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5-SUBSTITUTED 2-BENZYLOXAZOLIDINES

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The reaction of N-benzylhydroxylamine with α,β-unsaturated carbonyl compounds provides a method of synthesis of 5-hydroxy-2-benzyloxazolidines, nucleophilic replacement of the hydroxyl group in which gives the corresponding 5-amino- and 5-hydrazinoisoxazolidines.

The reaction of α,β-unsaturated aldehydes [1] and ketones [2] with N-substituted hydroxylamines constitutes a method for the preparation of hydroxyisoxazolidines, from which alkoxy-, amino-, and hydrazinoisoxazolidines may be obtained [3]. The course of the cyclization is sensitive to the substituent at nitrogen, arylhydroxylamines giving 5-hydroxy-, while hydroxamic acids give both 3-hydroxy- and (or) 5-hydroxyisoxazolidines. There have been no reports of the structures of products from hydroxylamines with donor substituents. For this reason, as well as to further examine the preparative potential of this reaction, we have studied the reaction of the α,β-unsaturated carbonyl compounds (Ia-d) with N-benzylhydroxylamine (see scheme on page 1304).

The reaction proceeds rapidly and smoothly, the sole products being the 5-hydroxyisoxazolidines (IIIa-d) (Table 1). The use of solid-phase synthesis on adsorbents of different types (silica gel and alumina) and prolonged heating of the reaction mixtures at 100°C in the presence of added acid catalysts had no effect whatsoever on the structures of the products. Proof of the location of the hydroxyl group was based on reliable criteria [1], the positions of the chemical shifts for $C_{(5)}$ being in the range ~100 ppm, indicating its O–C–O environment. The remaining features of the proton and carbon spectra were in full agreement with the proposed structure (Table 1).

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TABLE 1. Properties of Compounds (III-V)

Compound	Empirical formula	R_f	mp, °C	Form	Amount, %	PMR spectrum (DMSO-D_6), δ, ppm (J, Hz)					
						R^1, R^2	4-H	R^3	CH_2	Ar, m	5-X, s
IIIa	$C_{10}H_{13}NO_2$	0,32	71...73	A	100	3,23 m	2,30 m	5,56 m	4,06 s	7,48...7,63	6,52
IIIb	$C_{11}H_{15}NO_2$	0,35	69...71	A	100*1	1,06 d (J=4); 1,13 d (J=4); 3,31 m	2,23 m	5,40 m	3,71 and 4.00 (J=14, AB); 4,10 s	7,25...7,41	4,30
IIIc	$C_{11}H_{15}NO_2$	0,50	40...43	A	15	3,37 m	2,17 m	1,48 s	4,08 s	7,56...7,73	6,16
				B	85	2,86 m		2,21 s	3,87 s		8,15
IIId	$C_{13}H_{19}NO_2$	0,45	97...98	A	100	1,05 s; 1,20 s	2,05 and 2.25 (J=12, AB)	1,35 s	3,23 and 4.05 (J=18, AB)	7,48...7,62	5,92
IVa	$C_{16}H_{18}N_2O$	0,51	88...90	A	100	3,22 m	2,58 m	5,70 m	4,10 s	6,75...7,66	—
IVb	$C_{17}H_{20}N_2O$	0,50	95...97	A	90	1,19 d (J=5); 2,88 m; 1,13 d (J=6)	1,93 m	5,60 m	3,83; 4,20 (J=12, AB)	6,68...7,56	—
				A	10			5,69 m	4,05 s		—
Va*2	$C_{12}H_{19}N_3O$	0,25	Oil	B	95	2,71 m		6,92 t (J=5); HC=N	3,89 s	7,41...7,73	2,68 ($2CH_3$)
Vb*3	$C_{13}H_{21}N_3O$	0,25	Oil	A	55	1,15 d (J=6); 3,15 m; 1,20 d (J=5)	1,51 m	5,28 m	3,62...4,36*4	7,53...7,78	2,40 ($2CH_3$)
				A	45			5,58 m			2,88 ($2CH_3$)

*1 1:1 Mixture of stereoisomers (in solution in $CDCl_3$).

*2 Only the PMR signals (in $CDCl_3$) for form B are given.

*3 The PMR signals (in $CDCl_3$ for the cyclic stereoisomers A are given. For form B, reliable values found were 2.50 s (CH_3N), 7.05 t (4, H–C=N).

*4 Twelve signals for three AB systems.

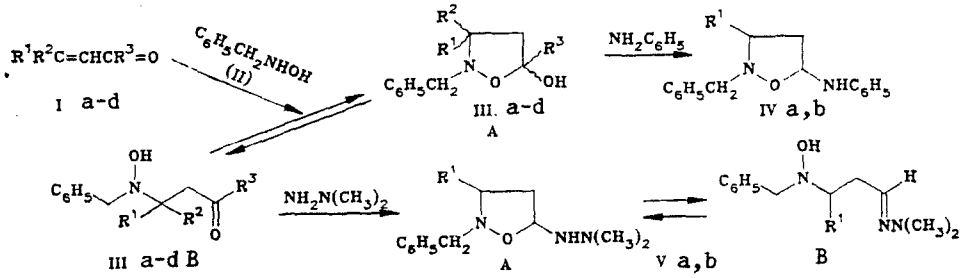
TABLE 2. ^{13}C NMR Spectra of (III-V)

Compound	Stereoisomer		Chemical shifts (in $CDCl_3$), δ, ppm (J, Hz)						yield, %
	form	amount, %	$C_{(3)}$	$C_{(4)}$, t	$C_{(5)}$	CH_2, t	C arom	other,	
IIIa	A	100	52,8 t	36,7	96,5 d	64,9	127,2 ... 136,5 (4 signals)	—	65
IIIb	A	100*1	59,0 d and 61.0 d	44,3 and 45.7	94,9 d and 96.8 d	59,7 and 63.2	127,0 ... 137,4 (8 signals)	16,5 q and 18,1 q ($2CH_3$)	70
IIIc	A	15	54,0 t	41,7	103,3 s	63,2	115,9 ... 136,4 (8 signals)	25,7 q (CH_3)	65
	B	85	54,1 t (C_β)	40,9 (C_α)	207,8 s (C=O)	64,8		29,6 q (CH_3)	
IIId	A	100	63,3 s	53,3	101,0 s	57,3	126,6 ... 138,4 (4 signals)	20,6 q; 24,6 q; 25,5 q ($3CH_3$)	60
IVa	A	100	54,0 d	35,9	83,6 d	64,2	114,5 ... 129,0 (8 signals)	—	50
IVb	A	90	59,6 d	44,9	82,2 d	59,3	114,3 ... 145,5 (8 signals)	17,0 q (CH_3)	65
	A	10	61,0 d	43,4	83,4 d	60,8		17,8 q (CH_3)	
Va*2	B	95	57,2 (C_β)	30,5 (C_α)	137,2 (C=N)	64,6	127,1 ... 137,2 (4 signals)	43,0 q	80
Vb*3	A	55	60,5 d	36,5	89,0 d	59,6	126,7 ... 137,6 (8 signals)	13,9 q (CH_3); 43,1 q (CH_3N)	70
	A	45	61,1 d	40,6	89,7 d			16,9 q (CH_3); 42,2 q (CH_3N)	

*1 1:1 Mixture of stereoisomers (in $CDCl_3$ solution).

*2 Signals for form B only given.

*3 Signals given for the cyclic stereoisomers A. For form B, the reliable figure found was 138.8 ppm (C=N).



I, III—V a $R^1=R^2=R^3=H$; b $R^1=CH_3$, $R^2=R^3=H$; I, III c $R^1=R^2=H$, $R^3=CH_3$; d $R^1=R^2=R^3=CH_3$

The possibility of obtaining 5-amino- and 5-hydrazino-2-benzylisoxazolidines in this way has been demonstrated in the case of the 5-hydroxyisoxazolidines (IIIa) and (IIIb). Treatment of these with aniline and dimethylhydrazine gave (IVa, b) and (Va, b), respectively.

Compounds (III-V) could exhibit ring-chain tautomerism A ⇌ B. The features of this equilibrium are in agreement with those previously reported for the related 2-phenylisoxazolidines [3]. For example, (IVa, b) show no tendency to undergo ring opening, whereas the hydrazinoisoxazolidines (Va, b) tend to exist as the linear tautomer B, probably as a result of stabilization by p,π-conjugation.

When R^3 = H, 5-hydroxyisoxazolidines (IIIa, b) exist in all solvents in the ring form A. When the steric accessibility of the carbonyl group is reduced by changing from derivatives of alkenals to methyl vinyl ketone, compound (IIIc) exists in solution as a tautomeric mixture A ⇌ B, the proportion of the linear form increasing on changing from $CDCl_3$ to DMSO-D_6. The existence of an A ⇌ B tautomeric mixture is shown clearly by the doubling of all the signals in the PMR and ^{13}C NMR spectra, and the appearance in the latter of a singlet signal for the carbonyl carbon at 208 ppm (Table 2). Derivative (IIId), obtained from mesityl oxide, exists completely in the cyclic form A in consequence of the well-known gem-dimethyl effect [4].

Compounds (IIIb-Vb), obtained from crotonaldehyde, consist of comparable amounts of the diastereoisomers, although the amounts of one of them increase from 50% in (IIIb) and (Vb) to 85% in (IVb).

On the basis of these findings and those reported previously [1, 2], therefore, the Michael addition of N-substituted hydroxylamines to α,β-unsaturated carbonyl compounds may be regarded as a general method for the construction of the isoxazolidine ring. A determining factor in the regiospecificity of this reaction is the nature of the substituent at nitrogen in the hydroxylamine.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-497 (100 MHz) and ^{13}C NMR spectra on a Tesla BS-497 (20.41 MHz in pulse mode with Fourier transformation). The purity of the products was established by TLC on Silufol UV-254 plates, and quantitative separations were carried out on a column (2.5 × 30 cm) of silica gel (100/160) in the system ether–petroleum ether, 4:1. Satisfactory elemental analyses for C, H, and N were obtained for (IIIa-d), (IVa, b), and (Va, b).

2-Benzyl-5-hydroxyisoxazolidines (IIIa-d). A mixture of 2.2 g (18 mmoles) of benzylhydroxylamine and 18 mmoles of the carbonyl compound (Ia-d) in 50 ml of chloroform was kept for 1 day. The solvent was removed under reduced pressure, and the residue chromatographed.

2-Benzyl-5-phenylaminoisoxazolidines (IVa, b) and 2-Benzyl-5-dimethylhydrazinoisoxazolidines (Va, b). A mixture of 14 mmoles of 2-benzyl-5-hydroxyisoxazolidine (IIIa, b) and 14 mmoles of aniline or dimethylhydrazine in 50 ml of chloroform with the addition of two drops of CF_3COOH was kept for 1 day. The solvent was removed under reduced pressure, and the residue subjected to column chromatography.

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