Condensation of *N*-(2-hydroxybenzylidene)-1,2-aminoalkanols with formaldehyde

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Dedicated to Boris A. Trofimov on the occasion of his 65th birthday with heartiest wishes
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Abstract
2,3-Dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazines have been prepared by the reaction of N-(2-hydroxybenzylidene)-1,2-aminoalkanols with formaldehyde in 43–84% yield. The effect of substituents in the N-(2-hydroxybenzylidene)-1,2-aminoalkanols upon the structures and yields of the condensation products has been shown.

Keywords: N-(2-Hydroxybenzylidene)-1,2-aminoalkanols, N-(5-bromine-2-hydroxybenzylidene)-1,2-aminoalkanols, formaldehyde, condensation, 2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazines, 9-bromine-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazines

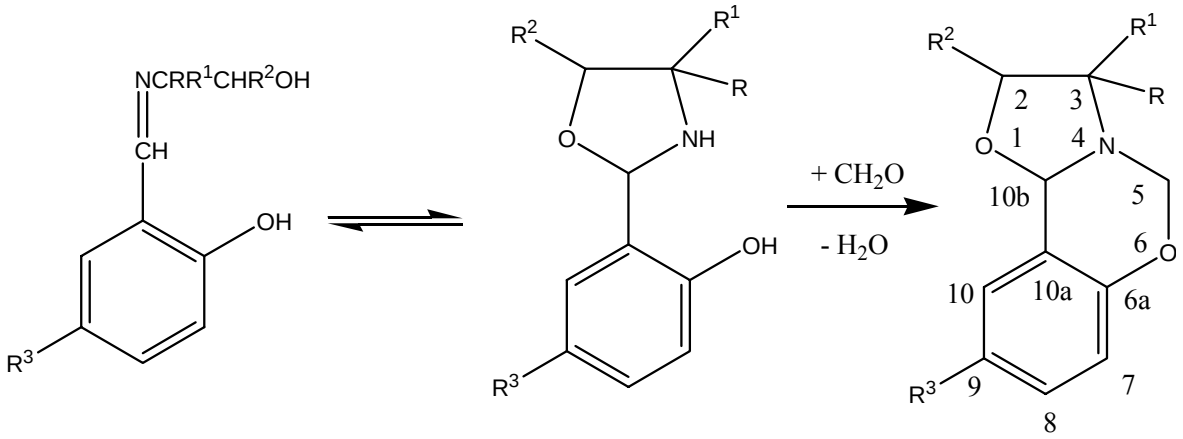
Introduction

It is known that penta- and hexacyclic O,N-acetals which show various biological activities are used as intermediate products in organic synthesis.[1] Recently we reported that the condensation of N-(2-hydroxybenzylidene)-2-aminoethanol with formaldehyde resulted in 2,3-dihydro-10*b*-H-[1,3]oxazolo-[3,2-*c*]-[1,3]benzoxazine.[2] The compounds of this class are promising as biologically active agents, owing to the presence of both penta- and hexa- O,N-acetal rings in their structures. In addition, the compounds were of interest for studies of the reactivity of the acetal rings. The present work deals with the effect of different substituents positioned in the amino-alcohol fragment and the benzene ring of N-(2-hydroxybenzylidene)-2-aminoethanol on the polycondensation reaction with aldehydes as well as on the structures and yields of the products obtained. New 2,3-dihydro-10*b*-H-[1,3]oxazolo-[3,2-*c*]-[1,3]-benzoxazines have been prepared.

Results and Discussion

The condensation of N-(2-hydroxybenzylidene)-1,2-aminoalkanols with formaldehyde is performed according to the new method,[2] which has now been modified. The reaction involves refluxing of an equimolar mixture of imino-alcohols with paraformaldehyde, followed by azeotropic distillation to remove water.

It is known that imino-alcohols are in tautomeric equilibrium with oxazolidines.[3,4]



1a-j A **1a-j B** **2a-j**

a: R=R^1=R^2=R^3=H; **b:** R=R^1=R^2=H, R^3=Br; **c:** R=R^1=CH_3, R^2=R^3=H; **d:** R=R^1=CH_3, R^2=H, R^3=Br; **e:** R=R^2=R^3=H, R^1=CH_2CH_3; **f:** R=R^2=H, R^1=CH_2CH_3, R^3=Br; **g:** R=R^1=R^3=H, R^2=CH_3; **h:** R=R^1=H, R^2=CH_3,R^3=Br; **i:** R=R^1=R^3=H, R^2= CH_2OCH_3; **j:** R=R^1=H, R^2=CH_2OCH_3, R^3=Br.

The syntheses have shown that introduction of alkyl substituents into the amino-alcohol fragment of the imino-alcohol**,** which causes a little shift of the imino-alcohol–oxazolidine tautomeric equilibrium to increase the oxazolidine concentration,[4,5] led to some little increased yields of oxazolo-benzoxazines **2** see for example **2a** and **2c** (Table 1).

When catalysis was tried with the acidic catalyst *N*-(2-hydroxy-5-nitrobenzylidene)-2-amino-ethanol, which has no almost oxazolidine form,[4] there was no condensation with formaldehyde. This suggests that the process studied involves the oxazolidine, which is the tautomeric form of the imino-alcohol.

Table 1. Yields and characteristics of the synthesized products, **2a–j**

Comp	Yield (%)	B.P./°C (p/mm Hg),	m.p./°C	n_D^{20}	d_4^{20}	Found / Calculated % C	H	Br	N	Formula
2a [a]	47.2	111–113 (3)		1.5624	1.2177	67.53 67.78	6.11 6.26		7.69 7.90	$C_{10}H_{10}NO_2$

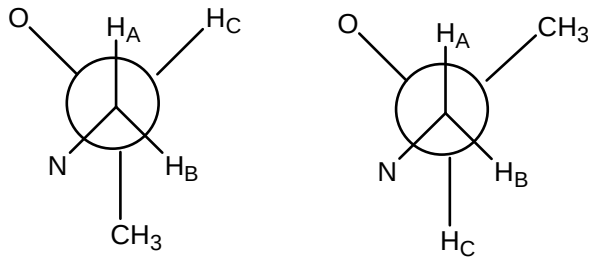
2b	46.3	151–153 (1)	52–53			46.98	4.07	31.41	5.27	$C_{10}H_{10}BrNO_2$
						46.90	3.94	31.20	5.47	
2c	48.6	129–131 (5)		1.5322	1.1287	70.03	7.51		6.53	$C_{12}H_{15}NO_2$
						70.22	7.37		6.82	
2d	65.3	170–172 (3)	43–44			50.94	5.06	28.03	4.77	$C_{12}H_{14}BrNO_2$
						50.72	4.97	28.12	4.93	
2e	46.7	148–149 (3)		1.5375	1.1161	70.48	7.55		6.68	$C_{12}H_{15}NO_2$
						70.22	7.37		6.82	
2f	63.6	178–180 (3)	86–87			50.53	4.83	27.95	4.80	$C_{12}H_{14}BrNO_2$
						50.72	4.97	28.12	4.93	
2g	67.0	120–123 (4)		1.5465	1.1335	69.17	6.97		7.11	$C_{11}H_{13}NO_2$
						69.09	6.85		7.32	
2h	57.3	158–160 (3)	61–62			48.74	4.59	29.17	5.02	$C_{11}H_{12}BrNO_2$
						48.91	4.48	29.58	5.19	
2i	41.5	156–158 (6)		1.5396	1.1656	65.38	6.96		6.12	$C_{12}H_{15}NO_3$
						65.14	6.83		6.33	
2j	42.7	155–157 (2)	66–67			48.19	4.88	26.79	4.50	$C_{12}H_{14}BrNO_3$
						48.02	4.70	26.62	4.67	

[a] Ref. 2 gives b.p. 111–113°C (3 mm Hg), η_D^{20} 1.5631, d_4^{20} 1.2180.

It is shown that the interaction of the imino-alcohols **1g–j A**, containing an asymmetric carbon atom in position 2, affords two diastereomeric oxazolobenzoxazines (the ratio of isomers is 1:1.1). When the imino-alcohols **1e, f A**, containing an asymmetric carbon atom in position 3 are involved, the reaction proceeds selectively to give only one isomer.

The PMR spectra of the compounds **2g–j** show doublets for all proton resonance signals, with an integrated intensity ratio of 1.0:1.1.

It should be noted that all proton resonance signals of the dominant isomers of the heterocycles, except for H_C, are shifted to low field. The protons of both CH_2 groups that are in the α-position with respect to the spirocyclic nitrogen atom are diastereotopic, their resonance signals being AB-quartets. The AB-type protons' signals are split further, owing to vicinal spin–spin interaction with the H_C protons. Similar values of vicinal constants in the slightly dominant *gauche* conformer, as well as different *J* values in the *anti* conformer, reveal the following configurations of these isomers (Figure 1).



Gauche *Anti*

Figure 1

Experimental Section

General Procedures. The imino-alcohols were prepared by condensation of 1,2-amino-alkanols with salicylic- and 5-bromo-salicylic aldehydes according to the published method.[6] ^{1}H NMR spectra of the compounds **2b–j** were recorded on a Bruker DPX-400 instrument (400 MHz, $CDCl_3$) with Me_4Si as internal standard.

General method for the synthesis of oxazolobenzoxazines 2a–j

The mixture of imino alcohol **1a–j A** (0.1 mol), paraformaldehyde (0.1 mol) and benzene (100 ml) was boiled in a Dean–Stark trap until the water evaluation stopped. The mixture was distilled in vacuum to give oxazolobenzoxazines **2a–j**.

9-Bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (2b). NMR: δ_H ($CDCl_3$) 3.08 m (2-CH_2), 3.81 m (3-CH_2), 4.74 d (H_A from 5-CH_AH_B, $^2J_{AB}$ = 9.7 Hz), 4.81 d (H_B from 5-CH_AH_B, $^2J_{AB}$ = 9.7 Hz), 5.81 s (10*b*-CH); 6.63 d (7-CH, $^3J_{7-8}$ = 8.8 Hz), 7.23 dd (8-CH, $^4J_{8-10}$ = 2.5 Hz, $^3J_{7-8}$ = 8.8 Hz), 7.35 d (10-CH, $^4J_{8-10}$ = 2.5 Hz).

3-Dimethyl-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (2c). δ_H ($CDCl_3$) 1.22 s (C_3–1-CH_3), 1.30 s (3-C–2-CH_3), 3.67 d (H_A from 2-CH_AH_B, $^2J_{AB}$ = 7.8 Hz), 3.72 d (H_B from 2-CH_AH_B, $^2J_{AB}$ = 7.8 Hz), 4.85 d (H_A from 5-CH_AH_B, $^2J_{AB}$ = 11 Hz), 4.94 d (H_B from 5-CH_AH_B, $^2J_{AB}$ = 11 Hz), 5.87 s (10*b*-CH), 6.73–7.28 m (CH_{phenyl}).

3-Dimethyl-9-bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (2d). δ_H ($CDCl_3$) 1.22 s (3-C–1-CH_3), 1.27 s (3-C–2-CH_3), 3.66 d (H_A from 2-CH_AH_B, $^2J_{AB}$ = 7.9 Hz), 3.71 d (H_B from 2-CH_AH_B, $^2J_{AB}$ = 7.9 Hz), 4.87 d (H_A from 5-CH_AH_B, $^2J_{AB}$ = 11.3 Hz), 4.92 d (H_B from 5-CH_AH_B, $^2J_{AB}$ = 11.3 Hz), 5.83 s (10*b*-CH), 6.64 d (7-CH, $^3J_{7-8}$ = 8.8 Hz), 7.25 dd (8-CH, $^4J_{8-10}$ = 2.4 Hz, $^3J_{7-8}$ = 8.8 Hz), 7.37 d (10-CH, $^4J_{8-10}$= 2.4 Hz).

3-Ethyl-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (2e). δ_H ($CDCl_3$) 0.93 t (3-C CH_2-*CH_3*, ^3J = 7.5 Hz), 1.46 m (H_A from 3-C–*CH_AH_B*–CH_3), 1.70 m (H_B from 3-C–*CH_AH_B*–CH_3), 3.29 m (3-CH), 3.57 m (H_A from 2-CH_AH_B), 3.97 m (H_B from 2-CH_AH_B), 4.73 d (H_A from 5-CH_AH_B, $^2J_{AB}$ = 9.88 Hz), 4.82 d (H_B from 5-CH_AH_B, $^2J_{AB}$ = 9.88 Hz), 5.72 s (10*b*-CH), 6.79 7.27 m (CH_{phenyl}).

3-Ethyl-9-bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (2f). δ_H ($CDCl_3$) 0.53 t (3-C–CH_2–*CH_3*, ^3J = 7.5 Hz), 1.04 m (H_A from 3-C–*CH_AH_B*–CH_3), 1.25 m (H_B from 3-C–*CH_AH_B*-CH_3), 2.86 m (3-CH), 3.23 m (H_A from 2-CH_AH_B), 3.51 m (H_B from 2-CH_AH_B), 4.31 d (H_A from 5-CH_AH_B, $^2J_{AB}$ = 10.43 Hz), 4.36 d (H_B from 5-CH_AH_B, $^2J_{AB}$ = 10.43 Hz), 5.41 s (10*b*-CH), 6.68 d (7-CH, $^3J_{7-8}$ = 8.7 Hz), 7.24 d (1 H, 8-CH, $^3J_{7-8}$ = 2.5 Hz, $^4J_{8-10}$ = 8.7 Hz), 7.38 d (10-CH, ^4J = 2.5 Hz).

2-Methyl-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*gauche*) (2g). δ_H ($CDCl_3$) 1.28 d (2-C–CH_3, ^3J = 6.1 Hz), 2.88 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 9.6 Hz, $^3J_{AC}$ = 6.8 Hz), 3.40 dd (H_B from 2-CHC–3-$CH_A$$H_B$, $^2J_{AB}$ = 9.6 Hz, $^3J_{BC}$ = 7.0 Hz), 4.11 m (H_C from CH_3–2-CH_C–3-$CH_A$$H_B$), 4.74 d ($H_A$ from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.7 Hz), 4.82 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.7 Hz), 5.75 s (10*b*-CH), 6.82 m (7-CH), 6.95 m (9-CH), 7.18 m (8-CH), 7.27 m (10-CH).

2-Methyl-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*anti*) (2g). δ_H ($CDCl_3$) 1.22 d (2-C–CH_3, ^3J = 6.1 Hz), 2.80 t (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 8.9 Hz, $^3J_{AC}$ = 8.9 Hz), 3.32 dd (H_B from 2-CHC–3-$CH_A$$H_B$, $^2J_{AB}$ = 8.9 Hz, $^3J_{BC}$ = 5.9 Hz), 4.28 m (H_C from CH_3–2-CH_C–3-$CH_A$$H_B$), 4.71 d ($H_A$ from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.6 Hz), 4.76 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.6 Hz), 5.61 s (10*b*-CH), 6.82 m (7-CH), 6.95 m (9-CH), 7.18 m (8-CH), 7.27 m (10-CH).

2-Methyl-9-bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*gauche*) (2h). δ_H ($CDCl_3$) 1.27 d (2-C–CH_3, ^3J = 6.2 Hz), 2.85 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 9.5 Hz, $^3J_{AC}$ = 6.5 Hz), 3.36 dd (H_B from 2-CH_C–3-$CH_A$$H_B$, $^2J_{AB}$ = 9.5 Hz, $^3J_{BC}$ = 7.0 Hz), 4.09 m (H_C from CH_3–2-CH_C–3-$CH_A$$H_B$), 4.76 d ($H_A$ from 5-$CH_A$$H_B$, ^{2JAB} = 10.2 Hz), 4.81 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ 10.2 Hz), 5.72 s (10*b*-CH), 6.67 d (7-CH, $^3J_{7-8}$ = 8.9 Hz), 7.24 dd (8-CH, $^4J_{8-10}$ = 1.8 Hz, $^3J_{7-8}$ = 8.9 Hz), 7.37 d (10-CH, $^4J_{8-10}$ = 1.8 Hz).

2-Methyl-9-bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*anti*) (2h). δ_H ($CDCl_3$) 1.20 d (2-C–CH_3, ^3J = 6.2 Hz), 2.79 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 8.9 Hz, $^3J_{AC}$ = 8.5 Hz), 3.29 dd (H_B from 2-CH_C–3-$CH_A$$H_B$, $^2J_{AB}$ = 8.9 Hz, $^3J_{BC}$ = 5.6 Hz), 4.29 m (H_C from CH_3–2-CH_C–3-$CH_A$$H_B$), 4.73 d ($H_A$ from 5-$CH_A$$H_B$, ^{2JAB} = 9.9 Hz), 4.75 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.9 Hz), 5.61 s (10*b*-CH), 6.70 d (7-CH, $^3J_{7-8}$ = 8.9 Hz), 7.24 dd (8-CH, $^4J_{8-10}$ = 1.8 Hz, $^3J_{7-8}$ = 8.9 Hz), 7.38 d (10-CH, $^4J_{8-10}$ = 1.8 Hz).

2-Methoxymethyl-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*gauche*) (2i). δ_H ($CDCl_3$) 3.10 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 10.1 Hz, $^3J_{AC}$ = 5.6 Hz), 3.39 m (2-C–CH_2-O), 3.40 s (CH_3-O), 3.52 dd (H_B from 2-CH_C–3-$CH_A$$H_B$, $^2J_{AB}$ = 10.1 Hz, $^3J_{BC}$ = 5.7 Hz), 4.20 m (H_C from CH_2–2-CH_C–3-$CH_A$$H_B$), 4.72 d ($H_A$ from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.7 Hz), 4.84 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.7 Hz); 5.75 s (10*b*-CH), 6.82 m (7-CH); 6.95 m (9-CH), 7.18 m (8-CH), 7.31 m (10-CH).

2-Methoxymethyl-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*anti*) (2i). δ_H ($CDCl_3$) 2.93 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 10.1 Hz, $^3J_{AC}$ = 7.9 Hz), 3.30 s (CH_3-O), 3.35 m (2-C–CH_2-O), 3.47 dd (H_B from 2-CH_C–3-$CH_A$$H_B$, $^2J_{AB}$ = 10.1 Hz, $^3J_{BC}$ = 4.9 Hz), 4.32 m (H_C from CH_2–2-CH_C–3-$CH_A$$H_B$), 4.67 d ($H_A$ from 5-$CH_A$$H_B$, $^2J_{AB}$ = 8.9 Hz), 4.72 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ = 8.9 Hz); 5.57 s (10*b*-CH), 6.82 m (7-CH); 6.95 m (9-CH), 7.18 m (8-CH), 7.31 m (10-CH).

2-Methoxymethyl-9-bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*gauche*) (2j). δ_H ($CDCl_3$) 3.10 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 10.1 Hz, $^3J_{AC}$ = 5.6 Hz), 3.38 m (2-C–CH_2-O), 3.39 s (CH_3-O), 3.51 dd (H_B from 2-CH_C–3-$CH_A$$H_B$, $^2J_{AB}$ = 10.1 Hz, $^3J_{BC}$ = 5.7 Hz), 4.20 m (H_C from CH_2–2-CH_C–3–$CH_A$$H_B$), 4.75 d ($H_A$ from 5-C–$H_A$$H_B$, $^2J_{AB}$ = 9.9 Hz), 4.84 d (H_B from 5-$CH_A$$H_B$, $^2J_{AB}$ = 9.9 Hz); 5.72 s (10*b*-CH), 6.69 m (7-CH); 6.85 m (8-CH), 7.25 m (10-CH).

2-Methoxymethyl-9-bromo-2,3-dihydro-10*b*-H-[1,3]oxazolo[3,2-*c*]-[1,3]benzoxazine (*anti*) (2j). δ_H ($CDCl_3$) 2.94 dd (H_A from 2-CH_C–3-C$H_A$$H_B$, $^2J_{AB}$ = 9.9 Hz, $^3J_{AC}$ = 8.4 Hz), 3.29 s (CH_3-O), 3.34 m (2-C–CH_2–O), 3.46 dd (H_B from 2-CH_C–3-CH_AH_B, $^2J_{AB}$ = 9.9 Hz, $^3J_{BC}$ = 5.0 Hz), 4.34 m (H_C from CH_2–2-CH_C–3-CH_AH_B), 4.70 d (H_A from 5-CH_AH_B, $^2J_{AB}$ = 9.6 Hz), 4.73 d (H_B from 5-CH_AH_B, $^2J_{AB}$ = 9.6 Hz); 5.56 s (10*b*-CH), 6.69 m (7-CH); 6.85 m (8-CH), 7.25 m (10-CH).

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