B. A mixture of IIc (4.44 g, 200 mmoles) in aqueous sodium hydroxide (40%, 10 ml) was triturated to formation of a homogeneous mass, stirred for 1 h, neutralized with acetic acid (3%, 80 ml), and the precipitate filtered. The product (4.44 g) was identical in all characteristics to compound IIIc obtained by method A.

Pyrido[2,3-d]pyrimidines (IIIa, b, d-h, k, *l*) (Table 1) were obtained by one of the above-mentioned methods.

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SYNTHESIS OF HYDROXYISOXAZOLIDINES ON THE SURFACE OF ADSORBENTS

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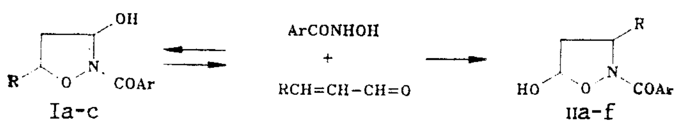
The reaction of arylhydroxamic acids with α, β-unsaturated carbonyl compounds on the surface of adsorbents without a solvent leads, depending on the properties of the adsorbent, to the formation of 2-aroyl-3-hydroxyisoxazolidines and/or 2-aroyl-5-hydroxyisoxazolidines. Reactions on the surface of silica gel and di- and triethylaminoethylcellulose proceed regioselectively.

It has been previously shown [1-4] that the reaction of hydroxamic acids with α, β-unsaturated carbonyl compounds in solution proceeds with the formation of 3- and/or 5-hydroxyisoxazolidines, depending on the character of the substituent in the hydroxamic acid. The aim of our research was to search for methods for the regioselective synthesis of hydroxyisoxazolidines that are independent of the structure of the hydroxamic acid. A new method, viz., reaction on the surface of adsorbents without a solvent [5-8], which makes it possible to increase the selectivity of the process and the yield of the product vis-à-vis shortening of the reaction time, has recently been used successfully for synthetic purposes.

We investigated the reaction of arylhydroxamic acids with α,β-unsaturated carbonyl compounds on the surface of various adsorbents.



It has been previously shown [8] that a ratio of the masses of the reagents and the adsorbent (SiO_2) from 1:10 to 1:20 is the optimum ratio for intermolecular condensation reactions, and we therefore selected a charge of 10% for all of the adsor-

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TABLE 1. Dependence of the Composition of the Products of the Reaction of Crotonaldehyde with Benzohydroxamic Acid on the Type of Adsorbent*

Adsorbent	Yield, %		
	overall	Ib**	IIb
Neutral Al_2O_3, pH 9-10	70...75	80...85	20...15
Neutral Al_2O_3/KF, 5%	70	75...80	25...20
Acidic Al_2O_3, pH 5-6	60...70	80...85	15...20
Florisil	50...70	85...90	15...10
Inerton AW	73	68	32
Silica gel	80...90	100	0
Carboxymethylcellulose	41	70	30
Diethylaminoethyl	95...98	0	100
Triethylaminoethy.	98	0	100

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*The reaction time in all cases was 15-16 h.

**The isomer ratio was determined from the PMR data.

TABLE 2. Melting Points and Yields of 2-Aroyl-3-isoxazolidines and 2-Aroyl-5-hydroxyisoxazolidines

Compound	Ar	R	Empirical formula	mp, °C	Yield, %
Ia	C_6H_5	H	$C_{10}H_{11}NO_3$	53	75
Ib	C_6H_5	CH_3	$C_{11}H_{13}NO_3$	51	65
Ic	p-BrC_6H_4	H	$C_{10}H_{10}BrNO_3$	91	81
IIa	C_6H_5	H	$C_{10}H_{11}NO_3$	73	92
IIb	C_6H_5	CH_3	$C_{11}H_{13}NO_3$	52	98
IIc	p-BrC_6H_4	H	$C_{10}H_{10}BrNO_3$	83	78
IId	p-BrC_6H_4	CH_3	$C_{11}H_{12}BrNO_3$	127	85
IIe	2,4,5-$(CH_3)_3C_6H_2$	H	$C_{13}H_{17}NO_3$	Oil	54
IIf	$PhCON(OH)CH_2CH_2COCH_3$		$C_{11}H_{13}NO_3$	97	85

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*The synthesis of I was carried out on silica gel, while the synthesis of II was carried out on diethylaminoethylcellulose.

TABLE 3. Kinetics of the Accumulation of Reaction Products Ib and IIb* on Diethylaminoethylcellulose

t, min	c_t(Ib)	c_t(IIb)	$\ln\left(1-\frac{c_t(\mathrm{IIb})}{c_\infty(\mathrm{IIb})}\right)$	t, min	c_t (Ib)	c_t (IIb)	$\ln\left(1=\frac{c_t(\mathrm{IIb})}{c_\infty(\mathrm{IIb})}\right)$
4	132,7	7,8	−0,05	94	89,0	97,8	−1,06
11	152,6	31,2	−0,23	104	70,8	96,2	−1,03
19	196,4	45,1	−0,36	116	70,0	90,4	−0,93
28	152,9	64,6	−0,56	131	68,9	98,0	−1,06
41	104,4	46,1	−0,37	151	55,6	120,0	−1,61
54	97,6	71,4	−0,65	183	35,1	116,1	−1,49
65	119,2	81,2	−0,78	233	30,1	126,7	−1,86
74	118,8	92,4	−0,96	291	20,0	148,5	−4,48
84	80,1	87,1	−0,87	361	10,0	133,7	−3,17

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*The concentrations were measured in arbitrary units corresponding to the areas of the peaks on the chromatogram: S = A(%)·v (ml).

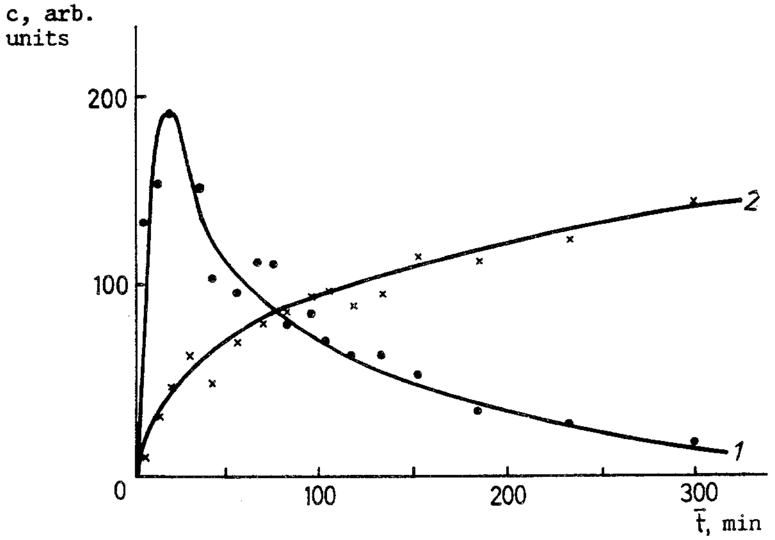

Fig. 1. Kinetics of the accumulation of isomers Ib (1) and IIb (2) during the reaction on diethylaminoethylcellulose. The concentrations were measured in arbitrary units (see the footnote to Table 3).

bents. Various adsorbents – from the widely known silica gel and aluminum oxide to cellulose derivatives that have not been previously used for these purposes – were used (Table 1).

The direction of addition and the ratio of the reaction products, as well as the overall yields, depend on the type of adsorbent. Equilibrium mixtures of 3- and 5-hydroxyisoxazolidines in various ratios are formed on most of the adsorbents. The most interesting results were obtained when the condensation was carried out on silica gel and di(tri)ethylaminoethylcellulose [subsequently abbreviated as DEAE(TEAE)-cellulose]. In both cases the reaction proceeds regioselectively; only isomer I (Ia-c) is formed on silica gel, while only isomer II (IIa-f) is formed on DEAE(TEAE)-cellulose (Tables 1 and 2).

Reversal of the direction of addition on DEAE-cellulose as compared with reactions in solution was observed for all of the investigated hydroxamic acids and α,β-unsaturated carbonyl compounds after equilibrium was reached (15-16 h).

The diastereomeric compositions of the products differ on different adsorbents. Thus, 2-benzoyl-3-hydroxy-5-methylisoxazolidine (Ib) is produced on silica gel in the form of a mixture of equal amounts of diastereomeric racemates, as in the case of synthesis in solution, while 2-benzoyl-3-methyl-5-hydroxyisoxazolidine (IIb) is obtained on DEAE-cellulose in the form of only one pair of enantiomers (according to the PMR spectral data).

Adsorption gives rise to an appreciable increase in the rate of the reaction of hydroxamic acids with alkenals as compared with the reactions in solution. For example, the reaction of benzohydroxamic acid with crotonaldehyde in methanol in the case of catalysis by TEAE- or DEAE-cellulose takes place in 5-7 h with a product yield of 57-65%; the reaction of the same compounds on the surface of silica gel leads to the formation of hydroxyisoxazolidine Ib in 80-90% yield in 30-40 min. On DEAE-cellulose the time of the addition reaction is shortened to 10 min; both the 3- and 5-hydroxyisoxazolidine are initially present in the reaction mixture.

Our kinetic investigations (see Experimental) of the reaction of benzohydroxamic acid with crotonaldehyde on DEAE-cellulose showed that significant amounts of 3-hydroxyisoxazolidine Ib are present in the reaction mixture shortly after the reagents are mixed. An increase in the time of contact with the adsorbent leads to a decrease in the amount of the 3-hydroxy derivative and to accumulation of isomer II (Fig. 1, Table 3). An inflection point that coincides in time with the maximum of the concentration curve of isomer Ib is absent on the curve of the accumulation of 5-hydroxyisoxazolidine IIb. This means that the formation of the 3- and 5-hydroxyisoxazolidines proceeds simultaneously* and that the reactions in the adsorbed state, just as in solutions, are subject to kinetic and thermodynamic control.

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*We arrive at the same conclusion when we examine the kinetic data in coordinates of t and $\ln[1 - (c_t(\mathrm{IIb})/c_\infty(\mathrm{IIb}))]$ [9] $[v_0(\mathrm{Ib})/v_0(\mathrm{IIb}) \approx 5.4]$.

The covering of the surface of the adsorbent in all cases is probably of the multilayer type, which leads to concentration of the reagents. Nevertheless, the acceleration of reactions of this type on adsorbents evidently cannot be explained only through the effect of concentration, since the reaction of the same reagents without a solvent in the absence of a catalyst does not lead to the formation of measurable amounts of the hydroxyisoxazolidine. The difference in the compositions of the reaction products on different adsorbents can apparently be explained by the differences in the basicities of the catalytic centers of the adsorbents.

EXPERIMENTAL

General Method. A 5-mmole sample of the hydroxamic acid was dissolved by heating in the minimum amount of absolute methanol, the solution was added to a previously dried portion of the necessary adsorbent,* and the mixture was stirred thoroughly and dried. A 5-mmole sample of the α,β-unsaturated carbonyl compound was applied to another portion of the adsorbent, and the two portions of the adsorbent were mixed. The masses of the reagents should be smaller by a factor of 10-20 than the mass of the adsorbent (a charge of 5-10%). The mixture was shaken for 30 min or allowed to stand overnight at 0-20°C. Application of the reagents to the same portion of the adsorbent was permissible. The product was extracted with chloroform, the solvent was evaporated, and the residue was purified by recrystallization from ether or ether–hexane.

Kinetic Measurements. A 1.37-g (10 mmoles) sample of benzohydroxamic acid was dissolved by heating in 3 ml of absolute methanol, the solution was applied to 13.7 g of DEAE-cellulose, and the mixture was stirred thoroughly and dried at 70°C. A 0.82-ml (10 mmoles) sample of crotonaldehyde was applied to 7 g of DEAE-cellulose, and the two portions of the adsorbent were mixed. The reaction mixture was shaken during the entire period of sample selection. The first sample was selected immediately after mixing of the reagents and weighed (the mass of the adsorbent with the substance in the sample should be ~0.8 g), after which it was extracted with chloroform (two 3-ml samples), and the filtrate was evaporated. The determination of the amounts of isomers Ib and IIb was carried out with a Pharmacia FPLC medium-pressure liquid chromatograph with a 5 × 50 mm column using Silasorb LC-600 as the sorbent with detection from the absorption at λ 280 nm. For preparation of the samples, the selected samples were dissolved in the calculated amount of chloroform in such a way as to obtain solutions with identical overall concentrations. A 25-μliter sample of the solution was applied to the column. The eluent was hexane–ethyl acetate (7:3).

The integration of the chromatograms was accomplished automatically. The calculations were made with an Iskra-226 computer by the method of least squares with biquadratic weighting.

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*The following adsorbents were used (the adsorbent, the particle size, and the drying time/temperature are given): neutral Al_2O_3, pH 9-10, Brockmann activity II (Reanal, Hungary), 100 × 250 μm, 20 h/300-400°C; acidic Al_2O_3, pH 5-6, Brockmann activity I (POCH, Poland, without additional drying); Florisil (Fluka AG, Switzerland), 100-200 mesh, 10 h/250-300°C; Inerton AW (Chemapol, Czechoslovakia), 200-250 μm, 10 h/250-300°C; silica gel (Chemapol, Czechoslovakia), 100 × 250 μm, 23 h/250°C; Servacel KM-32 (Reanal, Hungary), 100-200 μm, 15 h/70°C; Servacel DEAE-32 (Reanal, Hungary), 100-200 μm, 15 h/70°C; Servacel TEAE-23 (Reanal, Hungary) 50-200 μm, 15 h/70°C.