A STUDY OF NITROGEN- AND OXYGEN-CONTAINING HETEROCYCLES.

42.* PYRIMIDO[4,5-b]- AND PYRIDO[2,3-b]-1,4-BENZOXAZEPINES

L. G. Levkovskaya, N. V. Sazonov,
N. A. Grineva, I. E. Mamaeva,
L. A. Serochkina, and T. S. Safonova

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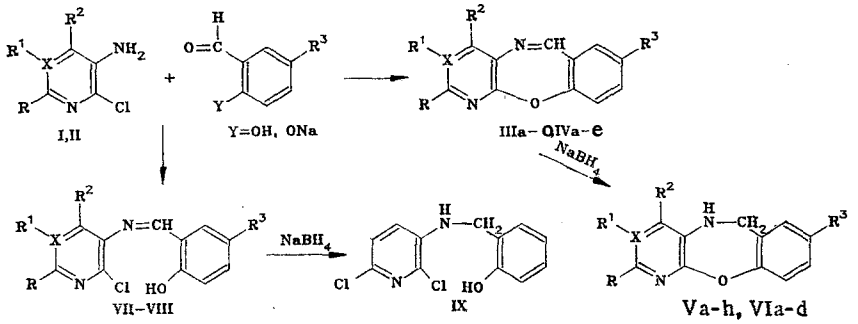
The reaction of o-haloamino derivatives of pyrimidine and pyridine with o-hydroxybenzaldehyde and its derivatives leads to the formation of tricyclic 1,4-oxazepine systems. Syntheses are reported for derivatives of pyrimido[4,5-b]- and pyrido[2,3-b]-1,4-benzoxazepines as well as of their 5,6-dihydro derivatives. The properties and structures of these compounds were studied.

Benzoxazepine derivatives and their aza and thio analogs have been found with a broad range of biological activity [2-4]. In a search for new biologically active 1,4-oxazepines, we studied the reaction of o-haloamino derivatives of pyrimidine and pyridine with aromatic aldehydes under various conditions. The properties and structures of both intermediates and final products were studied.

The reactions of 5-amino-6-chloropyrimidines (I) having a free or substituted amino group at C-4 and 2-chloro-3-aminopyridines (II) with a halogen atom at C-5 or C-6 with o-hydroxybenzaldehyde and its derivatives lead to the formation of a new heterocyclic system, namely, pyrimido[4,5-b]-1,4-benzoxazepine (III) as well as previously unreported pyrido[2,3-b]-,4-benzoxazepines (IV) [5, 6]. These reactions are carried out in DMF in the presence of NaH as a base at 100-120°C. Thus, the reaction of I and II with o-hydroxybenzaldehyde and its 5-chloro, 5-bromo- and 5-nitro-derivatives gave derivatives of pyrimido[4,5-b]- (IIIa-o) and pyrido[2,3-b]-1,4-benzoxazepines (IVa-e).



I, IIIa—o, Va-h, VII R=H, R¹—X=N; IIIa—c, Va, c, VII R²=NHCH₂C₆H₅; VII R³=H; Vb R²=NHCH₂C₆H₅·HCl; III, Va, f R³=Cl; b, g, R³=Br; c, d R³=H; d R²=NHC₆H₅; h R²=NH(CH₂)₃CH₃; IIIe, i Ve R²=piperidyl ; IIIe R³=Cl; IIIi, Ve R³=Br; IIIf, g, n, o, Vf, g R²=morpholino; IIIi R²=NH₂, j R²=1-methylpiperazinyl·HCl; k R²=Cl; i-k, o R³=H; n R³=NO₂; IVa—e VIa—d R²=H, R¹—X=CH; IVa—d, VIa, d, VIII, IX R=Cl; IVb, c, e, VIb, c R=H, R¹=Cl; IVc, d, VIII R³=H; IV, VIa, b R³=Cl; IVe R³=Br

The formation of pyrimidobenzoxazepine IIIc also occurs in the reaction of Ic with salicylaldehyde in the presence of NaOH or using the sodium salt of salicylaldehyde (methods b and c). However, the yields of IIIc in these reactions did not exceed 50%.

*For Communication 41, see [1].

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TABLE 1. Characteristics of IIIa-o, IVa-e, VIa-d, and VII-IX

Compound	mp,* °C	Found, %				Chemical formula	Calculated, %				Yield, %
		C	H	Cl (Br)	N		C	H	Cl (Br)	N	
IIIa	190—200	64,0	4,0	10,4	16,5	$C_{18}H_{13}ClN_4O$	64,4	3,9	10,4	16,5	90
IIIb	185—187	56,5	3,7	(20,6)	14,6	$C_{18}H_{13}BrN_4O$	56,6	3,4	(20,9)	14,6	90
IIIc	114—116	71,4	4,5	—	18,5	$C_{18}H_{14}N_4O$	71,5	4,7	—	18,5	95
IIId	132—134	70,8	4,2	—	19,3	$C_{17}H_{12}N_4O$	70,8	4,2	—	19,4	60
IIIe	142—143	61,1	5,0	11,3	17,7	$C_{16}H_{15}ClN_4O$	61,0	4,8	11,3	17,8	30
IIIf	200—201	57,1	4,2	11,3	17,9	$C_{15}H_{13}ClN_4O_2$	56,9	4,1	11,2	17,7	75
IIIg	140—142	49,9	3,6	(22,2)	15,5	$C_{15}H_{15}BrN_4O_2$	49,9	3,6	(21,1)	15,5	83
IIIh	123—125	52,2	4,2	(23,3)	16,4	$C_{15}H_{15}BrN_4O$	51,9	4,3	(23,0)	16,1	80
IIIi	236—238	62,3	3,8	—	26,4	$C_{11}H_8N_4O$	62,3	3,8	—	26,4	78
IIIj	263—264	57,9	5,6	10,8	21,3	$C_{16}H_{18}ClN_5O$	57,7	5,5	10,7	21,2	67
IIIk	148—150	56,6	2,6	18,0	15,0	$C_{11}H_6ClN_3O$	57,0	2,6	18,1	15,3	74
IIIl	133—135	53,6	4,2	—	15,6	$C_{16}H_{15}BrN_4O$	53,5	4,2	—	15,6	46
IIIm	259	61,8	3,3	—	19,9	$C_{11}H_7N_3O_2$	61,9	3,3	—	19,7	80
IIIn	249—251	55,2	3,9	—	21,5	$C_{15}H_{13}N_5O_4$	55,0	4,0	—	21,4	70
IIIo	148—149	63,7	5,0	—	19,9	$C_{18}H_{14}N_4O_2$	63,8	5,0	—	19,8	25
IVa	211—213	54,5	2,3	27,0	10,3	$C_{12}H_6Cl_2N_2O$	54,5	2,3	26,5	10,8	86
IVb	206—208	54,5	2,2	26,0	10,6	$C_{12}H_6Cl_2N_2O$	54,5	2,3	26,5	10,6	81
IVc	169—170	62,3	2,8	15,4	11,9	$C_{12}H_7ClN_2O$	62,5	3,0	15,4	12,1	71
IVd	155—156	62,5	3,1	15,3	12,4	$C_{12}H_7ClN_2O$	62,5	3,1	15,4	12,2	86,7
IVe	205—206	46,5	2,3	11,5 (25,9)	9,0	$C_{12}H_6BrClN_2O$	46,6	2,0	11,4 (25,8)	9,0	81
Va	143—144	64,1	4,6	10,6	16,4	$C_{18}H_{15}ClN_4O$	64,0	4,4	10,4	16,4	94
Vb	216—219	51,4	3,8	8,4 (19,0)	13,2	$C_{18}H_{15}ClBrN_4O$	51,5	3,8	8,4 (19,0)	13,3	90
Vc	164—165	71,1	5,0	—	18,3	$C_{18}H_{16}N_4O$	71,0	5,3	—	18,4	93
Vd	210—211	70,1	4,8	—	19,6	$C_{17}H_{14}N_4O$	70,3	4,8	—	19,3	76
Ve	163—164	53,2	4,3	(22,3)	15,8	$C_{16}H_{17}BrN_4O$	53,2	4,7	(22,1)	15,5	83
Vf	218—219	56,8	4,8	11,1	17,5	$C_{15}H_{15}ClN_4O$	56,5	4,7	11,1	17,6	77
Vg	221—222	49,7	4,1	—	15,4	$C_{15}H_{15}BrN_4O_2$	49,6	4,2	—	15,4	80
Vh	134—136	51,8	4,9	(22,8)	15,8	$C_{15}H_{17}BrN_4O$	51,6	4,9	(22,9)	16,0	85
VIa	187—188	54,3	3,1	26,6	10,5	$C_{12}H_8Cl_2N_2O$	54,1	3,0	26,3	10,5	92
VIb	230—232	54,3	2,8	26,4	10,4	$C_{12}H_8Cl_2N_2O$	54,1	3,0	26,3	10,5	99
VIc	240—241	61,9	3,9	15,3	12,2	$C_{12}H_9ClN_2O$	61,9	3,9	15,2	12,0	87
VId	225—226	62,3	4,1	15,5	12,2	$C_{12}H_9ClN_2O$	61,9	3,9	15,2	12,0	100
VII	133—135	63,7	4,4	10,5	16,9	$C_{18}H_{15}ClN_4O$	63,8	4,4	10,5	16,6	93
VIII	163—165	54,4	3,2	26,3	10,5	$C_{12}H_8Cl_2N_2O$	54,0	3,2	26,5	10,5	84
IX	181—182	53,2	3,8	26,7	10,3	$C_{12}H_{10}Cl_2N_2O$	53,5	3,7	26,3	10,4	95

*Compounds IIIa,b,d,e-j,o, IVa-d, Vb,d,f,h, VIa-c, and VIII were crystallized from ethanol, IIIk, Ve, and Vg were crystallized from ethyl acetate, IIIc and VId were crystallized from 2-propanol, IIIm was crystallized from 1:1 water—acetic acid, IIIn was crystallized from DMF, IIIn was crystallized from hexane, Va and IX were crystallized from aqueous ethanol, Vc was crystallized from 1:2 water—methanol, and IVe was crystallized from acetone.

Some derivatives of pyrimido[4,5-b]-1,4-benzoxazepine, in particular, IIIj and Vb were characterized as hydrochloride salts (see Table 1).

The reaction of 4-benzylamino-5-amino-6-chloropyrimidine (I) and 2,6-dichloro-3-aminopyridine (II) with o-hydroxybenzaldehyde in toluene in the presence of triethylamine permitted the isolation and characterization of the Schiff base intermediates VII and VIII.

A study of the chemical properties, in particular, relative to reduction reactions of pyrimido- and pyrido-1,4-benzoxazepines, the azomethine bond of the central oxazepine ring in these compounds were found to undergo facile reduction by the action of complex hydrides. Thus, the reactions of IIIa-h and IVa-d with $NaBH_4$ in ethanol at 18-20°C gave 5,6-dihydropyrimido[4,5-b]- (Va-h) and 5,6-dihydropyrido[2,3-b]-1,4-benzoxazepines (VIa-e). The action of $NaBH_4$ on VIII under analogous conditions gave the product of its reduction, namely, benzylamino derivative IX.

The structures of the compounds synthesized were confirmed by IR, UV, NMR, and mass spectroscopy.

The IR spectra of III and IV lack bands for amino, hydroxy and carbonyl groups present in the starting compounds. A band is found at 3220-3380 cm^{-1} for V and VI, which is characteristic for cyclic secondary amines. The NMR spectra do not contradict the structures of these compounds (see Table 2).

TABLE 2. Spectral Compounds of Compounds Studied

Compound*	UV spectrum in ethanol, λ_{max}, nm(log ε)	PMR spectrum in $CDCl_3$, ppm
IIId		8,64 (1H, s, 6-CH); 8,56 (1H, s, 2-CH); 6,45—7,2 (4H, m, 7,8,9,10-CH)
IIIg	277 (4,26), 372 (4,16)	
IIIh	260 (4,19), 375 (4,10)	
IIIi		8,71 (1H, s, 6-CH); 8,36 (1H, s, 2-CH); 6,5—7,25 (4H, m, 7,8,9,10-CH)
IIIk		9,32 (1H, s, 6-CH); 9,09 (1H, s, 2-CH); 6,45—7,30 (4H, m, 7,8,9,10-CH)
IIIm		8,91 (1H, s, 6-CH); 8,73 (1H, s, 2-CH); 6,3—7,25 (4H, m, 7,8,9,10-CH)
IVa	266 (4,18), 294 (3,63)	7,25 (1H, d, 3H); 7,71 (1H, d, 4-H); $J_{3,4}$=8 Hz; 8,43 (1H, C=CH); 7,33 (1H, d, 7-H); 7,50 (1H, q, 9-H); $J_{7,9}$= =2,4 Hz; 7,26 (1H, d, 10-H); $J_{9,10}$=8,7 Hz
IVb	214 (4,36), 302 (3,75)	7,75 (1H; d, 4-H); 8,13 (1H, d, 2-H); $J_{2,4}$=2,5 Hz; 8,46 (1H, C=CH); 7,35 (1H, d, 7-H); 7,49 (1H, q, 9-H); $J_{7,9}$=2,5 Hz; 7,24 (1H, d, 10-H); $J_{9,10}$=8,5 Hz
Va		2,84 (1H, s, 5-NH); 4,23 (2H, s, 6-CH_2); 4,6—4,65 (2H, d, 4-CH_2); 5,76 (1H, s, 4-NH); 8,1 (1H, s, 2-H); 7,18—7,29 (4H, m, 7,8,9,10-CH)
Vc		2,89 (1H, s, 5-NH); 4,3 (2H, s, 6-CH_2); 4,58 (2H, s, 4-CH_2); 5,76 (1H, s, 4-H); 5,06—7,27 (4H, m, 7,8,9,10-CH)
Ve		4,08 (1H, s, 5-NH); 4,38 (2H, s, 6-CH_2); 7,11—7,44 (4H, m, 7,8,9,10-CH)
Vf		4,10 (1H, s, 5-NH); 4,4 (2H, s, 6-CH_2); 7,22—7,25 (4H, s, 7,8,9,10-CH)
Vh	280 (4,00)	
Vg	310 (3,93)	
VIa		4,30 (2H, s, 6-CH_2); 4,10 (1H, s, 5-H); 6,8—7,2 (m, arom. ring protons)
VIb		4,46 (2H, e, 6-CH_2); 4,39 (1H, s, 5-H); $^3J_{CH_2NH}$ =4 Hz; 6,8—7,5 (m, arom. ring protons)

*The PMR spectra of IIIi, IIIk, and IIIm were taken in CF_3CO_2D.

An examination of the mass spectra of pyrido[2,3-b]-1,4-benzoxazepines IV and VI shows that the major direction for the fragmentation of their molecular ions (M^+) is the consecutive elimination of the following fragments as, for example, in the case of IVa and IVb: M^+ (264, 100),* $[M - CO]^+$, or $[M - H_2CN]^+$ (236, 10), $[M - Cl]^+$ (229, 7), $[M - 28, -Cl]^+$ (201, 21), $[M - 28, -2Cl]^+$ (166, 10). The characteristic direction for the fragmentation of M^+ (266, 100) of VIa and VIb is the formation of species: $[M - CO]^+$ or $[M - CNH_2]^+$ (238, 2), $[M - NHCH_2]^+$ or $[M - CHO]^+$ (237, 3), $[M - Cl]^+$ (231, 20), $[M - 28, -Cl]^+$ (203, 36).

These studies showed that the reaction of these pyrimidine and pyridine derivatives with o-hydroxybenzaldehyde and its derivatives is a general method for the synthesis of derivatives of pyrimido[4,5-b]- and pyrido[2,3-b]-1,4-benzoxazepines.

EXPERIMENTAL

The IR spectra of the compounds synthesized were taken in vaseline oil on a Perkin-Elmer 575 spectrometer. The UV spectra were taken in ethanol on a Perkin-Elmer 575 spectrometer. The NMR spectra were taken on a Varian XL-100 spectrometer with TMS as the internal standard. The electron impact mass spectra were taken on a Varian MAT-112 mass spectrometer with direct sample inlet into the ion source. The ionizing electron energy was 70 eV. The temperature of the ionization chamber was 180°C.

Data on the compounds synthesized and their spectral characteristics are given in Tables 1 and 2.

Derivatives of Pyrimido[4,5-b]- and Pyrido[2,3-b]-1,4-benzoxazepines (IIIa-o and IVa-e). General Preparative Method. A. A sample of 0.01 mole salicylaldehyde was added to a suspension of 0.01 mole NaH in 20 ml DMF and stirred for 10 min. A sample of 0.01 mole 4-R^2-5-amino-6-chloropyrimidine (I) or 6R(5R')-2-chloro-3-aminopyridine (II) was added to the solution obtained. The reaction mixture was heated to 110-120°C and stirred at this temperature for 4 h and then evaporated to dryness in vacuum. The residue was washed with water to give IIIa-o and IVa-e. In the case of IIIm, a solution is obtained upon the addition of water which was neutralized with acetic acid.

*The m/z values (relative to the ^{35}Cl isotope) and peak intensities in % are given in the parentheses.

B. A mixture of 2.35 g (0.01 mole) 4-benzylamino-5-amino-6-chloropyrimidine and 1.44 g (0.01 mole) sodium salt of salicylaldehyde in 20 ml DMF was heated at 110°C for 4 h. The solvent was evaporated and the residue was washed with water. The yield of IIIc was 1.43 g (47.3%). This product does give an undepressed mixed melting point with a sample obtained by method A.

C. A mixture of 2.35 g (0.01 mole) 4-benzylamino-5-amino-6-chloropyrimidine, 0.4 g (0.01 mole) NaOH and 1.22 g (0.01 mole) salicylaldehyde was heated in 20 ml DMF for 4 h at 110°C. The solvent was evaporated and the residue was washed with water to give 1.6 g (53%) IIIc. The product gives an undepressed mixed melting point with a sample obtained by method A.

4-Morpholino-8-bromo-4,5-dihydropyrimido[4,5-b]-1,4-benzoxazepine (Vg). A sample of 12.5 mmoles $NaBH_4$ was added in portions to a suspension of 5 mmoles 4-morpholino-8-bromopyrimido[4,5-b]-1,4-benzoxazepine (IIIg) in 30 ml ethanol and stirred for 3 h at 18-20°C. This mixture was then acidified with dilute hydrochloric acid until weakly acidic and the solvent was distilled off in vacuum. The residue was triturated with water to give Vg.

Products Va-f, VIa-d, and IX were obtained by analogy.

N-(2'-Hydroxybenzyliden)-3-amino-2,6-dichloropyridine (VIII). A solution of 1.63 g (0.01 mole) 2,6-dichloro-3-aminopyridine (II), 1.22 g (0.01 mole) salicylaldehyde and 1.01 g (0.01 mole) triethylamine in 30 ml toluene was heated at reflux for 4 h, cooled and evaporated to dryness in vacuum. A sample of 15 ml hexane was added to the residue, which was then filtered off, washed with water and dried to give VIII. IR spectrum: 3400 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 260 (4.16), 326 nm (3.30).

Product VII was obtained by analogy.

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