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REACTION OF 2-AMINOBENZOXAZOLES WITH COMPOUNDS WITH ACTIVATED MULTIPLE BONDS

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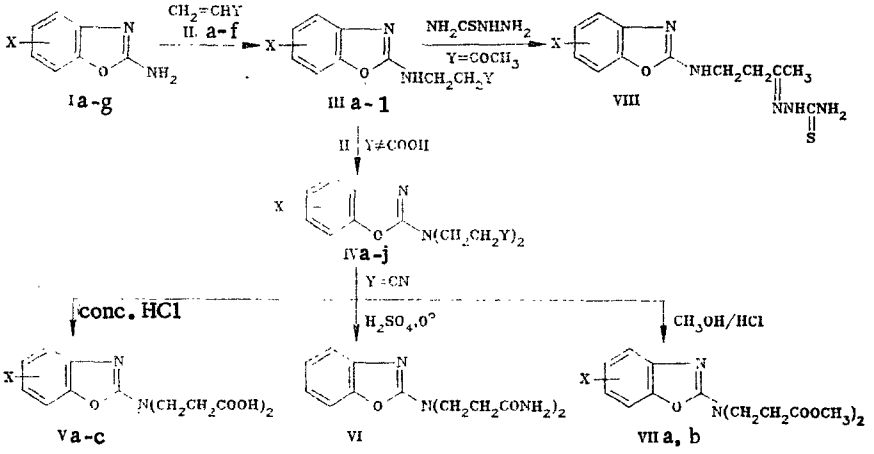
The reaction of 2-aminobenzoxazoles with activated alkenes of the acrylic acid type and its derivatives and methyl vinyl ketone proceeds in the presence of basic catalysts to give products of mono- and diaddition at the exocyclic nitrogen atom. The reaction of 5(6)-substituted 2-aminobenzoxazoles with esters of propyl and acetylenedicarboxylic acids in the absence of catalysts leads to the production of condensed 2-oxopyrimidines. The effect of substituents and the reaction conditions on the course of the process was investigated.

A considerable number of reactions involving the addition of heterocyclic amines to compounds that contain multiple carbon–carbon bonds have been described in the literature. The possibility of the synthesis, on the basis of these reactions, of new condensed heterocyclic compounds with potential pharmacological activity have continued to be of interest to synthetic chemists.

Continuing our study of the reactions of condensed 2-aminooxazoles with compounds with activated multiple bonds [1, 2], we have studied the reaction of 2-aminobenzoxazoles (Ia) and its derivatives (Ib-g) with activated alkenes and alkynes: esters of acrylic acid (IIa, b), acrylonitrile (IIc), acrylamide (IId), acrylic acid (IIe), methyl vinyl ketone (IIf), dimethyl acetylenedicarboxylate (IXa), and ethyl propiolate (IXb).



I a X=H; b X=5-CH_3; c X=5-Cl; d X=5-NO_2; e X=6-Cl; f X=6-Br; g X=6-NO_2; II a Y=$COOCH_3$; b Y=$COOC_2H_5$; c Y=CN; d Y=$CONH_2$; e Y=COOH; f Y=$COCH_3$; IIIa, c, g, k X=H; b, i X=5-Cl; d X=6-Cl; e X=6-Br; f, j X=5-NO_2; h, l X=5-CH_3; a Y=$COOC_2H_5$; b Y=$COOCH_3$; c-f Y=CN; g-i Y=$COCH_3$; j-l Y=COOH; IVa, d, i X=H; b, e X=5-CH_3; c-f X=5-Cl; g, j X=6-Cl; h X=6-Br; a-c Y=$COOCH_3$; d-h Y=CN; i, j Y=$COCH_3$; Va X=H; b X=5-CH_3; c X=6-Cl; VI X=H; VIIIa X=H; b X=5-Cl

We have found that 2-aminobenzoxazoles react with activated alkenes only upon heating in the presence of basic catalysts. The reaction proceeds with the formation of products of mono- (III) and diaddition (IV) at the exocyclic nitrogen atom. The yields of III and IV depend substantially on the structures of the reagents and the reaction conditions.

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An intense band of an endocyclic azomethine bond [3, 4] at 1640-1660 is observed in the IR spectra of diaddition products IV. Two bands for the C=N bond (1640-1660 and 1660-1670 cm^{-1}) and two bands for the NH group at 3400-3540 cm^{-1} show up in the spectra of the products of monoaddition III. Dilution of chloroform solutions of III from 3% to 10^{-3} mole/liter does not change the positions and intensities of these bands, and this constitutes evidence for the presence of two tautomeric forms in solutions. A multiplet of aromatic protons (6.5-7.5), two triplets of methylene protons (2.70-3.27 and 3.70-4.20), and a singlet of an NH proton (5.80-6.80 ppm) for the monoadducts are observed in the PMR spectra of mono- (III) and diadducts (IV). The signal of the NH proton was assigned on the basis of an experiment involving deuterium exchange.

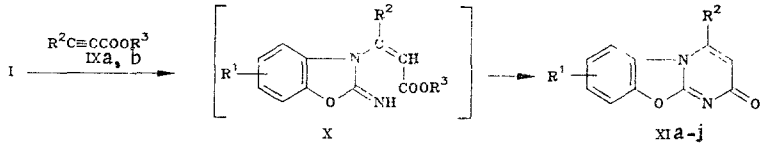
In the case of alkaline hydrolysis of III and IV the N–C bond in the amino group is cleaved, and the oxazole ring undergoes opening to give the corresponding 2-aminophenols. Hydrolysis of monoadducts III in the presence of concentrated hydrochloric acid leads to a mixture of 2-aminobenzoxazoles (23%) and 2-(3H)benzoxazolone (54%), which is the product of acetic hydrolysis of 2-aminobenzoxazole. Hydrolysis of 2-bis(2-cyanoethyl)aminobenzoxazoles IVd-h gives, depending on the reaction conditions, the corresponding carboxylic acids V, amides VI, and esters VII. Esters VII were found to be identical to the products of the reaction of I with acrylic acid esters. Ketones IIIi, g are converted to thiosemicarbazones VIII. Compounds IIIg, IV, and VIIIb displayed a distinct antivirus effect with respect to influenza and variolovaccines.

On the basis of the data regarding the yields of the final product and the time required for heating the mixture, one may conclude that the reactivities in this series decrease in the following order: acrylonitrile, acrylic acid esters, methyl vinyl ketone, and acrylic acid. Acrylamide does not react under the conditions that we selected. The presence of substituents in the benzene ring affect the reaction rate: electron-acceptor substituents decrease the reaction rate, whereas electron-donor substituents (methyl group) increase it. According to the experimental data, the activities of the catalyst that we used decrease in the following order: Triton B, sodium ethoxide, potassium hydroxide, and sodium hydroxide. Experiments carried out in various solvents under otherwise identical conditions demonstrated that in nonpolar solvents (benzene, toluene) virtually no addition takes place. Only traces of the monoadducts (according to TLC data) are formed when the mixtures are heated for 3 h.

In dioxane, acetonitrile, and DMF the reaction proceeds relatively rapidly (3h, 75°C) and leads to diadduct IVd (Y = CN, X = H) in 38, 42, and 44% yields, respectively. Primarily diadducts IV are formed at higher temperatures. The molar ratio of the reagents affects only the yields of the reaction.

It is known [5] that 2-aminobenzazoles react with esters of propiolic and acetylenecarboxylic acids to give the corresponding 2-oxopyrimido[2,1-b]benzazoles. We have shown that the reaction of 5(6)-substituted benzoxazoles Ia-g with dimethyl acetylenedicarboxylate (IXa) and with ethyl propiolate under mild conditions in the absence of a catalyst in benzene, dioxane, acetone, ethylacetate, ethanol, acetonitrile, or dimethyl sulfoxide (DMSO) lead to 2-oxopyrimido[2,1-b]benzoxazoles XIa-j in 21-61% yields. Bands of stretching vibrations of CO and C=N groups and of the pyrimidine ring at 1640-1690 cm^{-1} and a CO ester group at 1730-1750 cm^{-1} appear in the IR spectra of XI. In the PMR spectra one observes signals of aromatic protons (7.35-8.20, m), doublets of 3-H and 4-H protons (7.45 and 9.15) in the case of XIg, whereas in the PMR spectrum of XIa one observes a singlet of a 3-H proton (6.69) and a singlet of a CH_3 ester group (4.12 ppm).

On the basis of the results of the IR spectra of the reaction mixture we have demonstrated the formation of intermediate X with characteristic frequencies of 1720 (exo-c=N) and 3430 cm^{-1} (NH), which are absent in the IR spectra of the starting and final compounds. Evidently, the intermediate is a 3-substituted benzoxazoline, which in the case of Ig (R = 6-NO_2), becomes the principal reaction product.



IX a R^2=$COOCH_3$, R^3=CH_3; b R^2=H, R^3=C_2H_5; XI a, g R^1=H; b, h R^1=6-CH_3; c, i R^1=6-Cl; d, j R^1=7-Cl; e R^1=6-NO_2; f R^1=7-NO_2; a-f R^2=$COOCH_3$; g-i R^2=H

TABLE 1. Characteristics of Monoadducts III and VIII and Diadducts IV-VI with 2-Aminobenzoxazoles and 2-Oxopyrimido[2,1-b]benzoxazoles X and XI

Compound	mp, °C	N found, %	Empirical formula	N calc., %	M	Yield, % (method)
IIIa	125—126	11,7	$C_{12}H_{14}N_2O_3$	11,9	243,2	16
IIIb	136—137	11,4	$C_{11}H_{11}ClN_2O_3$	11,0	254,7	37
IIIg	142—143	14,1	$C_{11}H_{12}N_2O_2$	13,7	204,1	71
IIIh	159—160	12,9	$C_{12}H_{14}N_2O_2$	12,8	218,2	68
IIIi	171—172	11,7	$C_{11}H_{11}ClN_2O_2$	11,8	238,5	58
IIIj	167—168	17,2	$C_{11}H_{11}N_3O_4$	16,9	249,2	34
IIIk	177—178,5	13,5	$C_{10}H_{10}N_2O_3$	13,6	206,3	48
IIIl	132—133	12,7	$C_{11}H_{12}N_2O_3$	12,7	220,2	48
VIIIa	179—179,5	25,4	$C_{12}H_{15}N_5O$	25,3	277,2	72
VIIIb	162—162,5	22,8	$C_{12}H_{14}ClN_5O$	22,5	311,5	78
IVa	87—88	9,3	$C_{15}H_{18}N_2O_5$	9,2	306,3	82 (A) 81 (B) 85 (C)
IVb	72—73	9,1	$C_{16}H_{20}N_2O_5$	8,8	320,3	26
IVc	81—82	8,5	$C_{15}H_{17}ClN_2O_5$	8,2	342,8	23
IVi	158—159	9,9	$C_{15}H_{18}N_2O_3$	10,2	274,2	28
IVj	171—172	9,4	$C_{15}H_{17}ClN_2O_3$	9,1	308,5	34
Va	168—168,5	10,2	$C_{13}H_{14}N_2O_5$	10,1	278,2	82
Vb	181—182	9,7	$C_{14}H_{16}N_2O_5$	9,6	292,2	78
Vc	193—194	8,7	$C_{13}H_{13}ClN_2O_5$	8,9	312,7	67
VIa	221—223	20,0	$C_{13}H_{12}N_4O$	20,3	276,2	91
XIa	208—209	11,6	$C_{12}H_8N_2O_4$	11,5	244,0	51 [5]
XIb	179—179,5	10,7	$C_{13}H_{10}N_2O_4$	10,8	258,2	58
XIc	197—198	10,3	$C_{12}H_7ClN_2O_4$	10,1	278,5	35
XId	198—198,5	10,1	$C_{12}H_7ClN_2O_4$	10,1	278,5	50
XIe	192—193	8,4	$C_{12}H_7BrN_2O_4$	8,6	323,2	35
XIf	243—245	14,6	$C_{12}H_7N_3O_6$	14,5	289,1	31
XIg	232—232,5	14,6	$C_{12}H_7N_3O_6$	14,5	289,1	34
XIh	257—258	15,2	$C_{10}H_6N_2O_2$	15,0	186,0	42 [5]
XIi	235—235,5	13,7	$C_{11}H_8N_2O_2$	13,9	200,0	60
XIj	272—273	12,6	$C_{10}H_5ClN_2O_2$	12,7	220,5	61
XIk	302—303	12,9	$C_{10}H_5ClN_2O_2$	12,7	220,5	26
X	142—143,5	13,0	$C_{13}H_{11}N_3O_7$	12,6	331,8	65

EXPERIMENTAL

The starting 2-aminobenzoxazole and its derivatives were obtained by the method in [6]. The synthesis of IIIc-f and IVd-h has been described [1, 2]. Chromatographic monitoring of the course of reaction was carried out on SIF plates (Riedel de Haen) in a benzene—chloroform—ethyl acetate system (1:1:2) with development by iodine vapors or UV light. The melting points were determined by the capillary method and were not corrected. The IR spectra were recorded with a Zeiss UR-10 spectrometer, and the PMR spectra were determined with a Tesla-487 spectrometer (80 MHz) with tetramethylsilane (TMS) as the internal standard.

The characteristics of the synthesized compounds are presented in Table 1.

2-(2-Alkoxycarbonylethyl)aminobenzoxazoles (IIIa, b). A) A 15-mmole sample of acrylic acid ester and 0.1 g of potassium hydroxide were added to a solution of 10 mmole of the corresponding 2-aminobenzoxazole in 10 ml of acetonitrile, after which the solution was refluxed for 3-6 h. The solvent was removed by distillation, the dry residue was dissolved in 3% hydrochloric acid, and the acidic mixture was extracted with chloroform. The extract was dried, the solvent was removed by distillation, and the residue was recrystallized from ethanol—water (1:1).

B) A solution of 10 mmole of 2-bis(cyanoethyl)aminobenzoxazole in 10 ml of methanol saturated with HCl was refluxed for 3 h. The solvent was then removed by distillation, and the residue was recrystallized from water.

C) A 10-mmole sample of 2-bis(2-carboxyethyl)aminobenzoxazole was added in portions with stirring to 40 ml of ether containing 100 mmole of diazomethane. The solution was then stirred at 0-10°C for 10 h, after which the ether was removed by distillation, and the residue was recrystallized from water.

2-Bis(2-methoxycarbonylethyl)aminobenzoxazoles (IVa-c). A 40-mmole sample of methyl acrylate and two to three drops of Triton B (30% solution in methanol) was added. The solution was refluxed for 4-6 h, the solvent was removed by distillation, and the residue was recrystallized from water.

2-(3-Oxobutyl)aminobenzoxazoles (IIIg-j). A 150-mmole sample of methyl vinyl ketone and two to three drops of Triton B was added to a solution of 10 mmole of 2-aminobenzoxazole in 10 ml of acetonitrile, and the mixture was refluxed for 10 h (12 h for the 5-chloro derivatives and 40 h for the 5-nitro derivatives). Cooling produced a precipitate, which was recrystallized from aqueous ethanol (1:1).

2-Bis(3-oxobutyl)aminobenzoxazoles (IVi, j). A 40-mmole sample of methyl vinyl ketone and Triton B catalyst were added to a solution of mmole of 2-aminobenzoxazole in 10 ml of DMF, and the mixture was refluxed for 10-12 h. The solvent was removed by distillation, and the residue was recrystallized from aqueous ethanol (1:1).

2-(2-Carboxyethyl)aminobenzoxazoles (IIIk, l). A 15-mmole sample of acrylic acid was added to a solution of 10 mmole of the corresponding 2-aminobenzoxazole in 10 ml of acetonitrile and 0.1 ml of Triton B. Cooling of the mixture produced a precipitate, which was recrystallized from ethanol.

2-Bis(2-carboxyethyl)aminobenzoxazoles (Va-c). A solution of 10 mmole of 2-bis(2-cyanoethyl)aminobenzoxazole in 10 ml of concentrated hydrochloric acid was refluxed for 3 h, after which the precipitated 2-(3H)-benzoxazolone (10%) was removed by filtration. The filtrate was neutralized with 30% NaOH, and the mixture was extracted with ether. The ether was removed by distillation, and the residue was recrystallized from water.

2-(Bis(2-aminocarbonylethyl)aminobenzoxazoles (VIa). A 15-ml sample of concentrated hydrochloric acid was added in portions with stirring at 0-5°C to 10 mmole of 2-bis(2-cyanoethyl) aminobenzoxazole, after which the mixture was stirred for another hour and allowed to stand at room temperature for 2 days. The mixture was then poured into 200 g of crushed ice, and the aqueous mixture was neutralized with ammonia. The mixture was then allowed to stand in a refrigerator, and the resulting precipitate was recrystallized from benzene.

2-(3-Oxobutyl)aminobenzoxazole Thiosemicarbazones (VIIIa, b). A solution of 10 mmole of the thiosemicarbazide in 10 ml of water was added to a solution of 10 mmole of 2-(3-oxobutyl) aminobenzoxazole in 10 ml of ethanol, and the solution was refluxed for 2-3 h. It was then cooled, and the resulting precipitate was removed by filtration, washed, dried, and recrystallized from aqueous ethanol (1:1).

2-Oxo-4-methoxycarbonylpyrimido[2,1-b]benzoxazoles (XIa-f). A 15-mmole sample of dimethyl acetylene dicarboxylate was added to a solution of 10 mmole of the corresponding 2-aminobenzoxazole in 20 ml of absolute ethanol, and the mixture was refluxed for 40 min [2 h for the 5(6)-chloro derivative, 3 h for the 6-bromo derivative, and 10-12 h for the 5(6)-nitro derivative]. The precipitate that resulted upon cooling was removed by filtration, dried, and recrystallized from methanol.

2-Oxopyrimido[2,1-b]benzoxazoles (XIg-j). A 15-mmole sample of ethyl propiolate was added to a solution of 10 mmole of the corresponding 2-aminobenzoxazole in 20 ml of absolute ethanol, and the mixture was refluxed for 6 h [12 h for the 5(6)-chloro derivative]. Cooling gave a precipitate, which was removed by filtration and recrystallized from methanol.

6-Nitro-3-(1,2-dimethoxycarbonylethylene)-2-iminobenzoxazolene (X). A 10-mmole sample of dimethyl acetylenedicarboxylate was added to a solution of 5 mmole of 6-nitro-2-aminobenzoxazole in 20 ml of absolute ethanol, and the mixture was refluxed for 6 h. The solvent was removed by distillation, and the residue was recrystallized from dichloroethane.

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