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THE SIMPLEST PHENYLNITRONES AND THEIR CONVERSION INTO ISOXAZOLIDINE DERIVATIVES

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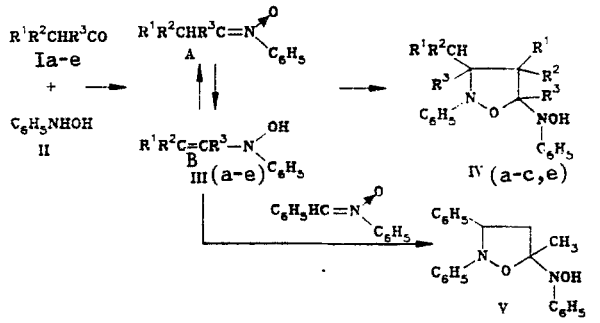
Reactions of N-phenylhydroxylamine with the simplest alkanals leads initially to the formation of N-phenylnitrones, dimerization of which gives 5-substituted isoxazolidine. Taking the reactions of N-phenylnitrones, benzaldehyde, and acetone as an example, the possibility of a crossover reaction has been established.

The possibility of using nitrones in 1,3-bipolar cycloaddition reactions has attracted some attention [1]. However, N-alkylnitrones of aliphatic enolizable aldehydes and ketones have only recently been characterized [2, 3] and reliable information on the corresponding N-phenyl nitrones is lacking. N-arylnitrones have been discovered only for carbonyl components with not more than one hydrogen atom at the α-position or with sterically displaced N-arylhydroxylamines [3].

The product of the reaction of acetone with N-phenylhydroxylamine was first isolated by Bamberger and Rudolf [4] but its dimer structure, 2-phenyl-3,3,5-trimethyl-5-(N-phenylhydroxylamino)isoxazolidine (IVe), was not established until sixty years later [5]. Recent work [2, 3] shows that the formation of similar dimers is a general feature of the reaction of the majority of N-arylhydroxylamines and their alkyl analogs with aldehydes and ketones.

Dimerization is regarded as the mechanism of the 1,3-bipolar cycloaddition of the corresponding nitrones IIIA to their enamine tautomers IIIB [6]. The applicability of this conversion to derivatives of N-phenylhydroxylamine leads one to expect the formation of the corresponding nitrones in this reaction also.



I, III, IV a $R^1=R^2=R^3=H$; b $R^1=CH_3$, $R^2=R^3=H$; c $R^1=C_2H_5$, $R^2=R^3=H$; d $R^1=R^2=CH_3$, $R^3=H$; e $R^1=R^2=H$, $R^3=CH_3$

It is found that the aldonitrones IIIAa-d are obtained practically instantaneously and quantitatively on mixing the reagents with $CDCl_3$, although the reaction with acetone is reversible in the presence of water-abstracting media or acidic catalysts.

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TABLE 1. Spectroscopic Data for Compounds IIIAa-e

Compound	Proton NMR spectra ($CDCl_3$), δ, ppm			Carbon-13 NMR spectra ($CDCl_3$), δ, ppm			
	HC=N	Ar	others	C=N	$C_{arom}N$	C_{arom}	Others
III a	7,28	7,33—7,43 (3H, m, $2H_m+1H_p$); 7,54—7,64 (2H, m, $2H_o$)	2,15 (3H, d, J=6 Hz, CH_3)	146,6	136,9	121,0; 128,4; 129,3	12,9 (CH_3)
III b	7,17	6,83—7,35 (3H, m, $2H_m+1H_p$); 7,54—7,64 (2H, m, $2H_o$)	1,14 (3H, t, J=7 Hz, CH_3); 2,65 (2H, d.q, CH_2)	151,5	149,3	116,3; 121,1; 128,9	26,5 (CH_3); 43,2 (CH_2)
III c	7,17	6,87—7,35 (3H, m, $2H_m+1H_p$); 7,54—7,64 (2H, m, $2H_o$)	1,01 (3H, t, J=7 Hz, CH_3); 1,59 (2H, d.q, CH_2)	—			
III d	—*	6,95—7,53 (3H, m, $2H_m+1H_p$); 7,55—7,68 (2H, m, $2H_o$)	1,05 (6H, d J=7 Hz, $2CH_3$); 2,28 (1H, m CH)	146,9	145,0	121,0; 123,0; 129,2	18,2 (CH_3); 26,1 (CH)
III e	—	6,76—7,24 (5H, m)	1,93 (3H, s CH_3); 2,12 (3H, s CH_3)	149,9	144,0	113,8; 128,0	18,9 (CH_3); 21,4 (CH_3)

*Obscured by H_{Ar} signals.

TABLE 2. Characteristics of Compounds IVa-c, e, and V

Compound	R_f (system)	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IV a	0,58 (1)	Oil	71,3	6,6	10,1	$C_{16}H_{18}N_2O_2$	71,1	6,7	10,4	70
IV b	0,62 (1)	Oil	72,7	7,3	9,6	$C_{18}H_{22}N_2O_2$	72,5	7,4	9,4	75
IV c	0,76 (1)	Oil	73,5	7,9	8,4	$C_{20}H_{26}N_2O_2$	73,6	8,0	8,6	83
IV e		130—131 (136 [5])	72,7	7,3	9,2	$C_{18}H_{22}N_2O_2$	72,5	7,4	9,4	85
V		97—99	76,5	6,5	8,0	$C_{22}H_{22}N_2O_2$	76,3	6,4	8,1	65

The aldonitrones IIIAa-d are characterized by the signal of the azomethine proton of the appropriate multiplet in the range 7.1-7.3 ppm in the proton NMR spectrum (Table 1) and in the carbon-13 NMR spectrum the carbon of the C=N bond gives a signal in the 146-152 ppm region. In comparison with the initial phenylhydroxylamine, the signals of the orthoprotons of the aromatic ring in the proton NMR spectrum undergo a marked downfield shift.

The conversion of the nitrones into their dimers begins almost immediately and in the case of compounds IIIa, b is complete within an hour. For the less active nitrones IIIc,e quantitative dimerization requires several days.

The individual 2-phenyl-5-(N-phenylhydroxylamino)isoxazolidines IVa-c, e were characterized by their proton and carbon-13 NMR spectra (Table 3) which were in general agreement with the data of [3, 5, 6, 8]. The structure of these compounds was also confirmed, for the example of IVa, by a synthesis from a different direction — the reaction of crotonaldehyde with a double quantity of phenylhydroxylamine [7]. According to [3] dimerization of the nitrones of propanal and butanal proceeds stereospecifically; however, we observed here the formation of two stereoisomers, but the existence of three chiral centers made it impossible to establish the structure of these.

The formation of the intermediate hydroxyenamines IIIB assumes that in principle the crossover dimerization of two nitrones of their participation in some other such transformations is possible; we have already demonstrated this in particular for the reaction of the N-phenylnitrone of acetaldehyde with an excess of carbonyl component [7]. Attempts to use other aldehydes in this type of reaction were unsuccessful because only dimerization of the nitrone IIIa was observed. Neither did the expected reaction of the nitrones IIIb-d, which are less prone to dimerization, take place since here practically instantaneous exchange of the carbonyl component of the nitrone occurred with the formation of the nitrone IIIa, followed by its dimerization to compound IVa. We did not succeed in carrying out a crossover condensation of nitrones IIIb and IIIc between themselves because of the preferential formation of dimers of symmetrical structure. However, it was established for the case of the reaction of benzaldehyde N-phenylnitrone with nitrone IIIe that a crossover reaction is possible. As a result we were able to separate by chromatography the isoxazolidine V in yield of 65% (Table 2).

TABLE 3. Spectroscopic Data for Compounds IVa-c, e, and V

Compound	Ratio of diastereomers, %	Proton NMR spectra ($COCl_3$), δ, ppm						Carbon-13 NMR spectra ($CDCl_3$) δ, ppm				
		3-H (3-CH_3)	4-H	5-H (5-CH_3)	H_{Ar}, m	others	OH	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	C_{Ar}	others
IVa	50	3,85 m	2,73 m	5,76 t, J=7,5 Hz	6,74—7,27	1,10 d, J=6Hz;	6,71 s;	60,7 d;	37,0 t;	92,4 d;	117,2—149,7	17,9 q (CH_3); 19,2 q (CH_3)
	50			5,72 d.d J_1=7,5, J_2=2,5 Hz		1,30 d, J=6Hz ($2CH_3$)	7,94 s	59,2 d	38,7 t	93,3 d		
IVb	80*	3,33 d.t J_1=6,5 Hz, J_2=4,5 Hz	2,85 m	5,29 d, J=7 Hz	6,70—7,17	0,93 t (CH_3);	8,00 s	76,2 d	43,1 d	99,2 d	116,0—152,0	10,3 q; 17,2 q ($2CH_3$); 26,1 t (CH_2)
	20	3,63 m		5,35 d, J=8 Hz		1,67 m (CH_2)	7,8 s	70,3 d	38,4 d	100,1 d		11,0 q; 14,8 q ($2CH_3$); 20,7 t (CH_2)
IVc	85	3,30 d.t	2,67 m	5,27 d, J=5 Hz	6,71—7,31	0,74 t, 0,80t ($2CH_3$);	—			—		
	15	3,88 d.t		5,37 d, J=7 Hz		1,37 m ($3CH_2$)						
IVe	100	(1,24 s, 6H, $2CH_3$)	2,04and2,98; 2H, AB- system J_{AB}=13 Hz	(0,81 s, 3H, CH_3)	6,98—7,30, 10H	—	8,16 s, 1H	66,4 s	54,0 t	95,2 s	119,8—148,0	21,6 q, 22,1 q, 25,8 q ($3CH_3$)
V	75	4,80 q; J_{AX}=10; J_{BX}=7 Hz	2,06 and 2,61; ABX system J_{AB}=12 Hz	(1,45 s, CH_3)	6,65—7,27	—	3,55 br.	69,1 d	51,6 t	104,0 s	113,8—153,2	23,9 q (CH_3)
	25	4,32 q; J_{AX}=9; J_{BX}=7 Hz	2,45 m	(1,87 s CH_3)				70,2 d	51,9 t	102,3 s		25,0 q (CH_3)

*Solution in $(CD_3)_2CO$.

Thus, the reaction of N-phenylhydroxylamine with simple aldehydes and with acetone is a convenient method for the synthesis of 5-substituted isoxazolidine derivatives and can be further considered as a route to other derivatives of this heterocycle, in particular to Δ^4-isoxazolines [9].

EXPERIMENTAL

Proton NMR spectra were run on a Tesla BS-497 (100 MHz) instrument and carbon-13 spectra on the same using pulsed Fourier transforms at 20.41 MHz. The progress of the reactions and the purity of the products were monitored by TLC using Silufol UV-254 plates or 40/100 silica gel in 1:1 benzene-acetone (system 1) or 5:1 benzene-acetone (system 2). Column chromatography was carried out on a column (2.5 × 30 cm) packed with 40/100 silica gel using system 2.

Phenylnitrones (IIIa-e). The aldehydes Ia-d (5 mmole) were mixed with 0.55 g (5 mmole) phenylhydroxylamine in 5 ml $CDCl_3$ (for Ie, with the addition of 1 drop of CF_3COOH) in the presence of 0.1 g $CaCl_2$. After 1 min the solution was filtered and the proton and carbon-13 spectra obtained.

2-Phenyl-5-(N-phenylhydroxylamino)isoxazolidines (IVa-c, e). A mixture of 50 mmole aldehyde Ia-c in 50 ml $CHCl_3$ and 5.45 g (50 mmole) phenylhydroxylamine (for Ie, with the addition of 1 drop CF_3COOH) was kept for 1 day over 1 g $CaCl_2$. The solution was filtered, the solvent evaporated in vacuum, and the residue chromatographed on a column.

2,3-Diphenyl-5-methyl-5-(N-phenylhydroxylamino)isoxazolidine (V). A mixture of 9.85 g (50 mmole) benzaldehyde nitrone, 2.9 g (50 mmole) acetone, and 5.45 g (50 mmole) phenylhydroxylamine in 200 ml benzene was heated at bp for 10 h. The solvent was removed in vacuum and the residue chromatographed on a column.

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