211, 1966

2-Aminobenzoxazole and a series of its N-substituted derivatives were prepared by the reaction of potassium benzoxazole-2-sulfonate with ammonia and various amines; some 6-nitro- and 6-acetamido-2-aminobenzoxazoles were also obtained. The reaction of 6-nitro-2-mercaptobenzoxazole with heterocyclic amines involves the initial formation of salt-like compounds with the mercapto-group, with subsequent elimination of hydrogen sulfide. Nitration of 2-aminobenzoxazole yields a mixture of 6-nitro-2-aminobenzoxazole and 6-nitro-2-nitraminobenzoxazole.

The object of this work was the synthesis of some 2-amino- and N-substituted 2-aminobenzoxazoles (unsubstituted in the benzene ring, and also with nitro- and acetamido groups in the 6-position) with a view to investigating their antibacterial and, in particular, tuberculostatic activity.

The methods most generally used for the preparation of 2-aminobenzoxazoles and their N-substituted derivatives are: reaction of 2-chlorobenzoxazole with various amines [1], condensation of the corresponding o-aminophenols with cyanogen bromide [2], and cyclization of substituted 2-hydroxyphenylthioureas by means of lead oxide [2, 3]. Some N-alkyl-substituted 2-aminobenzoxazoles have been prepared by reaction of the corresponding amines with 2-methylsulfonylbenzoxazole [4], but the authors give no yields for this reaction. Bearing in mind the fact that the sulfo group in the 2-position of the benzoxazole ring is very labile and can be replaced by various nucleophilic groups [5], we decided to try potassium 2-benzoxazole sulfonate as starting material. (A convenient method for the synthesis of this compound is given in [6]). This salt reacts with a variety of aliphatic, alicyclic, and heterocyclic amines; the reaction is usually carried out in aqueous solution, using a two- to threefold excess of the amine. By heating potassium 2-benzoxazole sulfonate briefly with aqueous ammonia, 2-aminobenzoxazole was obtained in 90% yield. Similarly, the reaction with piperidine and cyclohexylamine gave 2-(N-piperidino)- and 2-cyclohexylaminobenzoxazole, but in poorer yield. With diethanolamine, dimethylaminopropylamine, and β-morpholinoethylamine, syrupy products were obtained which were difficult to crystallize, and some of these were therefore isolated as dihydrochlorides. In obtaining 2-(2-pyridylamino)- and 2-(2-thiazolylamino) benzoxazoles, the low basicity of the corresponding amines made it necessary to heat the reaction mixture for 16–21 hr at 110–120° (bath temp.); under these conditions the potassium 2-benzoxazolesulfonate was partially converted to 2-benzoxazolone, which was isolated as a by-product. It is interesting to note that the hydrogen atom of the secondary amino group in 2-(2-thiazolylamino)-benzoxazole is acidic in character; this compound is insoluble in mineral acids but readily soluble in aqueous alkalies, ammonia, and triethylamine. In an attempt to react potassium 2-benzoxazolesulfonate with 2-amino-4, 6-dimethylpyrimidine, only 2-benzoxazolone was isolated.

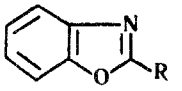
Attempts to obtain the monosubstituted compound from ethylenediamine using a large excess of the amine were unsuccessful, both amino groups reacting.

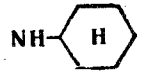
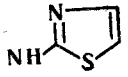
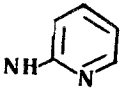
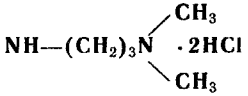
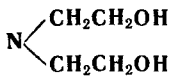
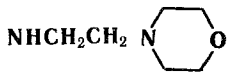
The synthesis of 6-nitro-2-aminobenzoxazole by the reaction of 4-nitro-2-hydroxybenzonitrile with sodium azide has been described in the literature [7]; we have synthesized this compound from potassium 6-nitro-2-aminobenzoxazole sulfonate and ammonia. The influence of the nitro group causes this reaction to proceed instantaneously, with cooling, to give 6-nitro-2-aminobenzoxazole in 93% yield. Potassium 6-nitro-2-benzoxazole sulfonate is, however, obtained in rather low yields, and the nitration of 2-aminobenzoxazole was therefore investigated. By carrying out this reaction with a mixture of nitric acid (d 1.5) and concentrated sulfuric acid, a mixture of two compounds was obtained. One of these, insoluble in mineral acids, was 6-nitro-2-nitraminobenzoxazole, and the other 6-nitro-2-aminobenzoxazole, identical with that obtained from potassium 6-nitro-2-benzoxazole sulfonate. The amount of 2-nitramino-6-nitrobenzoxazole obtained increases with increasing reaction time. Thus, on keeping the reaction mixture at room temperature for two weeks, only 2-nitramino-6-nitrobenzoxazole was obtained, in about 82% yield.

Since the presence of a nitro group in the 6-position of the benzoxazole nucleus increases the lability of the 2-mercapto group [8], to prepare 2-(2-pyridylamino)- and 2-(2-thiazolylamino)-6-nitrobenzoxazole we reacted 6-nitro-2-mercaptobenzoxazole with 2-aminopyridine and 2-aminothiazole. On carrying out this reaction in aqueous solution at 100°, stable salt-like compounds of the amines with the mercapto group were obtained. On heating above their melting points either in the absence of a solvent or in diphenyl ether, these compounds lose hydrogen sulfide to give the corresponding 2-(2-pyridylamino)- and 2-(2-thiazolylamino)-6-nitrobenzoxazoles.

* For Part X see [6].

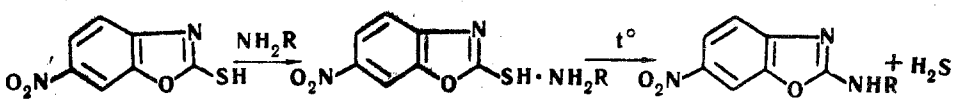
N–Substituted 2–Aminobenzoxazoles



R	Time (hr); reaction temp. (°C)	mp (°C) (solvent for recrystallization)	Molecular formula	C		H		N		Yield, %
				Found	Calc.	Found	Calc.	Found	Calc.	
	1.5; 60—70	73—74 (petroleum ether)	$C_{12}H_{14}N_2O$	71.17	71.20	6.87	6.97	14.12	13.85	69
	5; 60	108.5—110 (50% ethanol+water)	$C_{13}H_{16}N_2O$	72.39	72.19	7.45	7.41	12.77	12.95	77
	21; 100—110	240—242 (isobutyl alcohol)	$C_{10}H_7N_3OS$	55.14	55.29	3.17	3.24	19.13	19.34	50
	16; 100	223.5—224 (ethanol)	$C_{12}H_9N_3O$	68.23	68.23	4.49	4.29	19.63	19.89	50
	3; 60	235 (decomp) (abs. ethanol)	$C_{12}H_{17}N_3O \cdot 2HCl$*	49.30	49.32	6.67	6.58	14.10	14.38	37
	4; 90	112—114 (ethyl acetate)	$C_{11}H_{14}N_2O_3$	59.25	59.44	6.38	6.34	—	—	36
	7; 60—65	242 (decomp) (abs. ethanol)	$C_{13}H_{17}N_3O_2 \cdot 2HCl$**	—	—	—	—	13.17	13.12	50

* Found: Cl 24.29%. Calculated: Cl 24.26%.

** Found: Cl 22.29%. Calculated: Cl 22.15%.



R = 2-pyridyl and 2-thiazolyl

The last compound was also obtained by reaction of potassium 6-nitro-2-benzoxazole sulfonate with 2-aminothiazole.

Potassium 6-acetamido-2-benzoxazole sulfonate [6] and ammonia yielded 6-acetamido-2-aminobenzoxazole. An attempt to hydrolyze the acetyl group by heating with 10% NaOH led to complete resinification of the compound. Prolonged heating of potassium 6-acetamido-2-benzoxazole sulfonate with 2-aminothiazole led to the formation of 6-acetamido-2-(2-thiazolylamino) benzoxazole.

All the compounds prepared above were examined for antibacterial activity in the chemotherapy section of the All-Union Scientific Research Chemical-Pharmaceutical Institute by T. N. Zykovaya and S. N. Milovanovaya. In vitro tests showed high activity with 2-(2-thiazolylamino) benzoxazole (minimum tuberculostatic concentration in absence of serum 0.5γ/ml, and in serum 2γ/ml; strain H37Rv). The introduction of a nitro group or acetamido group in position 6 results in a marked reduction in activity. 2-(2-Pyridylamino) benzoxazole is less active (4γ/ml without serum; 15γ/ml in the presence of serum). However, in experiments with mice, 2-(2-thiazolylamino) benzoxazole was devoid of therapeutic effect. The remaining derivatives of 2-aminobenzoxazole were of low activity.

Experimental

2-Aminobenzoxazole. A suspension of 5 g potassium benzoxazole sulfonate [6] in 37 ml aqueous ammonia was heated at 60-70° for 1 hr 30 min. The precipitate which separated was filtered off after cooling and washed with ice water. Weight 2.59 g (yield 91%). Colorless crystals, mp 129-130° (literature values: 132° [7], 129-130° [10], 127° [11]). 2-Piperidino- and 2-cyclohexylamino-benzoxazole were obtained similarly (see table).

N, N'-Bis-(2-benzoxazolyl) ethylenediamine. A mixture of 1 g potassium 2-benzoxazole sulfonate, 5 ml of a 20% aqueous solution of ethylenediamine, and 10 ml water was stirred at room temperature for 2 hr, then kept overnight. The precipitate was filtered off after cooling and washed with cold water. There was obtained 0.7 g of colorless crystals, mp 215-217° (from 70% alcohol). Found: C 65.22, H 4.86, N 19.18% . Calculated for $C_{16}H_{14}N_4O_2$: C 65.25, H 4.79; N 19.03%.

2-(2-Thiazolylamino) benzoxazole. A mixture of 29.73 g potassium 2-benzoxazole sulfonate, 12.54 g 2-aminothiazole, and 188 ml water was heated at 118-125° (bath temp.) for 21 hr. The reaction mixture was filtered hot and the solid washed with hot water. There was obtained 13.84 g of lilac crystals. Recrystallization from isobutanol with carbon gave almost colorless crystals, mp 240-242°, insoluble in acids and readily soluble in alkalies (see table). On cooling the mother liquors, there separated 6.26 g of a colorless compound, mp 125-135°, readily soluble in alkalies and containing no sulfur. It was recrystallized from water to give crystals, mp 138-141°, which gave no depression of melting point on admixture with 2-benzoxazolone.

Similar results were obtained when the reaction was carried out with a twofold excess of 2-aminothiazole.

2-Dimethylaminopropylaminobenzoxazole dihydrochloride. A mixture of 2 g potassium 2-benzoxazole sulfonate, 2 g dimethylaminopropylamine, and 15 ml water was heated at 60° for 3 hr. The oil which separated was extracted with ether, and the ethereal extract washed with water and dried over magnesium sulfate. The residue after removal of the solvent was dissolved in 20 ml of absolute alcohol, the solution treated with carbon, and a saturated solution of HCl in alcohol added until it was acid to congo red. The solid (0.91 g) which separated was filtered off and washed with absolute ether.

2-(β-Morpholinoethylamino) benzoxazole dihydrochloride was obtained similarly.

2-Diethanolaminobenzoxazole. A mixture of 2 g of potassium 2-benzoxazole sulfonate, 2 g of diethanolamine, and 30 ml of water was heated at 90° for 4 hr, the reaction mixture evaporated in vacuo and the residue treated with absolute alcohol. The alcohol-insoluble material was filtered off, the alcoholic solution evaporated, and the syrupy residue triturated with a small quantity of cold water. The crystalline solid which formed was filtered off with strong cooling. There was obtained 0.67 g of a colorless, crystalline compound, readily soluble in water and alcohol, and insoluble in benzene, hexane, and petroleum ether (see table).

6-Nitro-2-aminobenzoxazole. A solution of 0.27 g potassium 6-nitro-2-benzoxazole sulfonate in 5 ml of water was added to 10 ml of aqueous ammonia, with ice-water cooling. The precipitate which formed was stirred for 30 min at room temperature, then filtered off. Weight 0.16 g (yield 93%), mp 241° (literature value [7], 244°). Found: C 47.53; H 3.04; N 23.80%. Calculated for $C_7H_5N_3O_3$: C 47.48; H 2.81; N 23.45%.

Nitration of 2-aminobenzoxazole. To 3.42 ml of concentrated sulfuric acid (d 1.83) was added 1 g 2-aminobenzoxazole at such a rate that the temperature did not rise above 30°; then the mixture was cooled to −5° and a mixture of 1 ml nitric acid (d 1.5), freed from oxides of nitrogen, and 1.1 ml concentrated sulfuric acid, cooled to −5°, added. The addition was carried out at such a rate that the temperature did not exceed 0°. The reaction mixture was then stirred for 30 min at room temperature and poured onto ice. The yellow precipitate which separated from the acidic solution was filtered off, washed with water, treated with an aqueous solution of ammonia, and again with water. There was obtained 0.48 g 6-nitro-2-nitraminobenzoxazole as a light yellow, crystalline substance, insoluble in water, mineral acids, and benzene. Decomposition temperature 327° (from dimethylformamide or aqueous alcohol). Yield 28.7%. Found: C 37.36; H 1.70; N 24.73%. Calculated for $C_7H_4N_4O_5$: C 37.50; H 1.78; N 25.00%.

The acid filtrate from the 6-nitro-2-nitraminobenzoxazole was basified with aqueous ammonia, with cooling. The solid which separated was filtered off, washed with water, and dried. There was obtained 0.83 g (62.4%) of a bright yellow crystalline compound, decomp. 246° (from water), which gave no depression of melting point on admixture with 6-nitro-2-aminobenzoxazole obtained from potassium 6-nitro-2-benzoxazolesulfonate (see above).

6-Nitro-2-(2-pyridylamino) benzoxazole. A mixture of 0.5 g 6-nitro-2-mercaptobenzoxazole [9], 0.5 g 2-aminopyridine, and 10 ml water was heated on a boiling water bath for 3 hr. The bright orange precipitate which formed initially, gradually turned yellow. After cooling, the precipitate was filtered off. There was obtained 0.74 g of yellow crystalline material (the aminopyridine salt of 6-nitro-2-mercaptobenzoxazole), soluble in ammonia and alkalies to give an orange color, and insoluble in ether. Decomp. 178° (from alcohol) with evolution of hydrogen sulfide and subsequent solidification. Found: C 49.78; H 3.48; N 19.30; S 10.83%. Calculated for $C_{12}H_{10}N_4O_3S$: C 49.64; H 3.47; N 19.30; S 11.04%.

This compound (0.54 g) was heated in an open flask for 30 min at 180–185°; at 175–178° the compound melted with liberation of hydrogen sulfide, then resolidified. The reaction mixture was treated with hot ethanol, and the insoluble material recrystallized from dimethylformamide with carbon. There was obtained 0.21 g of yellow crystalline material, decomposing at 354°, insoluble in alcohol, ether, and benzene. Found: C 56.14; H 2.93%. Calculated for $C_{12}H_8N_4O_3$: C 56.24; H 3.14%.

The same compound was obtained by heating a mixture of 0.5 g 6-nitro-2-mercaptobenzoxazole with 1 g 2-aminopyridine (a fourfold excess) for several hours at 170–180°.

6-Nitro-2-(2-thiazolylamino) benzoxazole. a) A mixture of 0.5 g 6-nitro-2-mercaptobenzoxazole, 0.5 g 2-aminothiazole, and 10 ml water was heated on a boiling water bath for 3 hr. After working up as described in the previous preparation, there was obtained 0.79 g of the aminothiazole salt as a yellow crystalline material, decomp. 193° (from alcohol). Found: C 40.80; H 2.89; N 18.41; S 21.64%. Calculated for $C_{10}H_8N_4O_3S_2$: C 40.54; H 2.72; N 18.98; S 21.64%. The salt obtained above (0.78 g) was heated for 30 min at 180–196° with 5 ml of diphenyl ether; the solid which separated was filtered off, washed with petroleum ether, and then with hot alcohol. The alcohol-insoluble yellow solid (0.13 g) was recrystallized from dimethylformamide; it decomposed at > 360°. Found: C 46.11; H 2.43; N 20.90; S 11.87%. Calculated for $C_{10}H_6N_4O_3S$: C 45.79; H 2.30; N 21.29; S 12.22%.

b) A mixture of 0.1 g potassium 6-nitro-2-benzoxazole sulfonate [6], 0.07 g 2-aminothiazole, and 3 ml water was heated on a boiling water bath for 30 min. The yellow precipitate which separated was washed with water; weight 0.06 g, decomposition temp. above 360°. The compound was identical with 6-nitro-2-(2-thiazolylamino) benzoxazole obtained by method a).

6-Acetamido-2-aminobenzoxazole. A mixture of 0.4 g potassium 6-acetamido-2-benzoxazole sulfonate [6] with 4 ml aqueous ammonia was heated at 60–70° for 1 hr 30 min. After cooling, the precipitate was filtered off and washed with cold water. Weight 0.29 g (yield 93.5%), mp 249–250° (from water). Found: C 56.48; H 4.67; N 21.92%. Calculated for $C_9H_9N_3O_2$: C 56.54; H 4.74; N 21.98%.

6-Acetamido-2-(2-thiazolylamino) benzoxazole. A mixture of 0.73 g potassium 6-acetamido-2-benzoxazole sulfonate, 0.5 g 2-aminothiazole, and 15 ml water was heated on a boiling water bath for 33 hr. The precipitate was filtered from the hot solution and washed with water. There was obtained 0.34 g of crystals, soluble in alkalies but insoluble in ether and cold alcohol. Mp 296–298° (from isobutyl alcohol). Found: N 20.37; S 11.83%. Calculated for $C_{12}H_{10}N_4O_2S$: N 20.43; S 11.69%.

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23 December 1964

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