to the diameter was 10:1) packed with L 40/100 silica gel. Elution with chloroform (20 ml) with subsequent removal of it by distillation gave 14 mg (20.0%) of dimethylparabanic acid (IVb) with mp 103-105°C (from chloroform). UV spectrum (water), λ_{max} (log ε): 261 (3.16), 216 nm (3.96). PMR spectrum ($CDCl_3$): 3.18 ppm (s, NCH_3). Mass spectrum: 142 (87.0), 114 (16.8), 86 (5.7), 57 (55.0). High-resolution mass spectrum: 142.0382 (M^+), calculated 142.0379 ($C_5H_6N_2O_3$); 114.0428 ($[M - CO]^+$), calculated ($C_4H_6N_2O_2$); 86.0475 ($[M - C_2O_2]^+$), calculated 86.0480 ($C_3H_6N_2O$).

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NUCLEOPHILIC SUBSTITUTION IN HYDROXYISOXAZOLIDINES

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Nucleophilic substitution of the hydroxy-group in 3- (or 5-)hydroxyisoxazolidines affords the aryl(alkyl)amino-, alkoxy-, and hydrazino-compounds. 5-Dimethylhydrazinooxazolidines exist preferentially in the linear form.

Functional derivatives of isoxazolidine are of particular interest as potentially physiologically active compounds, since they include antitumor [1] and antibacterial drugs [2], antidepressants [3], and fungicides [4]. The introduction of functional groups into the isoxazolidine ring was an important but difficult task, only the 5-alkoxy derivatives being available until recently [5]. In a previous communication [6], we reported a promising method for the synthesis of 3- and 5-hydroxyisoxazolidines. Bearing in mind the hemiaminal nature of the hydroxy-group in these compounds, and its tendency to undergo nucleophilic exchange, we developed a method for the synthesis of other 3- and 5-functionalized isoxazolidines from the hydroxyisoxazolidines. The nucleophilic reactants used were alcohols, aliphatic and aromatic amines, N-substituted hydrazones and hydrazides:

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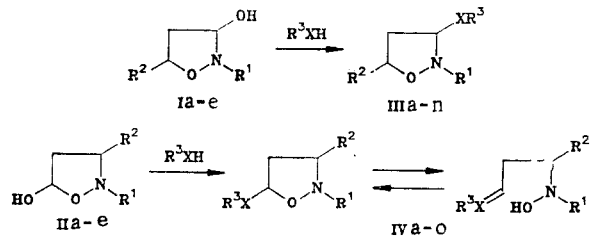
TABLE 1. Properties of Isoxazolidines (II) and (IV)

Compound	R^1	R^2	R^3	X	mp, °C*	Found, %		Empirical formula	Calculated, %		Yield, %
						C	H		C	H	
IIIa	COC_6H_5	CH_3	CH_3	O	53	65,4	7,1	$C_{12}H_{15}NO_3$	65,2	6,8	90
IIIb	COC_6H_5	H	CH_3	O	75	63,7	6,5	$C_{11}H_{13}NO_3$	63,8	6,3	79
IIIc	COC_6H_5	H	C_2H_5	O	Oil	65,6	7,0	$C_{12}H_{15}NO_3$	65,2	6,8	75
IIId	COC_6H_5	H	CH_2CHCH_2	O	44	67,8	6,6	$C_{13}H_{15}NO_3$	66,9	6,4	65
IIIe	COC_6H_5	H	$CH_2C_6H_5$	O	148	72,7	6,1	$C_{17}H_{17}NO_3$	72,1	6,0	56
IIIf	COC_6H_4Br	H	CH_3	O	63	46,0	4,1	$C_{11}H_{12}BrNO_3$	46,2	4,2	85
IIIg	$COC_6H_4NO_2$	H	CH_3	O	83	52,2	4,8	$C_{11}H_{12}N_2O_5$	52,4	4,8	83
IIIh	COC_6H_5	H	C_6H_4Br	NH	97	55,6	4,6	$C_{16}H_{15}BrN_2O_2$	55,3	4,3	65
IIIi	COC_6H_4Br	CH_3	C_6H_4Br	NH	159	46,5	3,6	$C_{17}H_{16}Br_2N_2O_2$	46,4	3,6	93
IIIj	COC_6H_4Br	H	C_6H_4Br	NH	154	45,7	3,4	$C_{16}H_{14}Br_2N_2O_2$	45,1	3,3	90
IIIk	COC_6H_4Br	H	C_6H_5	NH	124	55,6	4,6	$C_{16}H_{15}BrN_2O_2$	55,3	4,3	60
IIIℓ	COC_6H_4Br	H	$C_6H_4OCH_3$	NH	130	54,2	4,7	$C_{17}H_{17}BrN_2O_3$	54,1	4,5	86
IIIm	$COC_6H_4NO_2$	H	C_6H_4Br	NH	165	49,0	3,6	$C_{16}H_{14}BrN_3O_4$	49,0	3,6	85
IIIn	$COC_6H_4NO_2$	H	$C_6H_4OCH_3$	NH	143	59,7	5,2	$C_{17}H_{17}N_3O_5$	59,5	5,0	89
IVa	COC_6H_5	CH_3	CH_3	O	53	65,5	7,0	$C_{12}H_{15}NO_3$	65,2	6,8	87
IVb	$COC_6H_4CH_3$	H	C_2H_5	O	Oil	66,7	7,3	$C_{13}H_{17}NO_3$	66,4	7,2	70
IVc	COC_6H_5	H	C_2H_5	O	Oil	64,9	6,7	$C_{12}H_{15}NO_3$	65,2	6,8	75
IVd	COC_6H_5	CH_3	$C_6H_4OCH_3$	NH	115	70,1	6,7	$C_{18}H_{20}N_2O_3$	69,2	6,4	75
IVe	C_6H_5	H	C_6H_5	NH	Oil	74,9	6,8	$C_{15}H_{16}N_2O$	75,0	6,7	70
IVf	C_6H_5	H	$C_6H_4CH_3$	NH	64	75,8	6,8	$C_{16}H_{18}N_2O$	75,6	7,1	73
IVg	C_6H_5	H	$C_6H_4NO_2$	NH	164	63,0	5,1	$C_{15}H_{15}N_3O_3$	63,1	5,3	65
IVh	C_6H_5	H	$CH_2C_6H_5$	NH	50	75,5	7,3	$C_{16}H_{18}N_2O$	75,6	7,1	85
IVi	C_6H_5	CH_3	C_6H_5	NH	73	75,3	7,1	$C_{16}H_{18}N_2O$	75,6	7,1	55
IVj	C_6H_5	CH_3	$C_6H_4CH_3$	NH	76	76,3	7,5	$C_{17}H_{20}N_2O$	76,1	7,4	75
IVk	C_6H_5	H	$N(CH_3)_2$	NH	55	63,6	8,2	$C_{11}H_{17}N_3O$	63,7	8,3	55
IVl	$C_6H_4NO_2$	H	$N(CH_3)_2$	NH	Oil	52,2	6,7	$C_{11}H_{16}N_4O_3$	52,4	6,4	82
IVm	C_6H_5	H	NHCOH	$NCH(CH_3)_2$	115	62,5	7,9	$C_{13}H_{19}N_3O_2$	62,6	7,7	65
IVn	C_6H_5	H	$NHCOCH_3$	$NCH(CH_3)_2$	108	64,1	8,1	$C_{14}H_{21}N_3O_2$	63,9	8,0	75
IVo	C_6H_5	CH_3	$N(CH_3)_2$	NH	Oil	64,9	8,9	$C_{12}H_{19}N_3O$	65,1	8,7	50

*(IIIa, b, d-f, i, k) and (IVa, f, h-k, m, n) were recrystallized from hexane, (IIIg, h, j, ℓ-n) and (IVd) from dichloromethane, and (IVg) from benzene.



I a $R^1=COC_6H_5$, $R^2=CH_3$; b $R^1=COC_6H_5$, $R^2=H$; c $R^1=COC_6H_4Br$-*p*, $R^2=CH_3$; d $R^1=COC_6H_4Br$-*p*, $R^2=H$; e $R^1=COC_6H_4NO_2$-*p*, $R^2=H$; II a $R^1=COC_6H_5$, $R^2=CH_3$; b $R^1=COC_6H_4CH_3$-*p*, $R^2=H$; c $R^1=C_6H_5NO_2$-*p*, $R^2=H$; d $R^1=C_6H_5$, $R^2=H$; e $R^1=C_6H_5$, $R^2=CH_3$; R^3, X see Table 1

Replacement of the hydroxy-group in 2-acyl-3(5)-hydroxyisoxazolidines (Ia-e) and (IIa, b) on treatment with alcohols requires acid catalysis, which is heterophase, since the starting materials are unstable to acid. The reaction takes place at room temperature in 2-15 min to give quantitative yields. The resulting alkoxyisoxazolidines are much more stable than the hydroxy-compounds, and exist in the cyclic form, as shown by the presence of signals in the ^1H NMR spectra characteristic of the 3-H proton in (III), or 5-H in (IV) at 4.9-6.1 ppm, and in the ^{13}C NMR spectra for $C_{(3)}$ (~ 78 ppm) or $C_{(5)}$ (~95 ppm) (Table 2). These chemical shifts for $C_{(3)}$ and $C_{(5)}$ also confirm the assignment of the compounds to the 3- (III) or 5-functionalized isoxazolidines (IV), respectively.

In the replacement of the hydroxy-group of the isoxazolidine by alkoxy, the alcohol functions as the nucleophile, and this attacks the hemiaminal (or hemiacetal) carbon, which has reduced electron density. This mechanism is confirmed by experiments using compounds with tagged hydroxyl groups. Reaction of the hydroxyisoxazolidine (IIa) with $H_2{}^{18}O$ gives around 25% (by mass spectrometry) of the isotope-substituted product. Subsequent reaction with methanol in the usual way gives the methoxyisoxazolidine (IVa) free from the ^{18}O isotope, according to mass spectrometry.

Reaction of the hydroxy-compounds (Ia-e) and (IIa-e) with aromatic amines takes place readily without a catalyst, at room temperature, the yields of product being largely dependent on the nucleophilicity of the starting amine. For example, reaction of 2-p-bromobenzoyl-3-hydroxyisoxazolidine (Id) with p-anisidine and p-bromoaniline gives the aminoisoxazolidines (IIIℓ) and (IIIj) in yields of 85-90%, with aniline 60%, and the product of the reaction with p-nitroaniline was obtained in trace amounts only. With secondary aliphatic amines (dimethylamine, piperidine), and in the case of the 3-hydroxyisoxazolidines (Ia-e) with primary amines also, the initial isoxazolidines decomposed, perhaps as a result of the high basicity of the aliphatic amines.

The amino-compounds obtained (IIIh-n) and (IVd-ℓ) also exist in the cyclic form, and continue to exist as the 3- or 5-compounds, as shown by the ^1H and ^{13}C NMR spectra (Table 2). The absence of linear isomers in the amino-compounds (III) and (IV), as in the case of the alkoxy-compounds, is apparently due to their greater stability as compared with the starting hydroxyisoxazolidines.

The 2-aryl-5-hydroxyisoxazolidines (IIc-e) react readily both with primary aliphatic amines (IVh) and with other N-nucleophiles (hydrazines, hydrazides, and hydroxylamines). As reported previously [6], reaction of an excess of N-phenylhydroxylamine with alkenals affords, in addition to the hydroxyisoxazolidines (IId, e), products of the subsequent replacement of the hydroxy-group, namely N-phenylhydroxyaminoisoxazolidines. We here give some examples of the replacement of the hydroxy-group by hydrazines (IVk-p); it is noteworthy that (IVk, ℓ) (but not IVo), i.e., the dimethylhydrazino-compounds, like the starting materials [6] display ring-chain tautomerism, the open-chain form predominating (90%) (Table 2).

Since some of the closest nitrogen analogs of these compounds, namely 5-hydroxy- and 5-hydrazinopyrazolidines, show antiinflammatory activity [7], typical representatives of the 3- and 5-hydroxy, and 5-hydrazinoisoxazolidines (IId, IVm, IVn) were tested for antiinflammatory activity in an adrenalin edema model.* It was found that at these compounds, which are of low toxicity (LD_{50} 650-720 mg/kg), do in fact possess antiinflammatory activity, which is however lower than that of the pyrazolidines [7].

*The tests were carried out by E. G. Gromova, Lecturer, Department of Pharmacology, Leningrad Institute of Pharmaceutical Chemistry (Department Head, Prof. L. V. Pastushenkov).

TABLE 2. Spectral Characteristics of Isoxazolidines (III) and (IV)

Compound	Solvent	^{1}H NMR spectrum, δ, ppm (J, Hz)*					^{13}C NMR spectrum ($CDCl_3$), δ, ppm				
		3-H, m	4-H, m	5-H	R^2, d	R^3	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	R^2	R^3
IIIa**	$CDCl_3$	5,90	1,93, 2,08, 2,42, 2,70	3,93 m, 4,61 m	1,08 (6), 1,33 (6)	3,48 s, 3,50 s	—	—	—	—	—
IIIi**	$CDCl_3$	6,52	2,10, 2,62, 3,25	4,12 m, 4,87 m	1,34 (6), 1,68 (6)	7,0 . . . 7,6 q	79,2, 86,3	41,3, 42,8	66,6, 67,8	17,8, 19,7	111,6 . . . 142,0
IVa**	$CDCl_3$	4,49, 4,80	1,98, 2,48, 2,60	4,98 d.d (5; 0,5) 5,13 d.d (5; 1)	1,33 (6,5), 1,49 (6,5)	2,70 s, 2,71 s	52,4	40,5	104,4	20,4	56,2
IVb	$CDCl_3$	3,45, 4,30	2,20	5,10 m	—	0,85 t, 3,03 q	41,6	32,4	101,4		12,8, 62,3
IVf	CCl_4	3,15, 3,50	1,90, 2,40	5,45 m	—	6,49 . . , 7,15 m 2,15 s	52,6	34,7	84,7	—	20,2, 114,5 . . . 141,3
IVh	C_5D_5N	3,10, 3,25	2,05	4,96 d.d (7; 5)	—	6,73 . . . 7,35 m 3,88) (AB, 4,04) 14)	52,3	34,4	89,3	—	111,6 . . . 140,7, 49,7
IVk ring (15%)	$CDCl_3$	2,99	2,29	5,21 m	—	2,42 s	52,8	34,3	89,7	—	—
chain (85%)	$CDCl_3$	3,36	2,29	6,60 t (5)	—	2,55 s	56,7 (C_β)	29,8 (C_α)	137,8 (C=N)	—	—
IVn***	CCl_4	3,35	2,06	5,23 m	—	1,73 s, 1,86 s	—	—	—	—	—
IVo**	CCl_4	3,54	2,17	5,12 m	0,95 (7), 1,27 (7)	2,41 s, 2,45 s	—	—	—	—	—

*The signals for all the R^1 groups were located at 6.4-8.3 ppm in the ^{1}H NMR spectra, and at 111-153 ppm (for NC=O at 165-172 ppm) in the ^{13}C NMR spectra.

**Mixture of diastereoisomers.

***Mixture of rotational isomers.

EXPERIMENTAL

^1H NMR spectra were obtained on Tesla BS-497 (100 MHz), Bruker WM-250, and Tesla BS-467 (60 MHz) instruments, and the ^{13}C NMR spectra on Bruker WM-250 and Bruker HX-90 (22.63 MHz) instruments in impulse mode with Fourier transformation. The internal standard was TMS or HMDS. Chromatographic separation was carried out on a column of silica gel L 40/100 in the systems benzene–acetone, 5:1 [for (IVe-o)] or hexane–ethyl acetate [for (IIa-n) and (IVa-d)]. The purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in the system hexane–ethyl acetate, 1:2, visualized with UV and iodine vapor.

The hydroxyisoxazolidines (I) and (II) were obtained as described in [6]. The constants and yields of the products (III) and (IV) are given in Table 1, and their spectral data in Table 2.

3(5)-Alkoxy-2-acylisoxazolidines (IIIa-g) and (IVa-c). To a solution of 5 mmoles of the isoxazolidine (I) or (II) in 20 ml of chloroform or methylene chloride was added 7-10 mmoles of alcohol and 3-5 drops of concentrated sulfuric acid, and the mixture stirred for 5-15 min, until the starting material had been consumed (by TLC). The solution was filtered through a thin layer of alumina, washed with a large amount of chloroform, and the solvent removed under reduced pressure. The residue was recrystallized from hexane (the oil was chromatographed on a column of silica gel L 40/100 in hexane).

3(5)-Anilino-2-acylisoxazolidines (IIIh-n) and (IVd). A solution of 5 mmoles of the hydroxyisoxazolidine (I) or (II) and 5 mmoles of the substituted aniline in 50 ml of methylene chloride was stirred for 2 h at ambient temperature, and the solvent removed. The residue was recrystallized from methylene chloride or a mixture of hexane and ether.

5-Amino-2-arylsoxazolidines (IVe-j) and 2-Aryl-5-hydrazinoisoxazolidines (IVk-o). A mixture of 0.05 mole of the hydroxyisoxazolidine (II) and 0.05 mole of the amine in 100 ml of benzene* was kept in the presence of 1 g of $CaCl_2$ for one day. The solvent was removed under reduced pressure, and the residue recrystallized from hexane or chromatographed on a column.

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*In the case of (IVf), 50 ml of methanol was added.