SYNTHESIS OF ISOXAZOLIDINE DERIVATIVES FROM N-SUBSTITUTED HYDROXYLAMINES AND α,β-UNSATURATED KETONES

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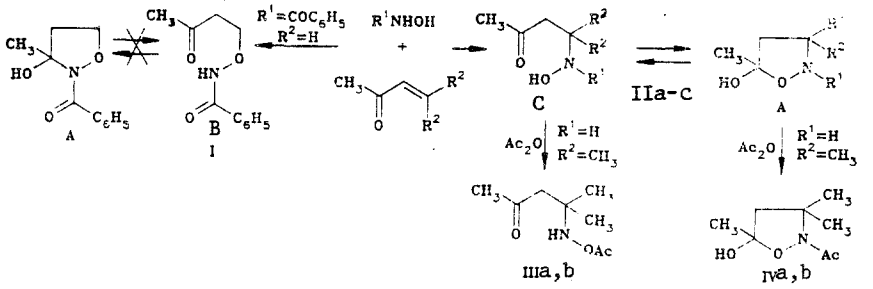
The reaction of methyl vinyl ketone with N-Phenyl-hydroxylamine leads to a tautomeric mixture of 5-hydroxy-2-phenyl-5-methylisoxazolidine and its linear form, while the reaction with benzohydroxamic acid leads to linear products of addition to the oxygen or nitrogen atoms, depending on the reaction conditions. The first representatives of 5-hydroxyisoxazolidines with the residue of an aliphatic carboxylic acid attached to the nitrogen atom were obtained by acylation of 5-hydroxy-3,3,5-trimethylisoxazolidine.

The direction of the addition of N-substituted hydroxylamines to alkenals is completely determined by the nature of the substituent: if alkyl- [1] and arylhydroxylamines [2] give products of addition at the nitrogen atom, which then undergo cyclization to the corresponding 5-hydroxyisoxazolidines, arylhydroxamic acids attack the double bond with both the nitrogen and oxygen atoms [2] with the formation of the corresponding 5- or 3-hydroxyisoxazolidines. In order to further investigate the preparative properties of this reaction we examined the addition of phenylhydroxylamine and benzohydroxamic acid to methyl vinyl ketone.

As in the case of alkenals, the attack of phenylhydroxylamine at the double bond of methyl vinyl ketone takes place with the nitrogen atom to give IIa, regardless of the conditions.



II a $R^1=C_6H_5$, $R^2=H$; b $R^1=H$, $R^2=CH_3$; c $R^1=C_6H_5CO$, $R^2=H$; III a Ac=CH_3CO; b Ac=C_6H_5CO; IV a Ac=CH_3CO; b Ac=HCO

In the crystal state IIa exists completely in cyclic form A; this is confirmed by the absence in its IR spectrum of a band of carbonyl group vibrations. In solutions IIa exists in the form of a tautomeric mixture of cyclic and linear isomers: absorption at 1700 cm^{-1} appears in its IR spectrum, while signals of linear form B [2.10 (CH_3), 8.79 ppm (OH)] appear in the ^1H NMR spectrum along with signals of cyclic isomer A [1.50 (CH_3), 6.18 ppm (OH)]. Signals of both a cyclic form [103.0 ($C(_5)$), 24.5 (CH_3), 53.3 ppm ($C(_3)$)] and a linear form [208.6 (CO), 29.7 (CH_3), 53.9 ppm ($C(R^2)_2$)] are also present in the ^{13}C NMR spectrum of IIa. In addition, in conformity with the data for 5-hydroxyisoxazolidines [97-98.5 ($C(_5)$), 45-62 ppm ($C(_3)$) [2] such chemical shifts of the $C(_5)$ and $C(_3)$ atoms of form A and the carbon atom of the NCH_2 group of form B confirm the structures of these compounds as products of attack by the nitrogen atom at the C=C bond. The amount of the cyclic isomer decreases as the polarity of the solvent increases (50% in CCl_4, 30% in DMSO).

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TABLE 1. Spectral Characteristics of I-IV

Compound	Form	^{1}H NMR spectrum δ, ppm (J, Hz)						^{13}C NMR spectrum, δ, ppm						
		solvent	CH_3, s	$C(CH_2)C$	R^2	R^1 (Ac)	other signals	solvent	$C(R^2)_2$	CH_2, t	$C(CH_3)_2$, s	CH_3, q	R^2, q	R^1 (Ac)
IIa	B A	d6-DMSO	2,10 1,50	2,67 m	3,45 m	6,75 ... 7,40 m	8,79 s (OH) 6,18 s (OH)	$CDCl_3$	53,9 t 53,3 t	40,6, 39,6	208,6 103,0	29,7 24,5	—	115,1 ... 152,0, 8 signals (C_{arom})
IIb	A	$CDCl_3$	1,46	2,2 (AB, 13)	1,16 s, 1,10 s	5,90	4,96 br.s(OH)	$CDCl_3$	61,4 s	54,6	108,0	27,7	25,2; 14,4	—
IIc	B	$CDCl_3$	2,10	2,90 t(6)	3,90 (6)	7,60 m	9,0 br. s (OH)	$CDCl_3$	45,7 t	40,5	207,2	30,0	—	128,1 ... 132,7, 4 signals (C_{arom}); 168,1 (NC=O)
I	B	$CDCl_3$	2,10	2,80 t(6)	4,20 t (6)	7,20 ... 7,90 m	9,70 br.s(NH)	$CDCl_3$	70,8 t	41,8	207,1	30,0	—	126,9 ... 131,7, 5 signals (C_{arom}); 166,1 s (NC=O)
IIIa	B	CCl_4	2,00	2,44 s	1,02 s	1,94 s	7,62 (NH)	$CDCl_3$	56,3 t	49,6	184,2	31,0	24,0	169,5 s (CO); 18,3 q (CH_3)
IIIb	B	$CDCl_3$	2,03	2,60 s	1,14 s	7,20 ... 8,00 m	7,6 br.s(NH)	—	—	—	—	—	—	—
IVb	A	$CDCl_3$	1,59, 1,56	2,20, 2,18 (AB, 13)	1,39 s	8,26 s 7,98 s	5,80 br. s	CD_3OD	64,5 s	56,3, 55,2	106,1	30,6, 28,3	26,0, 24,9	158,9 s (CO); 154,8 s (CO)
IVa	A	$CDCl_3$	1,57	2,20, 2,35 (AB, 13)	1,45 s, 1,37 s	1,91 s	5,15 br.s(OH)	$CDCl_3$	62,9 s	55,2	102,9	30,0	25,5, 24,2	169,8 s (CO); 21,8 q (CH_3)

Just as in the case of the reaction with alkenals, the direction of the reaction of benzohydroxamic acid with methyl vinyl ketone depends on the reaction conditions. 4-(Benzamidoxy)-2-butanone (I), which, according to spectral data (^1H and ^{13}C NMR and IR spectroscopy), exists only in linear form B, is formed in methanol solution in the presence of a basic heterogeneous catalyst — trimethylaminoethylcellulose.

When the reaction was carried out without a solvent (both reagents were applied to diethylaminoethylcellulose), N-isomer IIc, which also exists completely in the linear form, was obtained in high yield. In its ^1H NMR spectrum the signal of the NCH_2 group is found at stronger field (3.9 ppm) than in the case of I (4.2 ppm). In the ^{13}C NMR spectrum of IIc the signal of the carbon atom bonded to the heteroatom also lies at stronger field.

The direct acylation of unsubstituted IIb may be another method for the synthesis of N-acyloxyisoxazolidines. Its reaction with benzoic anhydride leads to the formation of only a product of O acylation with linear structure IIIb in low yield. However, the acetylation of IIb proceeds ambiguously: a mixture of products with cyclic (IVa) and linear (IIIa) structures with substantial preponderance of the latter is formed; in the isolation of the product by column chromatography and fractional distillation the equilibrium is shifted to favor IIIa. A product with a cyclic structure (IVb) is formed in high yield in the reaction of IIb with formylacetic anhydride. The criteria for the proof of structures III and IV are similar to those presented above (Table 1). Doubling of some of the signals, which may be due to either retarded rotation about the amide bond or inversion of nitrogen, is observed in the ^1H and ^{13}C NMR spectra of solutions of IVb. Another piece of evidence for the formation of precisely an N-acyl grouping is the development of a violet-red coloration, which is characteristic for hydroxamic acids and their N-alkyl derivatives, when IVa and IVb are treated with $FeCl_3$ solution [3, 4] — in contrast to the colorless solutions of IIIa,b.

Thus the IVa and IVb that we obtained are the first representatives of 5-hydroxyisoxazolidines with a saturated carboxylic acid residue in the 2 position.*

Since biologically active substances have been detected among 3(5)-hydroxy-2-aroylisoxazolidines [5], IVb, being a representative of 5-hydroxy-2-acylisoxazolidines, was presented for biological testing.** This substance has low toxicity (LD_{50} 700 mg/kg) and displays pronounced antiphlogistic activity in a dose of 50 mg/kg in models involving "quilted granuloma" and adrenalin emphysema; however, its activity is inferior to that of model compounds — butadione and voltaren.

EXPERIMENTAL

The IR spectra of suspensions in mineral oil and solutions in choroform were obtained with UR-20 and Specord 75 IR spectrometers. The ^1H NMR spectra were recorded with a Tesla BS-497 spectrometer (100 MHz), while the ^{13}C NMR spectra were obtained with Bruker HX-90 (22.63 MHz) and Bruker H-250 spectrometers under pulse conditions with Fourier transformation and hexamethyldisiloxane (HMDS) as the internal standard (Table 1). Chromatographic separation was carried out with a column packed with L 40/100 silica gel in a chlorofom—methnol system (100:3) (for IIa and IIIa) or an ether—petroleum ether system (1:1) (for IIIb). The purity of the compounds obtained and the course of the reaction were monitored on Silufol UV-254 plates in the following systems: chloroform—methanol (100:3) (1), benzene-acetone (1:1) (2), and ether—petroleum ether (1:1) (3). The chromatograms were developed with iodine vapors*** and UV light.

5-Hydroxy-3,3,5-trimethylisoxazolidine (IIb) was obtained by the method in [6]. The results of elementary analysis for C, H, and N were in agreement with the calculated values.

Reaction of Methyl Vinyl Ketone with N-Phenylhydroxylamine. A 5.0-g (0.071 mole) sample of frehly distilled methyl vinyl ketone was added with stirring at 20°C to a suspension of 7.8 g (0.07 mole) of N-phenylhydroxylamine in 50 ml of benzene. After 24 h, the solvent and excess ketone were evaporated in vacuo, and the residual orange oil (12 g) was chromatographed with collection of the fraction with R_f 0.65 (system 1). A 1.4-g sample of the reaction mass yielded 0.8 g (55%) of a yellow oil — IIa ($C_{10}H_{13}NO_2$), which darkened and decomposed on storage. IR spectrum ($CHCl_3$): 1700 (CO), 3580, 3304 cm^{-1} (OH).

*A previous attempt to subject acetoxyhydroxamic acid to reaction with acrolein was unsuccessful [2].

**The testing was carried out by docent É. G. Gromova in the department of pharmacology of the Leningrad Institute of Pharmaceutical Chemistry (department head Professor L. V. Pastushenkov).

***Compounds III and IV are poorly developed by iodine vapors; however, fast development is observed when the chromatographic plate is heated to 120-150°C.

4-(N-Benzoyl-N-hydroxyamino)-2-butanone (IIc, $C_{11}H_{13}NO_3$). A saturated methanol solution of 0.6 g (5 mmole) of benzohydroxamic acid was applied to thoroughly dried diethylaminoethylcellulose (6 g), after which the support was dried in vacuo to remove the solvent. A 0.5-ml (5 mmole) sample of methyl vinyl ketone (a 10% charge) was applied to another portion of the support (6 g), and both portions were shaken and allowed to stand overnight at 20°C. The reaction product was washed out with chloroform (three 10-ml portions) and passed through a thin layer of Al_2O_3 and activated charcoal. The solvent was removed in vacuo, and the residue was recrystallized from ether to give 1.04 g (85%) of a product with mp 94-97°C.

4-(Benzamidoxy)-2-butanol (I, $C_{11}H_{13}NO_3$). A 1-ml (0.01 mole) sample of methyl vinyl ketone and 20 mg of triethylaminoethylcellulose were added to a solution of 1.37 g (0.01 mole) of benzohydroxamic acid in 100 ml of methanol, and the mixture was allowed to stand for a week at 0°C. The catalyst was removed by filtration, and the solvent was evaporated in vacuo. The residue was dissolved in chloroform, and the solution was passed through a thin layer of Al_2O_3 and activated charcoal. The solvent was removed, and the residue was recrystallized from hexane to give 1.53 g (74%) of a product with mp 48-51°C. IR spectrum (mineral oil): 3200 (NH), 1720 (CO), 1647 cm^{-1} (NCO).

5-Hydroxy-2-formyl-3,3,5-trimethylisoxazolidine (IVb, $C_7H_{13}NO_3$). A 12.2-g (0.15 mole) sample of formylacetic anhydride was added to a cooled (with ice water) solution of 13.1 g (0.1 mole) of 5-hydroxy-3,3,5-trimethylisoxazolidine (IIb) in 50 ml of ether, and the resulting precipitate [12 g, Rf 0.45 (2)] was separated. The ether solution was washed with a saturated solution of $NaHCO_3$ and dried with $MgSO_4$. According to the TLC data, the solution contained a substance with Rf 0.45 and a small amount of a product with Rf 0.69.* The solvent was evaporated, and the combined product was recrystallized from ethyl acetate—ethanol (100:1) to give 10.9 g (68%) of IVb in the form of colorless crystals with mp 121-122°C. IR spectrum ($CHCl_3$): 1637 (CO); 3580, 3300 cm^{-1} (OH).

Acetylation of 5-Hydroxy-3,3,5-trimethylisoxazolidine. A 13.3-g (0.129 mole) sample of acetic anhydride was added dropwise to a cooled (to 0°C) solution of 15.2 g (0.116 mole) of isoxazolidine IIb and 13.1 g (0.129 mole) of triethylamine in 50 ml of benzene, after which the reaction mixture was stirred for 2 h at 20°C. It was then treated with 20 ml of ice water, the benzene layer was separated, and the aqueous layer was extracted with benzene. The extracts were dried with $MgSO_4$, the solvent was removed by distillation in vacuo, and the residue was chromatographed with a column. A 2-g sample of the residue yielded 1.5 g of 4-(acetoxyamino)-4,4-dimethyl-2-butanone (IIIa) [Rf 0.79 (2)] and 0.3 g of 5-hydroxy-2-acetyl-3,3,5-trimethylisoxazolidine (IVa) (Rf 0.54). The overall yield was 60%, and the III:IV ratio was 83:17. From 11 g of the reaction mixture we removed 0.8 g of IVa ($C_8H_{15}NO_3$), with mp 98-99°C (from ethyl acetate), by filtration, and the residue was fractionated in vacuo to give 8.7 g of IIIa ($C_8H_{15}NO_3$) with bp 111-112°C (5 mm Hg).

4-(Benzoxyamino)-4,4-dimethyl-2-butanone (IIIb, $C_{13}H_{17}NO_3$). A 2.26-g (0.01 mole) sample of benzoic anhydride was added to a solution of 1.31 g (0.01 mole) of IIb in 10 ml of ether at 20°C. After 24 h, the solvent was evaporated, and the crystalline precipitate (according to TLC data, the starting compounds and benzoic acid) was removed by filtration. Column chromatography of the oily filtrate (0.8 g) gave 0.6 g (25%) of IIIb with Rf 0.29 (3).

*We were unable to isolate this product by column chromatography.

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