OXAZOLIDINES.

2.* SYNTHESIS OF 2-METHYLOXAZOLIDINES BY CYCLIZATION OF VINYL ETHERS OF 1,2-AMINO ALCOHOLS

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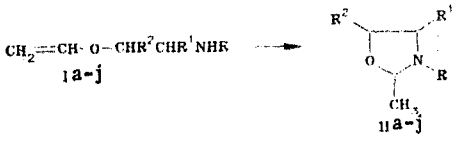
A study has been made of the catalytic activity of a number of proton acids and Lewis acids, amongst which mercury salts were particularly active, in the cyclization of N-phenylethanolamine vinyl ether to 2-methyl-3-phenyloxazolidine. A method for the preparative synthesis of 2-methyloxazolidines has been developed.

Condensation of amino alcohols with carbonyl compounds is not very suitable for the synthesis of 2-methyloxazolidines [2] since the aldehyde used readily undergoes self-condensation. Taking into account the future prospects for using oxazolidines [3], it is of interest to search for new ways of synthesizing them.

It is known that by the action of proton acids N-acetylethanolamine vinyl ether is converted quantitatively to 3-acetyl-2-methyloxazolidine [4], N-phenylethanolamine vinyl ether forms 2-methyl-3-phenyloxazolidine with 13% yield [5], while the vinyl ethers of mono- and diethanolamine are not cyclized at all [5, 6]. According to our data [7], they are all converted to 2-methyloxazolidines by the action of palladium chloride.

With the aim of elucidating the possibilities of preparative synthesis, in the present work the isomerization of N-phenylethanolamine vinyl ether (Ia) on treatment with proton acids and Lewis acids at concentrations up to 0.05 moles/liter in a solution of 1-methyl-2-pyrrolidone at 40°C was studied with the help of GLC. Under these conditions acetic acid, $SnCl_4$, salts of copper, zinc, cadmium, lead, and thallium did not bring about the cyclization of ether Ia. In the presence of perfluoroacetic and p-toluenesulfonic acids and also $SnCl_2$, together with the formation of 2-methyl-3-phenyloxazolidine (IIa) the reaction mixture becomes tarry and the yield of oxazolidine IIa does not exceed 65% for a 20-25% degree of conversion of ether Ia. With an increase in conversion of ether Ia the yield of oxazolidine IIa falls to 10-15%. Silver nitrate, although causing ether Ia to cyclize, is rapidly deactivated, being reduced to metallic silver. Only salts of mercury and palladium bring about a quantitative conversion of Ia → IIa.

The catalytic rate constants of the first-order reaction were $1.24 \cdot 10^{-4}$, $7.5 \cdot 10^{-5}$, and $2.81 \cdot 10^{-4}$ sec^{-1} for mercuric acetate, mercuric chloride, and palladium chloride, respectively.



I, II a R=C_6H_5, b R=H, c R=CH_2CH_2OH, d R=$CH_2CH_2OCH{=}CH_2$, e, i, j R=CH_3, f R=CH_2CH_2CN, g R=$CH_2C_6H_5$, h R=CH_3CO; a–i R^1=H, j R^1=CH_3; a–d, f, i R^2=H, e R^2=CH_2OCH_3, j R^2=CH_3

For the preparative synthesis of 2-methyloxazolidines we proposed carrying out the cyclization of vinyl ethers of 1,2-amino alcohols in inert solvent media (diethyl ether, hexane,

*For Communication 1, see [1].

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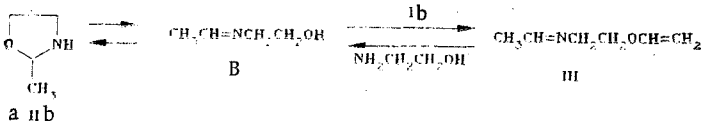
TABLE 1. Oxazolidines IIa-j

Compound	Data	bp, °C (mm)	n_D^{20} (n_D^{25})	d_4^{20} (d_4^{25})	Yield, %
IIa		—	—	—	
IIb	Ours	53—56 (60)	1,4345	0,9668	48
	[9]	50—60 (60)	(1,4336)	(0,9651)	
IIc	Ours	55—58 (2)	1,4680	1,0543	76
	[9]	69 (4,5)	(1,4663)		
IId	Ours	78—80 (11)	1,4590	0,9855	98
	[9]	76—78 (9)	(1,4552)	(0,977)	
IIe		60—63 (15)	1,4332	0,9609	81
IIf		91—93 (2,5)	1,4620	1,0215	90
IIg	Ours	106—108 (4)	1,5203	1,0217	98
	[10]	190—195 (25)			
IIh	Ours	105—108 (10)	1,4660	1,0810	99
	[4]	92 (4)	1,4670	1,087	
IIi	Ours	106—108 (720)	1,4235	0,9046	86
	[2]	109 (758)			
IIj		50—52 (60)	1,4247	0,8864	76

benzene, etc.) in the presence of 0.2-0.5% mercuric acetate. Oxazolidines IIa, IIc-j were obtained with yields from 76% to quantitative (Table 1). Oxazolidines IIe and IIj were equimolecular mixtures of two and four stereoisomers, respectively.

On cyclization of monoethanolamine vinyl ether (Ib), 2-methyloxazolidine (yield 20%), monoethanolamine, and N-ethylideneethanolamine vinyl ether (III) are formed. Such an outcome can evidently be explained by the ability of oxazolidine IIb to tautomerize to azomethine B [8]. Even by simply mixing ether Ib and oxazolidine IIb the following reaction occurs:



a IIb

Taking into account the reversibility of the reaction it is possible to increase the yield of oxazolidine IIb to 48%, on conducting the cyclization of vinyl ether Ib in a monoethanolamine medium.

EXPERIMENTAL

Chromatographic analysis was carried out on a LKhM-8MD instrument, with catharometer detector, column 2 m × 3 mm, Chromatone N-AW-HMDS as solid phase, 15% polyethylene glycol 20,000 as liquid phase, thermostat temperature programmed from 50 to 170°C with a rate 4°/min, and helium carrier gas. The initial ethers I were obtained according to methods [5, 6].

2-Methyl-3-phenyloxazolidine (IIa). We boiled 16.32 g (0.1 mole) N-phenylethanolamine vinyl ether (ia), 0.08 g (0.28 mmole) mercuric acetate, and 20 ml diethyl ether under reflux for 3 h with stirring. After removal of solvent by distillation at atmospheric pressure the reaction mass crystallized out. 16.4 g (100%) oxazolidine IIa was obtained, with mp 55-60°C, 59.5-60°C (from diethyl ether); according to the data of [5], mp 58.5-59°C.

2-Methyl-3-cyanoethyloxazolidine (IIf). We heated 14.02 g N-cyanoethylethanolamine vinyl ether (If), 0.07 g (0.24 mmole) mercuric acetate, and 35 ml benzene for 3 h at 70°C with stirring. 12.67 g (90%) oxazolidine IIf was separated by vacuum distillation. Found: C 60.1; H 8.9; N 19.9%. Mr_D 37.03. $C_7H_{12}N_2O$. Calculated: C 60.0; H 8.9; N 20.0%. Mr_D 37.48.

Oxazolidines IIc-e, g-j. These were obtained in a similar manner. IIe. Found: C 57.6; H 10.4; N 9.8%. Mr_D 39.29. $C_7H_{15}NO_2$. Calculated: C 57.9; H 10.4; N 9.6%. Mr_D 39.42. IIj, found: C 64.9; H 11.7; N 11.0%. Mr_D 37.25. $C_7H_{15}NO$. Calculated: C 65.1; H 11.7; N 10.8%. Mr_D 37.63.

2-Methyloxazolidine (IIb) and N-Ethylideneethanolamine Vinyl Ether (III). 87 g (1000 mmoles) monoethanolamine vinyl ether (Ib), 0.43 g (1.5 mmoles) mercuric acetate, and 100 ml hexane were heated for 4 h at 60°C with stirring. On distillation under vacuum on a rectification column (20 theoretical plates), 17.4 g (20%) oxazolidine IIb [53-56°C (60 mm)], 26.1 g monoethanolamine, and 28.3 g vinyl ether III were separated. III: bp 74-75°C (100 mm); n_D^{20}

1.4405; d_4^{20} 0.8784. IR spectrum (thin layer): 1620 (C=C), 1660 (C=N), 3100 cm^{-1} (=C-H). PMR spectrum (in CCl_4): 7.53 (1H, q, N=CH), 6.32 (1H, q, OCH=C), 4.08 (1H, q, trans-C=CH), 3.87 (1H, q, cis-C=CH), 3.75 (2H, m, OCH_2), 3.54 (2H, m, NCH_2), 1.87 ppm (3H, d, CH_3). Found: C 63.3; H 9.6; N 12.2%. Mr_D 34.02. $C_6H_{11}NO$. Calculated: C 63.7; H 9.8; N 12.4%. Mr_D 34.37.

On conducting the reaction in a similar manner in 200 ml monoethanolamine, 41.6 g (48%) oxazolidine IIb was obtained.

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MASS SPECTROMETRIC STUDY OF 1,2,4- AND 1,3,4-OXADIAZOLES CONTAINING INDOLE SUBSTITUENTS

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1,2,4- and 1,3,4-Oxadiazoles containing indole substituents decompose upon electron impact due to breakage of bonds in the oxadiazole ring. Skeletal rearrangements may occur in the molecular ions of 2,5-diaryl-1,3,4-oxadiazoles due to migration of the aryl groups.

There has recently been increasing interest in indole derivatives containing 1,2,4- and 1,3,4-oxadiazole fragments since compounds have been found among these bisheterocyclic systems possessing a broad range of biological activity.

Extensive information is not available on the dissociative ionization of aryloxadiazoles [1-6] upon electron impact and the possibility of the mass spectrometric differentiation of substituted 1,2,4- and 1,3,4-oxadiazoles and of positional isomers has not been adequately evaluated. In this regard, we studied the electron impact mass spectra of 1,2,4- (I-IV) and 1,3,4-oxadiazoles (V-X) containing a 3-indolyl or (3'-indolyl)methyl group as one of the substituents. We studied both common and specific pathways for the decomposition of these compounds and elucidated diagnostic fragmentation patterns suitable for the differentiation of isomers. The mass spectral data for 1,2,4-oxadiazoles I-IV at 70 eV ionizing electron energy are given in Table 1, while the corresponding data for V-X are given in Table 2.

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