SYNTHESIS OF TETRAHYDROOXAZOLE DERIVATIVES BY REACTION OF 2-HYDROXYETHYLHYDRAZONES WITH PARAFORMALDEHYDE

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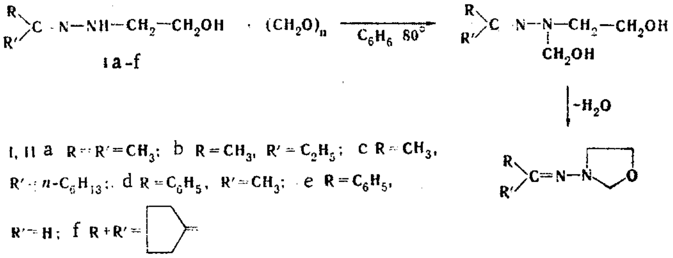
The condensation of 2-hydroxyethylhydrazones with paraformaldehyde gives N-substituted tetrahydrooxazoles.

It is well known that condensation of alkyl(aryl)hydrazines with formaldehyde gives N-alkyl(N-aryl)-hydroxymethylhydrazines [2, 3].

In an attempt to extend this reaction to aldehyde and ketone 2-hydroxyethylhydrazones we observed that the reaction does not stop at the hydroxymethylation stage but is accompanied by cyclization to give N-alkylidene(arylidene) aminotetrahydrooxazoles.



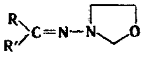
I, II a $R = R' = CH_3$; b $R = CH_3$, $R' = C_2H_5$; c $R = CH_3$, $R' = n\text{-}C_6H_{13}$; d $R = C_6H_5$, $R' = CH_3$; e $R = C_6H_5$, $R' = H$; f $R + R' =$

An analogous synthesis of N-methyloxazolidines is known in the case of the condensation of N-methylethanolamine with aldehydes [4].

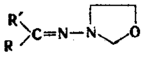
The yields of tetrahydrooxazoles IId,e are higher than in the case of derivatives of aliphatic series (IIa-c) and in the case of a saturated ring (IIf), the preparation of which is accompanied by appreciable polymerization. The purity of the synthesized IIa, b, c was proved by means of gas–liquid chromatography (GLC) (derivatives IId, e, f are not sufficiently volatile). The properties of the compounds obtained in this research are presented in Table 2.

Absorption bands at 3100-3400 cm^{-1}, which correspond to the stretching vibrations of OH or NH bonds, are absent in the IR spectra of II. The signals of the $-NCH_2CH_2O$ grouping in the PMR spectra form an A_2B_2 system with a spin–spin coupling constant (SSCC) (J_{AB}) on the order of 6-7 Hz. The spectra of IIb and IIc, which contain nonequivalent R and R' substituents, attest to the presence of syn-anti isomerism.

This is expressed in the appearance of signals of lower intensity with the same multiplicity next to the signals of the principal groups (Table 3).



syn form



anti form

However, on the basis of these data it does not seem possible to draw a conclusion as to which of the two isomers predominates in each mixture.

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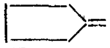
TABLE 1. 2-Hydroxyethylhydrazones

Compound	R	R′	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %
						found	calc.		C	H	N	C	H	N	
Ia*	CH_3	CH_3	104—105 (5)	1,0004	1,4800	32,94	32,93	$C_5H_{12}N_2O$	51,7	10,3	24,2	51,7	10,3	24,1	88
Ib	CH_3	C_2H_5	110 (5)	0,9835	1,4820	37,73	37,58	$C_6H_{14}N_2O$	55,2	10,7	21,4	55,4	10,8	21,5	86
Ic	CH_3	C_6H_{13}	140—141 (5)	0,9334	1,4750	56,27	56,17	$C_{10}H_{22}N_2O$	64,3	11,8	15,2	64,5	11.8	15,0	79
Id	C_6H_5	CH_3	163—164 (4)	1,1061	1,5790	53,47	54,34	$C_{10}H_{14}N_2O$	67,3	7,9	15,7	67,4	7,9	15,7	72
Ie	C_6H_5	H	164—165 (5)	1,1282	1,6080	50,12	49,72	$C_9H_{12}N_2O$	65,8	7,2	16,7	65,8	7,3	17,1	44
If			122—123 (5)	1,0516	1,5115	40,39	39,95	$C_7H_{14}N_2O$	58,9	9,7	19,8	59,2	9,8	19,7	84

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*The physical constants of acetone 2-hydroxyethylhydrazone are in agreement with the values described in [5].

TABLE 2. Alkylidene(arylidene)aminotetrahydrooxazoles

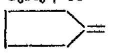
Compound	R	R′	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %
						found	calc.		C	H	N	C	H	N	
IIa	CH_3	CH_3	74—75 (10)	1,0106	1,4720	35,35	35,97	$C_6H_{12}N_2O$	56,3	9,4	21,6	56,2	9,2	21,9	45
IIb	CH_3	C_2H_5	84—85 (10)	0,9861	1,4700	40,17	40,61	$C_7H_{14}N_2O$	58,8	9,6	19,7	59,2	9,8	19,7	52
IIc	CH_3	C_6H_{13}	102—103 (3)	0,9301	1,4630	58,62	59,21	$C_{11}H_{22}N_2O$	66,4	11,2	14,0	66,7	11,1	14,1	85
IId	C_6H_5	CH_3	122—123 (2)	1,0974	1,5670	56,45	56,30	$C_{11}H_{14}N_2O$	69,4	7,3	14,7	69,5	7,4	14,7	81
IIe	C_6H_5	H	119—120 (3)	1,1182	1,6050	54,31	55,24	$C_{10}H_{12}N_2O$	68,2	6,8	15,9	68,2	6,8	15,2	41
IIf			83—84 (5)	1,0656	1,5020	42,44	42,99	$C_8H_{14}N_2O$	62,8	8,8	18,0	63,0	9,7	18,2	35

TABLE 3. PMR Spectra of Tetrahydrooxazoles (IIa-f)

Compound	δ_R	$\delta_{R'}$ (J, Hz)	δ (J, Hz)	δ
IIa	1,87 s*	1,96s	3,06 (6,4)	3,68; 4,36s
IIb	1,73s 1,67 s†	0,87t, CH_3 1,04t†, (7,5), 2,00q; CH_2, 2,13 q†	2,87 (6,5)	3,52; 4,15s
IIc	7,27m	7,61	3,15 (7,0)	3,75; 4,71s
IId	7,10m—7,85m 7,23m†—7,98m†	2,21s 2,43†	3,08 (6,6)	3,60; 4,43s
IIe	1,39 (broad multiplet)	1,00m	3,14 (6,3)	3,77; 4,47s
IIf	1, 4-CH_2 group 1,66 m	2, 3-CH_2 group 2,22 m	3,05 (6,5)	3,65; 3,35s

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*The chemical shifts are presented on the δ scale, s is singlet, t is triplet, q is quartet, and m is multiplet.

†These are the signals of the isomer present in lesser amounts in the mixture.

EXPERIMENTAL METHOD

The PMR spectra of 25% solutions of the compounds in CCl_4 were recorded with an RYa-2305 spectrometer (60 MHz). The IR spectra of 2-5-nm-thick layers of the compounds were obtained with UR-20 and IKS-29 spectrometers.

Analysis by GLC was carried out with a Khrom-3 chromatograph with a flame-ionization detector and a 1.2-m-long column filled with 5% lucoprene G 1000 impregnated with porovina (Czechoslovakian SSR) at 190°. The molecular weights were determined cryoscopically in benzene.

2-Hydroxyethylhydrazones (Ia-f). 2-Hydroxyethylhydrazine (1 mole) was added dropwise in the course of 1.5 h at 15° with stirring to 1 mole of the ketone or aldehyde, after which the mixture was stirred for another h. It was than allowed to stand over potassium carbonate for 12 h, after which it was vacuum distilled in a stream of nitrogen.

Alkylidene(arylidene)aminooxazoles (IIa-f). The 2-hydroxyethylhydrazone (1 mole) was added dropwise in the course of 20 min to a stirred mixture of 30 g (1 mole) of paraformaldehyde and 50 ml of benzene, after which the mixture was stirred at 80° for 1.5 h. It was then cooled and allowed to stand over potassium carbonate for 12 h, after which it was vacuum fractionated in a stream of nitrogen with a rectification column with a glass packing and an efficiency of 25 theoretical plates.

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PECULIARITIES OF THE REACTIVITIES OF 3-CARBOXYALKYLSYDNONES

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In contrast to the 3-alkyl analogs, the heteroring in 3-carboxyalkylsydnones is cleaved by the action of hydrogen chloride in alcohols. The kinetics of the previously known alkaline cleavage of the ring in 3-carboxyalkylsydnones and sydnoneimines were studied by a spectrophotometric method.

We have previously shown [1] that the carboxyl group and the heteroring in 3-carboxyalkylsydnones (I) have a mutual effect on one another. The peculiarities of the reactivities of these groups in the indicated compounds are set forth in the present paper.

In contrast to sydnone-4-carboxylic acids [2], which are smoothly converted successively to acid chlorides and ester, 3-carboxymethylsydnone (Ia) does not react with thionyl chloride. Under the combined action of thionyl chloride and methanol (the Brenner method) this sydnone undergoes cleavage to give methyl hydrazinoacetate hydrochloride (IIa).

It was shown in [2] that cleavage of 3-alkylsydnones by the action of hydrogen chloride does not take place in anhydrous media. Ring opening also was not observed when hydrogen chloride was bubbled briefly through

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