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STUDY OF THE REACTIVITY OF THE METHYLENE HYDROGEN ATOMS OF SOME AZOLIDINES. III*. KINETICS OF THE REACTION OF AZOLIDONES-4 WITH BENZALDEHYDE

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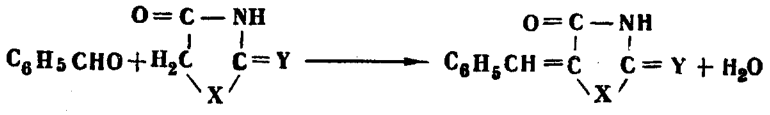
UV spectroscopy is used to study the kinetics of formation of 5-benzylideneazolidones-4. The reaction is shown to be irreversible and follows a second-order equation. The effect of various hetero atoms (sulfur, nitrogen, and oxygen) in position 1 or 2 on the methylene group reactivity of azolidones-4 is investigated. The azolidones-4 fall into two series with respect to decreasing activity of the group in acetic acid in the presence of anhydrous sodium acetate: rhodanine>2-thiohydantoin>pseudo-thiohydantoin>glycocyamidine> thiazolidinedione-2,4>2-thionoxazolidone-4>hydantoin>pseudo-hydantoin>oxazolidinedione-2,4.

Earlier papers have shown that, by making use of various carbonyl, nitroso, and diazo compounds, methylene group reactivities in azolidones-4 could be qualitatively compared, and that the compounds could be arranged in a definite order in respect to methylene group reactivity.

However, lack of kinetic studies made this result approximate and qualitative.

For quantitative characterization of the mobility of the methylene hydrogen atoms in azolidones-4, the rates of reaction of these compounds with benzaldehyde were studied at 100° and 125° in glacial acetic acid in the presence of anhydrous sodium acetate.

The equation for the reaction was



I-IX

I, X = S, Y = S (rhodanine); II, X = NH, Y = S (2-thiohydantoin); III X = S, Y = NH (pseudo-thiohydantoin); IV, X = NH, Y = NH (glycocyamidine); V, X = S, Y = O (thiazolidine-2,4); VI, X = O, Y = S (2-thionoxazolidone-4); VII, X = NH, Y = O (hydantoin; VIII, X = O, Y = NH (pseudo-hydantoin); IX, X = O, Y = O (oxazolidinedione-2,4).

The amount of 5-benzylideneazolidone-4 formed was determined spectroscopically. It was previously shown that this reaction could be used for kinetic studies. The ranges for which optical density is a linear function of concentration were ascertained. Ad hoc experiments established that the reaction does not give rise to by-products interfering with the spectroscopic determination of 5-benzylideneazolidones-4. The reaction is not reversible. A 1:1 molar ratio is optimal. Other ratios sometimes used when preparing 5-benzylideneazolidones-4 are undesirable.

A second-order reaction was found using the known formula

$$n=\frac{\lg\tau_2-\lg\tau_1}{\lg c_2-\lg c_1}+1,$$

where n is the reaction order, τ the half-life period of the reaction in minutes, c the initial concentration in mole/*l*. The same reaction order was also confirmed by the method of successive substitution of experimental data in the equations deduced for various reaction orders.

Table 1 gives reaction rate constants for the formation of 5-benzylideneazolidones-4 at 100° and 125°, the activation energies, and pre-exponential factors.

It is evident from the data given that in the case of the same series of azolidones-4 (i.e., with a sulfur atom, NH group, or oxygen atom in position 1) the most reactive methylene group will be possessed by the azolidone-4 with a thio group (Y = S) at position 2, next comes the imino group (Y = NH), and finally, the oxo group (Y = O). The azolidones-4 can be placed in the following order with respect to hydrogen atom mobility: I>III>V; II>IV>VII; VI>VIII>IX, which confirms the conclusion previously reached regarding the greater electronegativity of the sulfur atom compared with the imino group and oxygen in these compounds.

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*For Part II see [1].

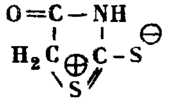
TABLE 1

Combined data for kinetics of formation of 5-benzylideneazolidones-4

Compound	K^*_{100}	K^*_{125}	E	lg PZ
I	0.03005 ±0.0055	0,1335 ±0,0020	16.2	8.01
II	0,01603 ±0,00046	0,07945 ±0.0011	18.8	8.50
III	0.00605 ±0,00012	0.04360 ±0.00082	21,4	10.39
IV	0,005128 ±0.00027	0,04238 ±0,00071	23,0	11.25
V	0,0006321 ±0,000062	0.005459 ±0.00034	23,3	10.57
VI	0,0005991 ±0.000052	0,006454 ±0.00042	25,8	11.95
VII	0.00005907±0.0000066	0,0005364±0.000024	23.7	9,74
VIII	No reaction	0,0002923±0,000016	—	—
IX	No reaction	No reaction	—	—

*Average value of the rate constant from n measurements at the temperature stated.

The greater electronegativity of the thio group as compared with the carbonyl group is probably due to the presence of free d-levels in the sulfur atom and the possibility of realizing the following structure:



If the azolidones contain the same substituent in position 2 but different hetero atoms at position 1 (X = S, NH, O), on passing from thiazolidones-4 to imidazolidones-4 (hydantoins) and oxazolidones-4, methylene hydrogen mobility decreases in the order I>II>VI; III>IV>VIII; V>VII>IX.

With the substituent at position 2 always the same, the greatest methylene hydrogen mobility is found in azolidones-4 with a sulfur atom at position 1 (X = S). This may be due not only to the readiness with which the effect of the electrophilic substituent at position 2 is transmitted to the methylene group, but also to the possible formation of an intermediate carbenium ion $H-\overset{\ominus|}{C}-\overset{|}{S}-$, stabilized by its immediate proximity to the sulfur atom. There are abundant examples of this in the literature on organic sulfur compounds [3, 4].

EXPERIMENTAL

The azolidones-4 required for the kinetic investigations were prepared by the methods given in the literature. Their 5-benzylidene derivatives were obtained by condensing the appropriate azolidone-4 with benzaldehyde in glacial acetic acid in the presence of anhydrous sodium acetate. 5-Benzylidenehydantoin was obtained by desulfurizing 5-benzylidene-2-thiohydantoin with a 30% aqueous monochloracetic acid solution [5].

5-Benzylidene-2-imino-oxazolidone-4 is obtained in 26.4% yield by refluxing equimolecular amounts of 2-imino-oxazolidone and benzaldehyde for 3 hrs in a mixture of glacial acetic acid, acetic anhydride, and anhydrous sodium acetate. M.p. 217°, found: N 14.7%, calculated for $C_{10}H_8N_2O_2$: N 14.89%.

The azolidones-4 and their 5-benzylidene derivatives were purified by repeated crystallization from various solvents. The benzaldehyde was purified via the bisulfite compound and then twice distilled in a vacuum. The alcohol for spectroscopy was treated with bromine, boiled with caustic soda and zinc dust, then fractionated through a column. The physical constants of all the substances used were the same as those given in the literature for chemically pure substances.

Method of measuring reaction rate. The rates of formation of 5-benzylidene derivatives of the azolidones-4 were measured spectroscopically using an SF-4 photometer*. A definite volume of a solution of the azolidone-4 of known concentration was introduced into a small flask fitted with a reflux condenser, and dissolved in the acetate mixture (10% solution of anhydrous sodium acetate in glacial acetic acid). When it had attained the reaction temperature, an equivalent amount of benzaldehyde, heated to the reaction temperature, was added. To facilitate calculation, and to lessen errors due to thermal decomposition of the acetate mixture, from 20° to the reaction temperature empirical solutions of the starting materials were made up, giving a volume of exactly 50 ml at the reaction temperature. At fixed intervals of time a 1 ml sample of the reaction mixture was quenched by running it into 50 ml of alcohol, after which the optical density of the resulting solution was determined. The precision of the results obtained was evaluated using a statistical method [6] (reliability 0.95). The rate constants were calculated from the formula

$$K=\frac{x}{t\cdot c(c-x)},$$

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*The measurements were made by the L'vov State Medical Institute Biochemistry Department.

where c = initial concentration of the starting material, in mole/l; x = reaction product concentration after time t, in mole/l.

The Arrhenius activation energy and the pre-exponential factor were found from the formulas

$$E=\frac{4.575\cdot T_1\cdot T_2}{T_2-T_1}\lg\frac{K_2}{K_1};\quad \lg PZ=\lg K+\frac{E}{4.575\cdot T}.$$

Results of typical experiments on the kinetics of formation of 5-benzylideneazolidones-4 are given in Tables 2 and 3.

TABLE 2

Kinetics of formation of 5-benzylidenerhodanine (c = 0.02)

100°				125°			
t_i^* min.	Yield mmole/liter	K_i l/mole. sec.	n_i	t_i^* min.	Yield mmole/liter	K_i l/mole. sec.	n_i
30	0.3524	0.03032	3	15	0.7333	0.1332	3
60	0.7208	0.03096	3	30	1.5130	0.1354	3
90	1.0116	0.02965	3	45	2.1662	0.1312	3
120	1.2682	0.02927	3	60	2.9432	0.1343	3

$K=0.03005\pm0.0055$ $\quad K=0.1335\pm0.0020$

$E=16.2;\quad \lg PZ=8.01$

TABLE 3

Kinetics of formation of 5-benzylidenehydantoin (c = 0.05)

100°				125°			
t_i^* min.	Yield mmole/liter	K_i l/mole. sec.	n_i	t_i^* min.	mmole/liter	K_i l/mole. sec.	n_i
360	0.05342	0.00005942	3	240	0.2995	0.0005025	3
480	0.07114	0.00005885	3	300	0.4126	0.0005832	3
600	0.08851	0.00005898	3	480	0.6058	0.0005110	3
				600	0.8723	0.0005825	3

$K=0.00005907\pm0.00000066$ $\quad K=0.0005364\pm0.00002377$

$E=23.7;\quad \lg PZ=9.74$

*t_i — time over which n_i measurements are spread; K_i — average of rate constants for n_i measurements; K — mean of rate constants for all Σn_i measurements at a particular temperature.

Optical density measurements on solutions, for determining the amounts of 5-benzylideneazolidones-4, were made at the following values of λ : I 375, II 370, III 333, IV 328, V 329, VI 346, VII 318, VIII 320 mμ, corresponding to a wide and intense absorption maximum for these compounds.

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