REACTIONS OF CHLORINATED FURANIDINES. VIII.*

THE INFLUENCE OF THE STRUCTURE
OF 2-ALKOXY-3-HALOTETRAHYDROFURANS
ON THE RATE OF THEIR DEHYDROHALOGENATION

V.Zezula and M.Kratochvíl

Department of Organic Chemistry,
J. E. Purkyně University, Brno

Dehydrohalogenation of 2-alkoxy-3-chlorotetrahydrofurans were described for the first time by Quenehen and Normant[1] who gave 2-alkoxy-2,5-dihydrofurans as the reaction products. The comparison of the reactivity of chlorine atoms in 2-(2-chloroethoxy)-3-chlorotetrahydrofuran with bases shows clearly that the chlorine atom in the side chain[2] is more reactive. Bolotina, Kučenko and Moškin[3] described qualitatively the reactions of 2-alkoxy-3-chlorotetrahydrofurans with bases and also found 2-alkoxy-2,5-dihydrofurans as primary products which at higher temperatures give furan and alcohol. The product of substitution could not be detected in the reaction mixture. After the elaboration of the method enabling the identification and the separation of isomeric *cis*- and *trans*-2-alkoxy-3-halotetrahydrofurans[4] *Ia,b — XIa,b*, we investigated the ease of the reaction of single isomers with sodium ethoxide and the influence of the bulkiness of the alkoxy group and the nature of the halogen atom on the dehydrohalogenation rate.

EXPERIMENTAL

The preparation of substances *Ia,b — VIIa,b* was carried out according to[4]; their purity and the proportion of *cis*- and *trans*-isomers in the mixture was determined by gas chromatography[4]. Substances *VIIIa — XIa* were prepared according to[5].

Measurement of the Conversion Curve

The reaction components were mixed in ground-joint test tubes, stoppered, and put into an ultra-thermostat. The samples taken out at definite time intervals were diluted with 50 ml of water, acidified with nitric acid, and titrated potentiometrically with 0.1M-AgNO_3 for halogen anions. The rate constants were calculated on the basis of the equation for an irreversible bimolecular reactions.

2-Ethoxy-2,5-dihydrofuran

From the reaction products 2-ethoxy-2,5-dihydrofuran was isolated and identified, as an illustration, using a procedure analogous to procedure[3]. As starting material for this synthesis 2-ethoxy-3-bromotetrahydrofuran was found better than 2-ethoxy-3-chlorotetrahydrofuran. B.p. 41°C/17 Torr, n_D^{20} 1·4395, d_D^{20} 1·0352, M_R 29·253 (theoretical M_R 30·572). Literature[1] gives b.p. 35°C/13 Torr, d_{16}^{17} 0·988. The IR spectrum of 2-ethoxy-2,5-dihydrofuran taken on a UR 10 Zeiss spectrophotometer in sodium chloride cells (film thickness) is identical with that of the same substance prepared according to ref.[6].

DISCUSSION

The comparison of the dehydrohalogenation rate of 3-chloro- with 3-bromosubstituted 2-alkoxytetrahydrofurans shows that the latter are more reactive. The measurement of the dehydrobromination rate of substances *VIIIa* and *Xa* at various concentrations of the reactants shows that the reaction is bimolecular and of the second order. The results are given in Table I. If potassium isopropoxide in isopropyl alcohol was used as a base (concentration of the substrate 1.375 mol/l, concentration of the base 2.333 mol/l), the dehydrobromination rate of substance *VIII* increases more than ten times ($k = 317.58 \cdot 10^{-5}$ l mol^{-1} s^{-1}). These findings permit the conclusion that these reactions probably take place by E 2 mechanism. With increasing bulkiness of the alkoxy group the dehydrohalogenation rate decreases (Table II). The tendency of this unusual influence on the reaction centre of a relatively remote group is manifest in the possibility of correlating the logarithms of the rate constants of dehydrohalogenations with E_s values of alkyls. In Fig. 1 the correlation relations of substances *Ia* and *VIIIa* are not satisfactory. Evidently, the departing halogen can be hindered only by the alkoxy group of other members of the homologous series. The methoxy group (in substances *Ia* and *VIIIa*) has no such possibility as is evident from the spacefilling model. The rate of dehydrohalogenation of isomeric *cis*- and *trans*-2-ethoxy-3-chlorotetrahydrofurans (*IIa* and *IIb*) is dependent on the proportion of single isomers in the reaction mixture. Thus, at 83·0°C and at the ratio *IIa*/*IIb* 1 : 4 the calculated rate constant was $k = 7.67 \cdot 10^{-6}$ l mol^{-1} s^{-1}, at the ratio *IIa*/*IIb* 9 : 1, $k = 15.33 \cdot 10^{-6}$ l mol^{-1} s^{-1}. The higher proportion of *cis*-isomer in the reaction mixture corresponds to the decrease of the reaction rate of dehydrohalogenation. From the model of *cis*-2-ethoxy-3-chlorotetrahydro-
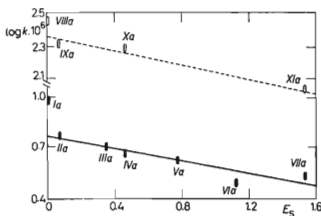

FIG. 1

Correlation of the Logarithms of Rate Constants of Dehydrohalogenation of Compounds *Ia* to *XIa* by Sodium Ethoxide in Ethanol at 74·3°C with E_s Factors[13]

	R	X		R	X
Ia,b	CH_3	Cl	*VIIa,b*	t-C_4H_9	Cl
IIa,b	C_2H_5	Cl	*VIIIa,b*	CH_3	Br
IIIa,b	n-C_3H_7	Cl	*IXa,b*	C_2H_5	Br
IVa,b	i-C_3H_7	Cl	*Xa,b*	i-C_3H_7	Br
Va,b	cyclo-C_6H_{11}	Cl	*XIa,b*	t-C_4H_9	Br
VIa,b	s-C_4H_9	Cl			

furan it is evident that the molecule contains two hydrogen atoms in favourable *trans*-position to the chlorine atom, and that in the *trans*-isomer only one hydrogen atom is in the *trans* position suitable for a bimolecular elimination. However, according to the authors of ref.[3] (similar examples can also be found in the case of β-haloacetals of the aliphatic series[7-10]) we eliminate the possibility of dehydrochlorination on $C_{(2)}$—$C_{(3)}$ bonds. Hence, the explanation must be sought again in the sterical hindrances caused by the alkoxy group. We can imagine that in compound *IIb* the departing chloride anion will be blocked by the ethoxy group still more than in compound *IIa*. The influence of the temperature on the rate of dehydrohalogenation, in Table III, shows that the rather high value of the activation energy, comparable with the values published for a bimolecular reaction of a similar type[11] remains constant for these reactions within the limits of accuracy (approx. 22 kcal/mol). The change of activation entropy, serving as an indication of the sterical arrangement of the transition state of the substrate is reflected in the difference of the activation entropy decrease between *IIb* (80%) and *IIa* (90%), being 7·5 e.u., while between

TABLE I

The Effect of Reactants on the Reaction Rate of Substances *VIIIa* and *Xa* with Sodium Ethoxide in Ethanol at 74·3°C

Substance	Concentration, mol/l		$k \cdot 10^{6a}$
	substrate	base	$1\ mol^{-1}\ s^{-1}$
VIIIa	1·200	2·240	294·83
	1·375	2·267	312·00
	1·375	1·133	280·00
	1·375	1·133	291·67
Xa	1·185	2·216	195·83
	1·185	1·108	226·17

[a] The difference between the rate constants can be explained by the fact that the measurements were carried out on separate samples.

TABLE II

The Effect of the Alkoxy Group on the Dehydrohalogenation Rate of Substances *Ia—XIa* at 74·3°C

Substance $k \cdot 10^6$ $1\ mol^{-1}\ s^{-1}$	*Ia*	*IIa*	*IIIa*	*IVa*	*Va*	*VIa*	*VIIa*
	9,67	6·00	5·07	4·52	4·18	3·00	3·57

Substance $k \cdot 10^6$ $1\ mol^{-1}\ s^{-1}$	*VIIIa*	*IXa*	*Xa*	*XIa*
	293·30	203·10	195·83	114·17

TABLE III
The Effect of Temperature on the Dehydrochlorination Rate

Temperature °C	$k \cdot 10^6$ $l \, mol^{-1} \, s^{-1}$	
		Mixture *IIa* : *IIb* 1 : 4
65·0	1·50	$E_A = 21·67$ kcal/mol
74·3	3·67	$\log A = 8·18 \, l \, mol^{-1} \, s^{-1}$
83·0	7·67	$\Delta S^{\neq} = 21·40$ j.e.
		Mixture *IIa* : *IIa* 9 : 1
64·0	2·33	$E_A = 23·85$ kcal/mol
74·3	6·00	$\log A = 8·70 \, l \, mol^{-1} \, s^{-1}$
83·0	15·33	$\Delta S^{\neq} = -13·95$ j.e.
		Compound *Ia*
65·0	4·50	$E_A = 23·59 \pm 3·02$ kcal/mol
74·3	9·67	$\log A = 9·87 \, l \, mol^{-1} \, s^{-1}$
83·0	26·17	$\Delta S^{\neq} = -13·68$ j.e.
		Compound *VIIIa*
65·0	123·20	$E_A = 21·62 \pm 0·10$ kcal/mol
74·3	293·30	$\log A = 10·06 \, l \, mol^{-1} \, s^{-1}$
83·0	626·60	$\Delta S^{\neq} = -12·80$ j.e.
		Compound *IVa*
66·5	2·48	$E_A = 20·58 \pm 1·68$ kcal/mol
74·3	4·52	$\log A = 7·62 \, l \, mol^{-1} \, s^{-1}$
83·0	10·22	$\Delta S^{\neq} = -27·30$ j.e.

Ia (95%) and *VIIIa* (97%) it is only approx. 1 e.u., and between *Ia* (95%) and *IVa* (98%) on the contrary, the difference in the drop of activation entropies is appreciable, *i.e.* approx. 13.5 e.u.

From the obtained values for rate constants, activation energies, and the changes of activation entropies considerations can be made on the mechanism of this reaction. The rate constants agree well with the assumption of a bimolecular irreversible reaction. Activation energies of these reactions do not differ appreciably; the nuances in the reaction mechanism of dehydrochlorination of compounds *IIa* and *IIb* should be sought, therefore, in a differently strained transition state of the reaction, as evidenced by the differences in the changes of the activation entropy. Thus, while in compound *Ia* we may expect a classical E 2 mechanism[12], larger substitutents will sterically hinder the departing halogenide ion; this hindrance may be still stronger in the *cis* isomer. Therefore, for the dehydrohalogenation of substrates with a bulkier alkoxy group, and especially of *cis*-isomers, an intermediary reaction step can be supposed, accompanied by the formation of a negative fractional charge on the $C_{(4)}$-atom, followed by the splitting off of the

halogenide anion under formation of 2-alkoxy-2,5-dihydrofurans. Almost the same values of activation energies do not indicate that in an extreme case this intermediary reaction step should change up to a ElcB mechanism.

REFERENCES

1. Quenehen F., Normant H.: Compt. Rend. *228*, 1301 (1949).
2. Kratochvíl M., Jonas J., Zezula V.: Z. Chem. *7*, 149 (1967).
3. Bolotina L. M., Kučenko N. I., Moškin P. A.: Dokl. Akad. Nauk SSSR *174*, 601 (1967).
4. Zezula V., Kratochvíl M.: This Journal *35*, 1745 (1970).
5. Holík M., Štern P., Kratochvíl M.: Chem. zvesti *25*, 9 (1971).
6. Rice F. A. H. Tenney J. M.: Carbohydrate Res. *2*, 207 (1966).
7. Price R. W., Moos A.: J. Am. Chem. Soc. *67*, 207 (1945).
8. Dornow A., Schacht W.: Chem. Ber. *82*, 117 (1949).
9. McElvain S. M., Morris L. R.: J. Am. Chem. Soc. *73*, 206 (1951).
10. Bedoukian P. Z.: J. Am. Chem. Soc. *79*, 889 (1957).
11. Zezula V., Friedl Z., Kratochvíl M.: This Journal, in press.
12. Ridd J. H. (Ed.): *Studies on Chemical Structure and Reactivity*, p. 33. Methuen, London 1966.
13. Pritzkow W.: *Theoretische Gesichtspunkte in der Organischen Chemie*, p. 72. Steinkopf, Dresden 1963.