INVESTIGATION OF 2,3-POLYMETHYLENEQUINOLINES

XVIII.* KINETICS OF THE REACTION OF 4-CHLORO-2,3-POLYMETHYLENEQUINOLINES WITH SODIUM METHOXIDE

M. E. Konshin, D. I. Uvarov,
and É. S. Abramochkin

UDC 541.127: 547.831

The rate of the reaction of 4-chloro-6-R-2,3-polymethylenequinolines with sodium methoxide decreases as the number of methylene groups increases; this is explained by the inductive and steric effects of the polymethylene chain. The rate constants of the reaction are in conformity with the Arrhenius equation and are found to exist in a correlation relationship with the σ_{cat} substituent constants for quinoline.

Although the kinetics of the nucleophilic substitution reactions of the chlorine atom in 2- and 4-chloroquinolines have been investigated in detail [2, 5], there are only qualitative observations with respect to the lability of the halogen in 4-chloro-2,3-polymethylenquinolines [6-8]. In order to make a quantitative evaluation of the effect of the polymethylene chain on the rate of nucleophilic substitution of the halogen in 4-chloro-2,3-polymethylenequinolines, we investigated the kinetics of the reaction of these compounds (I-XIV) with sodium methoxide, as a result of which 4-methoxy-2,3-polymethylenequinolines (XV-XXVII, Table 1) are formed.

I-XIV XV-XXVII

I-V, XV-XIX n=3; VI-X, XX-XXIII n=4; XI-XIV, XXIV-XXVII n=5

The results of the kinetic measurements are presented in Table 2. The reaction is in conformity with the Arrhenius equation, and this made it possible to calculate its activation parameters, which are presented in Table 2. It is seen from the data in Table 2 that the methoxydechlorination rate constants (k) at 76.2°C decrease as n increases. The decrease in the rate in the order I-V > VI-X > XI-XIV should be explained by the electron-donor properties of the methylene group, by which the compounds of the three reaction series under consideration are distinguished, and also by steric hindrance on the part of the methylene groups bonded to the $C_{(2)}$ and $C_{(3)}$ atoms of the quinoline ring, which is manifested most markedly in VI-XIV. The considerable decrease in the activation entropy attests to an increase in steric hindrance on passing from compounds of the first reaction series (n=3) to compounds of the second (n=4) and third (n=5) reaction series. The observed phenomenon must be explained by the following reasons.

In the compounds of the second and third reaction series the angles between the $C_{(2)}-CH_2$ or $C_{(3)}-CH_2$ bond and the $C_{(2)}-C_{(3)}$ bonds approach 120°. In 4-chloro-2,3-trimethylenquinolines, owing to the great rigidity of the system, these same valences are directed at a smaller angle (113°). As a consequence of this, the carbon atom of the CH_2 groups in I-V is found at a sufficient distance from the chlorine atom and is not overlapped with it, while the carbon atom of the CH_2 group in VI-XIV is closer to the chlorine atom and partially overlaps it. In addition, the hydrogen atoms of the CH_2 groups of I-V, which contain a five-

---

[*] For Communication XVII see [1].

Perm Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1106-1109, August, 1974. Original article submitted March 15, 1973.

TABLE 1. 4-Methoxy-2,3-polymethylenequinolines (XV-XXVII)

Compound	n	R	mp, °C*	Empirical formula	N, %		Yield, %
					found	calc.	
XV	3	H	71—72	$C_{13}H_{13}NO$	7,1	7,0	67
XVI	3	CH_3	108—109	$C_{14}H_{15}NO$	6,5	6,6	70
XVII	3	Cl	110—111	$C_{13}H_{12}ClNO$	6,1	6,0	79
XVIII	3	CH_3O	117—118	$C_{14}H_{15}NO_2$	6,3	6,1	67
XIX	3	Br	100	$C_{13}H_{12}BrNO$	5,2	5,0	78
XX	4	H	58	$C_{14}H_{15}NO$	6,4	6,6	40
XXI	4	CH_3	80	$C_{15}H_{17}NO$	6,1	6,2	35
XXII	4	Cl	110	$C_{14}H_{14}ClNO$	5,4	5,7	52
XXIII	4	Br	101	$C_{14}H_{14}BrNO$	4,7	4,8	50
XXIV	5	H	74	$C_{15}H_{17}NO$	6,3	6,2	27
XXV	5	CH_3	65	$C_{16}H_{19}NO$	6,05	5,8	42
XXVI	5	Cl	95	$C_{15}H_{16}ClNO$	5,3	5,4	70
XXVII	5	Br	110—112	$C_{15}H_{16}BrNO$	4,5	4,6	42

---

* Compounds XV, XX, and XXV were crystallized from petroleum ether, while the remaining compounds were crystallized from methanol.

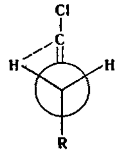
TABLE 2. Kinetic and Thermodynamic Parameters of the Reaction of 4-Chloro-2,3-polymethylenequinolines with Sodium Methoxide

Compound	n	R	$k \cdot 10^4$, liter · mole^{-1} · sec^{-1}				E, kcal/mole	lg A	$\Delta S^{\neq}$, e.u.	$\Delta F^{\neq}$, kcal/mole
			66°	76,2°	85,7°	97,2°				
I	3	H	—	0,230	0,57	1,81	25,16	11,18	−9,97	27,95
II	3	CH_3	—	0,115	0,38	0,92	25,30	11,18	−10,95	28,43
III	3	CH_3O	—	0,089	0,29	0,860	27,63	12,26	−4,78	28,61
IV	3	Cl	0,41	1,20	2,86	—	23,86	11,00	−10,41	26,80
V	3	Br	0,52	1,61	3,82	—	24,58	11,57	−7,78	26,60
VI	4	H	—	0,095	0,17	0,47	19,56	7,20	−27,72	28,55
VII	4	CH_3	—	0,052	0,11	0,24	18,53	6,32	−31,90	28,98
VIII	4	CH_3O	—	0,035	0,067	0,14	16,75	5,03	−37,76	29,25
IX	4	Cl	0,19	0,43	0,74	—	16,65	6,02	−33,12	27,52
X	4	Br	0,22	0,67	1,057	—	19,24	7,78	−24,82	27,21
XI	5	H	—	0,045	0,111	0,28	22,52	8,82	−20,78	29,08
XII	5	CH_3	—	0,0245	0,06	0,16	23,28	8,97	−19,81	29,50
XIII	5	Cl	—	0,285	0,645	1,71	22,45	9,50	−17,31	27,80
XIV	5	Br	—	0,43	1,042	2,70	22,70	9,87	−15,78	27,52

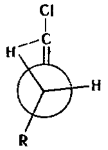
TABLE 3. Parameters of the Correlation Dependence of log k on σ_{cat}

Compound	ρ	Calc. log k°	r	s
I—V	4,72	−4,60	0,994	0,054
VI—X	4,56	−4,99	0,993	0,058
XI—XIV	5,06	−5,36	0,991	0,107

membered ring situated in the same plane with the quinoline ring, also are not overlapped with chlorine, inasmuch as the latter is located in the middle of the dihedral angle formed by the valences of the hydrogen atoms (conformation *a*).



a



b

The cycloalkene ring of VI-XIV has a half-chair form (compare with tetralin [9]), and owing to this the dihedral angles between the pseudoequatorial and pseudoaxial hydrogen atoms of the methylene groups adjacent to the quinoline ring are divided by the plane of the quinoline ring into unequal fractions (conformation b). Moreover, the pseudoaxial hydrogen is closer to the chlorine atom and partially shields it.

Steric hindrance to solvation of VI-XIV is also observed due to the formation of hydrogen bonds between the methanol and the heteroring nitrogen. The effect of methanol on the reaction rate, which, as is well known [3, 5], considerably accelerates side processes, is thereby weakened.

The methoxydechlorination rate constants of I-V at 76.2° are lower by a factor of 6-14 as compared with the rate constants of the same reaction of 4-chloroquinolines at 75.2° [2]; this is associated primarily with the inductive effect of the polymethylene chain in I-V and, to a lesser extent, with steric hindrance on the part of this same chain.

The rate of methoxydechlorination of the investigated compounds depends on the group attached to the $C_{(6)}$ atom and increases as the electronegativity of the substituents increases: $CH_3O < CH_3 < H < Cl < Br$. A correlation dependence between the methoxydechlorination rate constants of I-XIV at 76.2° and the σ_{cat} substituent constant of quinoline [10] was found. The parameters of the correlation dependence $\log k - \sigma_{cat}$ (Table 3) attest to great sensitivity of the reaction center to the effect of substituents attached to $C_{(6)}$. The introduction of a polymethylene chain does not bring about a substantial change in the reaction constant.

EXPERIMENTAL

4-Chloro-2,3-polymethylenequinolines. These compounds were obtained by the methods in [6, 11-14] and were recrystallized three times from hexane. Anhydrous methanol was prepared by the method in [15]. Sodium methoxide was prepared by the usual method from analytically pure-grade sodium and anhydrous methanol. The sodium methoxide concentration was determined by titration with 0.1 N hydrochloric acid with methyl red as the indicator.

The reaction mixture for the kinetic measurements was prepared in a 25-ml volumetric flask by dissolving a weighed sample of 4-chloro-2,3-polymethylenequinoline in 15 ml of anhydrous methanol and by subsequent addition of the calculated volume of sodium methoxide and the necessary amount of methanol. The initial 4-chloro-2,3-polymethylenequinoline and sodium methoxide concentrations were 0.012-0.052 M and 0.060-0.160 M, respectively. Samples (2 ml) of the prepared solutions were used for the determinations and were placed in 20-ml glass ampuls. The ampuls were sealed and simultaneously immersed in a thermostat; the temperature was maintained constant with an accuracy of ±0.05°. The time of immersion of the sample in the thermostat was taken as the start of the reaction. At the end of the reaction, the ampul was cooled with ice, and the contents were poured into 20 ml of 0.3 N nitric acid solution. The chloride ion concentration was determined by the Volhard method. The rate constants were calculated from the second-order equation

$$k = \frac{2.303}{t(a-b)} \lg \frac{b(a-x)}{a(b-x)},$$

where a and b are the molar concentrations of sodium methoxide and the halo derivative, respectively, and x is the chloride ion concentration at time t (in seconds). The slope of the dependence of $\log [(a-x)/(b-x)]$ on t was calculated by the method of least squares. A correction for the thermal expansion of methanol [16] was introduced.

4-Methoxy-2,3-polymethylenequinolines (XV-XXVII, Table 1). A 0.005-mole sample of 4-chloro-2,3-polymethylenequinoline was added to a solution of 0.5 g of sodium in 15 ml of methanol, and the mixture was refluxed for 20-200 h. It was then cooled and poured into water, and the resulting precipitate was removed by filtration and crystallized.

LITERATURE CITED

1. D. I. Uvarov, A. S. Zaks, L. G. Zil'bermints, T. A. Kapitonenko, and M. E. Konshin, Izv. Vuzov, Ser. Khim. (1973, in press).
2. G. Illuminati and G. Marino, J. Amer. Chem. Soc., 80, 1421 (1958).
3. G. Illuminati and G. Marino, Chem. and Ind., 1287 (1963).
4. G. Bressan, G. Giardi, P. Linda, G. Sleiter, and G. Illuminati, J. Chem. Soc., B, 225 (1971).
5. G. Illuminati, G. Sleiter, and M. Speranza, J. Org. Chem., 36, 1723 (1971).
6. O. Yu. Magidson and A. I. Travin, Zh. Obshch. Khim., 7, 842 (1937).
7. L. Sargeat and L. Small, J. Org. Chem., 11, 359 (1946).
8. A. Albert, R. Goldacre, and E. Heymann, J. Chem. Soc., 654 (1943).
9. É. Eliel, N. Allinger, S. Angyal, and G. Morrison, Conformational Analysis, Wiley (1965).
10. Chemist's Handbook [in Russian], Vol. 3, Khimiya, Leningrad (1964), p. 964.

11. V. Petrow, J. Chem. Soc., 634 (1947).
12. M. S. Chadha, K. K. Chakravarti, and S. Siddighi, J. Sci. Ind. Res., 10B, 1 (1951).
13. L. Sargent and L. Small, J. Org. Chem., 12, 567, 571 (1947).
14. É. S. Abramochkin and M. E. Konshin, Khim.-Farmats. Zh., No. 7, 10 (1970).
15. Preparative Organic Chemistry [in Russian], GKhI, Moscow (1959), p. 157.
16. Chemist's Handbook [in Russian], Vol. 1, GKhI, Moscow (1962), p. 555.