The Kinetics of the Reaction of Some Chloroisoxazolo[4.5-*c*]- and [5,4-*b*]pyridines with Methoxide Ion

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Arrhenius parameters were measured for the methoxy-dechlorination reactions of some chloroderivatives of isoxazolo[4,5-*c*]- and [5,4-*b*]pyridine. A comparison of these results with the kinetic data for the corresponding chloropyridines shows that fusion of the isoxazole ring with the pyridine ring strongly increases the reactivity of the 4- and 6-positions toward nucleophilic substitution.

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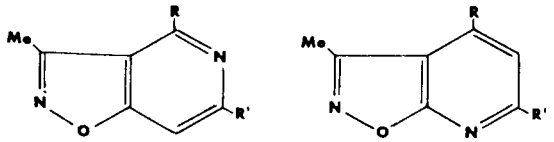
Fusion of an isoxazole ring with an electron-withdrawing pyridine ring gives systems which retain certain chemical properties of both rings, but of a higher order of reactivity toward nucleophilic displacement. This expected result is a consequence of a higher delocalization of the negative charge in the reaction intermediates.

There has been no systematic study of isoxazolopyridine systems, although some isoxazolo[4,5-*c*]pyridines have been reported to exhibit biological activity. In order to investigate the case of substitution of chlorine atoms in these ring systems, we recently prepared some chloroderivatives of isoxazolo[4,5-*c*] (1) and [5,4-*b*]-pyridine (2).

The scope of the present work is to study the kinetics of the methoxy-dechlorination reaction of the chloroderivatives **1a-d** and **2a-d** with methoxide ion in methanol and to give quantitative data in regard to the influence of the position of ring fusion on the reactivity of the chlorine atoms. Methoxide was chosen as the nucleophile to avoid autocatalysis reported for the reaction of halopyridines with aniline (3), where protonation of the annular nitrogen by acid liberated during reaction increases the electron-withdrawing power of the annular nitrogen.

The kinetics measurements show that the methoxy-dechlorination is second order overall. The rate constants at 50° and the Arrhenius activation parameters are reported in Table I. The rate constants at experimental temperatures are summarized in Table II. The recorded values (Table I and Table III) for compounds **1a**, **2a** and **4** are rate factors for substitution reactions at the 4-position. A comparison of the present results with those for the corresponding chloropyridines at 50°, shows that fusion of the isoxazole ring with the pyridine ring increases the rate constant between 10^2 and 10^5 fold (Table III).

SCHEME



1a R = R' = Cl
1b R = OCH_3, R' = Cl
1c R = H, R' = Cl
1d R = Cl, R' = OCH_3

2a R = R' = Cl
2b R = OCH_3, R' = Cl
2c R = H, R' = Cl
2d R = Cl, R' = H

From the values of the relative reactivities (k/k_o) it is evident that the fusion of the isoxazole ring on 2-chloropyridine to give 6-chloroisoxazolo[5,4-*b*]pyridine (**2c**) produces a greater increase in the rate constant than when the fusion gives 6-chloroisoxazolo[4,5-*c*]pyridine (**1c**). The rate constant ratio (k_{2c}/k_{1c}) is 229. It is also evident that the difference between the reaction rates of compounds **2c** and **1c** is a consequence of a greater decrease in activation energy (about 3 Kcal/mole).

A comparison of the reaction rate of chloroisoxazolopyridine **2d** and chloroisoxazolopyridine **2c** with those for 4-chloropyridine (6) and 2-chloropyridine (5), respectively, shows that the 6-position is more activated (about 4 fold). However, the chlorine atom at position 4 reacts 8.2 times as fast as the chlorine atom at position 6. The rate constant for the chlorine atom at position 4 in

Table 1

Kinetic Data for the Methoxy-dechlorination Reaction in Methanol of some Chloroisoxazolo[4,5-*c*] and [5,4-*b*]pyridines (at 50°)

Compound	$10^5 k_2$ (a)	E (b)	log A (a)	$-\Delta S$
1a (c)	9710	16.7 ± 0.10	10.28	13.4
2a (c)	34900	16.5 ± 0.14	10.70	11.5
2d	1820	17.3 ± 0.060	9.96	14.9
1b	0.116	25.4 ± 0.30	11.24	9.46
1c	0.965	22.9 ± 0.023	10.47	12.9
1d	129	18.9 ± 0.032	9.89	15.3
2b	54.1 (d)	19.8 ± 0.145	10.15	14.2
2c	221	19.5 ± 0.010	10.53	12.4

All kinetic runs were duplicated, the average values of the two sets of rate constants obtained agreeing within 2%. (a) Units of k and A are 1 $mole^{-1}$ $sec.^{-1}$ (b) Units of E are K cal $mole^{-1}$ and errors are standard deviations. (c) The values are referred to the chlorine at position 4. (d) Value measured directly at 50°.

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Table II

Rate Constants (k_2 1 mol^{-1} sec^{-1} ± 2%) at Various Temperatures

	t/°C	10^5 k_2	t/°C	$10^5 k_2$	t/°C	$10^5 k_2$
Compound		1a		1b		1c
	20.00	684.0	95.00	14.2	85.00	31.1
	10.00	252.0	85.00	5.49	75.00	12.3
	0.00	84.0	75.00	1.93	65.00	4.63
Compound		1d		2a		2b
	40.00	46.8	20.00	2661.0	50.00	54.1
	30.00	17.2	10.00	977.0	40.00	19.9
	20.00	5.86	0.00	329.0	30.00	7.04
Compound		2c		2d		3
	40.00	81.9	30.00	312.0	85.00	41.8
	32.50	37.9	20.00	118.0	75.00	16.2
	25.00	16.9	10.00	41.1	65.00	6.03

Table III

Kinetic Data of some Chloropyridines and Rate Constant Ratios (Isoxazolopyridines/Chloropyridine) at 50°.

	10^5 k_2	E	$-\Delta S$	10^{-3} k/k_o
(3) 2,6-dichloropyridine	1.16	23.3	11.3	$k_{1a}/k_3 = 8.4$ $k_{1d}/k_3 = 0.111$
(4) 2,4-dichloropyridine (a)	9.41	21.3	13.2	$k_{2a}/k_4 = 3.71$
(5) 2-chloropyridine (b)	0.00248	29.6	3.89	$k_{1c}/k_5 = 0.39$ $k_{2c}/k_5 = 89$
(6) 4-chloropyridine (c)	0.0888	25.2	10.4	$k_{2d}/k_6 = 20.5$
(7) 2-chloro-4-methoxypyridine (b)	0.00217	28.9	6.33	$k_{2b}/k_7 = 25$

4,6-dichloroisoxazolopyridine (**2a**) indicates that an electron-withdrawing substituent at position 6 in the isoxazolo[5,4-*b*]pyridine system facilitates methoxydechlorination. The rate constant ratio (k_{2a}/k_{2d}) is 19.1. This effect is probably due to both activation energy and entropy.

As far as the activation parameters are concerned, the higher rate constant for the chlorine atom at position 4 in 4,6-dichloroisoxazolopyridine (**2a**) in comparison with that of the corresponding chlorine atom in 4,6-dichloroisoxazolopyridine (**1a**) is entirely due to a higher value for the activation entropy. The rate constant ratio (k_{2a}/k_{1a}) is 3.5.

The introduction of a methoxy group at the meta-position reduces the rate constant in both series of compound (**1**) and (**2**). This effect is slightly different in the two series. The deactivation factor is *ca.* 8 in the case of the isoxazolo[4,5-*c*]pyridine system (k_{1c}/k_{1b} = 8.3), and 4 in the case of the isoxazolo[5,4-*b*]pyridine system (k_{2c}/k_{2b} = 4.0).

EXPERIMENTAL

Materials.

4,6-Dichloro-3-methylisoxazolo[4,5-*c*]pyridine (**1a**), 4,6-dichloro-3-methylisoxazolo[5,4-*b*]pyridine (**2a**), 6-chloro-4-methoxy-3-methylisoxazolo[4,5-*c*]pyridine (**1b**), 6-chloro-4-methoxy-3-methylixoxazolo[5,4-*b*]pyridine (**2b**), 6-chloro-3-methylisoxazolo[4,5-*c*]pyridine (**1c**), 6-chloro-3-methylisoxazolo[5,4-*b*]pyridine (**2c**), 4-chloro-6-methoxy-3-methylisoxazolo[4,5-*c*]pyridine (**1d**), 4-chloro-3-methylisoxazolo[5,4-*b*]pyridine (**2d**) were prepared as already described (1,2) and further purified by extraction of the ethereal solutions with aqueous alkali. The residue from evaporation of the ethereal solutions was repeatedly sublimed in the dark. 2-6-Dichloropyridine (Schuchardt purum) was crystallized from ethanol-water (charcoal) and repeatedly sublimed, m.p. 87-88°.

Solvent and Methoxide Reagent.

Dry methanol was prepared by refluxing commercially pure methanol with magnesium and iodine and taking the median fraction on distillation through a fractionating column. Methoxide reagent was prepared by rapidly transferring freshly cut sodium lumps in dry methanol and filtering the resulting solution through a fine-mesh glass funnel in a system free from moisture and carbon dioxide.

Kinetic Measurements.

All experiments were performed by using the sealed tube technique. The concentrations were in the range 0.0125-0.025*M* for the chloro derivatives and 0.05-0.1*M* for sodium methoxide reagent. The progress of the reaction was followed by titration of the liberated chloride ions by the Vohlard method, and rate constants were corrected for the thermal expansion of methanol.

Product Analysis.

Samples of the reaction mixture were left for sufficient time to ensure completion of the reaction. The solution was then evaporated and the residue washed with water, and dried and purified by repeated crystallizations and/or sublimations.

6-Chloro-2-methoxypridine.

This compound had b.p. 183-184° (lit. (6) b.p. 184-185°).

6-Chloro-4-methoxy-3-methylisoxazolo[4,5-*c*]pyridine.

This compound had m.p. 89-90° (lit. (1) m.p. 90-91°).

6-Chloro-4-methoxy-3-methylisoxazolo[5,4-*b*]pyridine.

This compound had m.p. 149-150° (lit. (2) m.p. 150°).

4,6-Dimethoxy-3-methylisoxazolo[4,5-*c*]pyridine.

This compound had m.p. 96-97° (lit. (1) m.p. 96-98°).

4,6-Dimethoxy-methylisoxazolo[5,4-*b*]pyridine.

This compound had m.p. 145-146° (lit. (2) m.p. 146°).

6-Methoxy-3-methylisoxazolo[4,5-*c*]pyridine.

This compound had m.p. 107-109°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.5; H, 4.9; N, 17.0.

6-Methoxy-3-methylisoxazolo[5,4-*b*]pyridine.

This compound had m.p. 109-111°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.45; H, 5.0; N, 16.9.

4-Methoxy-3-methylisoxazolo[5,4-*b*]pyridine.

This compound had m.p. 160-162°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.8; H, 5.2; N, 16.8.

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