683. Stability of N-Heterocyclic Oxime Derivatives. Part II.[1] Decomposition of N-Methylacetylpyridinium O-Acetylketoxime Iodides in Aqueous Solution

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The kinetics of the decomposition of N-methyl-2-, -3-, and -4-acetyl-pyridinium O-acetylketoxime iodides have been studied in the pH range 5·5—9·5. The reaction with water and hydroxyl ions yields the corresponding oximes and acetic acid in contrast with the reaction of the aldoxime derivatives with hydroxyl ions, which also yield nitriles. The logarithm of the second-order rate constants increases linearly with decrease in pK of the parent oxime.

In the preceding Paper,[1] it was pointed out that the O-acetyl-aldoximes decompose to the nitriles as well as re-forming the parent oximes. To elucidate these reactions the corresponding O-acetylketoximes were synthesised, and their decompositions in aqueous solution studied.

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[1] Part I, preceding Paper.

EXPERIMENTAL

Materials.—2-, 3-, and 4-Acetylpyridine ketoximes (2-, 3-, and 4-MPA) were prepared from 2-, 3-, and 4-acetyl-pyridine according to literature methods: [3] 2-MPA, m. p. 121°; 3-MPA, m. p. 116°; and 4-MPA, m. p. 157·5°.

The acetylpyridine *O*-acetylketoximes (MPA-*O*-Ac) were prepared by heating the oximes with an excess of acetic anhydride (25 g. in 50 ml.). The 2-derivative was heated to 80° for 25 min., the 3- and 4-derivatives to 100° for 2 hr. The reaction mixtures were cooled to room temperature, poured into ice–water, neutralised with sodium carbonate, and extracted with ether. After evaporation of the solvent, the 2- and 4-MPA-*O*-Ac solidified, and were recrystallised from dry ether. 3-MPA-*O*-Ac remained a liquid and it was distilled under a high vacuum. After some days the distillate solidified and could be recrystallised from dry ether. Analytical data for the compounds are listed in Table 1.

N-Methyl-2-, -3-, and -4-acetylpyridinium *O*-acetylketoxime iodides (2-, 3-, and 4-MPAM-*O*-Ac) were prepared from the tertiary compounds by quaternisation with an excess of methyl iodide in acetone, and purified by recrystallisation from ethanol. For additional data see Table 1.

TABLE 1

Analytical data for tertiary and quaternary acetylpyridine

O-Acetylketoximes

Compound	Yield (%)	M.p.	Found (%) C	H	I	N.	Hydrol. equiv.	Formula	Calc. (%) C	H	I	N	Hydrol. equiv.
2-MPA-*O*-Ac	72	65°	60·2	6·1	—	15·7	177	$C_8H_{11}N_2O_2$	60·65	5·65	—	15·7	178
3-MPA-*O*-Ac	40	46	60·05	5·1	—	15·65	178	,,	60·65	5·65	—	15·7	178
4-MPA-*O*-Ac	45	68	60·2	5·95	—	15·45	178	,,	60·65	5·65	—	15·7	178
2-MPAM-*O*-Ac	42 *	138	37·5	4·2	39·65	8·65	—	$C_{10}H_{13}IN_2O_2$	37·5	4·05	39·65	8·75	—
3-MPAM-*O*-Ac	78 †	115	37·25	4·0	39·6	8·65	—	,,	37·5	4·05	39·65	8·75	—
4-MPAM-*O*-Ac	56 †	129	37·8	4·1	39·7	8·4	—	,,	37·5	4·05	39·65	8·75	—

* Reaction time 4 weeks. † Reaction time 10 hr.

The *N*-methyl-2-, -3-, and -4-acetylpyridinium oxime iodides (2-, 3-, and 4-MPAM) were prepared from 2-, 3-, and 4-MPA by quaternisation with methyl iodide in acetone,[3]

TABLE 2

Analytical data of *N*-methylacetylpyridinium oxime iodides

Compound	Yield (%)	M. p.	pK 25°	pK 35°	Found (%) I	Formula	Calc. (%) I
2-MPAM	68	186	9·08	8·90	45·6	$C_8H_{11}IN_2O$	45·7
3- ,, ...	72	220	9·88	9·70	45·7	,,	45·7
4- ,, ...	68	190	9·23	9·11	45·7	,,	45·7

and purified by recrystallisation from ethanol. Determination of dissociation constants, and kinetic and spectrophotometric measurements were carried out as in Part I.[1]

RESULTS

The decompositions of 2-, 3-, and 4-MPAM-*O*-Ac were studied at constant pH using an automatic recording titrator. The alkali consumption was plotted according to the Guggenheim method. As in the previous study of the 3- and 4-PAM-*O*-Ac decompositions, straight lines were obtained, indicating first-order kinetics. The pH dependence of the rate of decomposition at 25° can be seen from Table 3.

The velocity of the decomposition, $-d[Ac]/dt$, was studied at different potassium chloride concentrations, and may be described by the reduced Brönsted–Bjerrum equation: [1]

$$-d[Ac]/dt = (k_2^{OH} \cdot f_{Ac} \cdot a_{OH} + k_2^{H_2O}[H_2O])[Ac] \qquad (1)$$

[2] A. Pinner, *Ber.*, 1901, **34**, 4241, 4251; C. Engler and W. Kiby, *ibid.*, 1889, **22**, 598.
[3] S. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.*, 1957, **78**, 481.

TABLE 3

Experimental data (log k_1 values in sec.$^{-1}$) for the decomposition of 2-, 3-, and 4-MPAM-O-Ac in 0·01 mole l.$^{-1}$ KCl at 25°

pH	2-MPAM-O-Ac	3-MPAM-O-Ac	4-MPAM-O-Ac
9·50	0·380—3	0·080—3	0·255—3
8·50	0·386—4	0·090—4	0·270—4
7·50	0·430—5	0·195—5	0·380—5
6·50	0·740—6	0·460—6	0·894—6
5·50	0·518—6	0·450—6	0·795—6

where the activity coefficient of the MPAM-O-Ac, f_{Ac}, is expressed by the equation: [1]

$$-\log f_{Ac} = 0\cdot3582\, I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) \qquad (2)$$

I = ionic concentration.

From equation (1) the experimental first-order rate constant, k_1, is given by:

$$k_1 = k_2{}^{OH} \cdot f_{Ac} \cdot a_{OH} + k_2{}^{H_2O}[H_2O] \qquad (3)$$

In Figure 1, the logarithm of k_1 is plotted against $I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})$, and the theoretical curves are drawn.

Spectrophotometric investigations of the end-products proved that hydrolysis of the MPAM-O-Ac compounds yields the oximes quantitatively. Further, the composition of sodium hydroxide of the completed kinetic runs, equal to the amount of acid produced corresponds closely to the theoretical values calculated from the dissociation constants of acetic acid and the oxime [see equation (6), Part I]. The individual second-order rate constants, $k_2{}^{OH}$ and $k_2{}^{H_2O}$, can therefore be calculated directly from equation (3). Values and additional kinetic data are listed in Table 4.

TABLE 4

Kinetic data for the decomposition of 2-, 3-, and 4-MPAM-O-Ac in the reaction with hydroxyl ions and water

Compound	Nucleophilic agent	k_2 (l. mole^{-1} sec.$^{-1}$) 25°	35°	A (l. mole^{-1} sec.$^{-1}$)	E_a (kcal. mole^{-1})	$-\Delta S^{\ddagger}$ (e.u.)
4-MPAM-O-Ac	Hydroxyl ion	63·2	118·0	$1\cdot4 \times 10^{10}$	11·4	14·0
3- ,,	,,	42·1	81·1	$2\cdot5 \times 10^{10}$	12·0	13·0
2- ,,	,,	83·3	145·0	$2\cdot2 \times 10^{9}$	10·1	17·8
4- ,,	Water	$1\cdot09 \times 10^{-7}$	$2\cdot33 \times 10^{-7}$	$1\cdot6 \times 10^{3}$	13·9	45·8
3- ,,	,,	$0\cdot48 \times 10^{-7}$	$1\cdot035 \times 10^{-7}$	$0\cdot89 \times 10^{3}$	14·0	47·0
2- ,,	,,	$1\cdot78 \times 10^{-7}$	$3\cdot74 \times 10^{-7}$	$1\cdot5 \times 10^{3}$	13·6	45·9

DISCUSSION

In the preceding Paper,[1] it was found that the alkaline decompositions of 3- and 4-PAM-O-Ac yield the parent oximes as well as the nitriles. The reactions with water, however, yield oximes only.

In the case of 2-, 3-, and 4-MPAM-O-Ac the mobile hydrogen atom of the aldehyde group is replaced by a methyl group. Nitrile formation is thus excluded, and the decompositions yield the oximes quantitatively.

The oxime formation was found to follow a second-order rate law. The ratio between the second-order rate constants for the reaction with hydroxyl ions and with water molecules $k_2{}^{OH} : k_2{}^{H_2O}$ at 25° are of the same order of magnitude as that obtained for the hydrolysis of *p*-nitrophenylacetate and the acetylimidazolium cation.[4] The difference in rate between the water and the hydroxyl-ion catalysed reactions is predominantly caused by a great increase in the entropy of activation.

The acidity of the oximes may be interpreted as proton-binding capacity. A high pK value in this case means a weak acid, and implies a relatively high negative character of the oxygen atom. The difference in acidity between the quaternary pyridinium oximes is evidently due to the difference in resonance in the conjugated systems. In the acetyloximes,

[4] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

this system includes the carbonyl group. The electrophilic character of the carbon atom of this group, which is a determining factor in the rate of hydrolytic oxime formation, would therefore be related to the acidity of the parent oxime. The relation between the second-order rate constants and the pK values of the parent oximes is given in Figure 2.

A small anomaly is observed in the reaction rates of the 2-acetylketoxime derivative, probably caused by the interaction between the carbonyl and the quaternary pyridinium groups (Field effect).

It has been known for some time that O-acetylaldoximes may exist in two geometrical forms, the *syn*- and *anti*-isomers, and that the decomposition of both forms may yield the
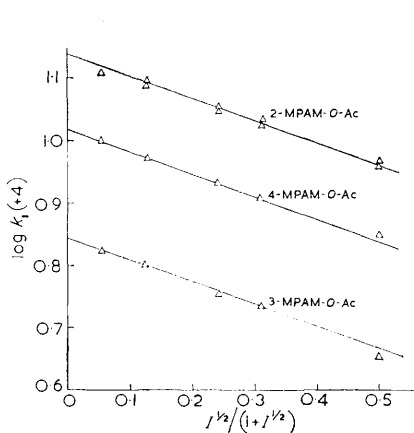

FIGURE 1. Values of $\log k_1$ (pH = 9·22, 25°) plotted against $I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})$ for the alkaline hydrolysis of 2-, 3-, and 4-MPAM-O-Ac in potassium chloride solutions. I is the total ionic concentration
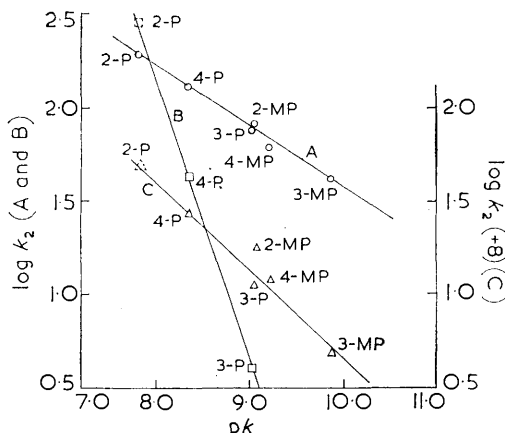
FIGURE 2. The logarithm of the second-order rate constants versus pK of the parent oxime (25°); (A) alkaline hydrolysis to oximes ($\bigcirc$), (B) alkaline hydrolysis to nitriles ($\square$), (C) hydrolysis by water ($\triangle$)

parent oximes by hydrolysis, as well as nitriles by an elimination reaction.[5] It is usually found that nitrile formation is faster from the *anti*-isomer. This leads us to investigate the following reaction scheme:

SCHEME 1
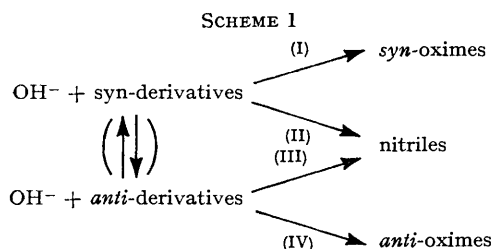
If the rate of isomerisation in aqueous solutions is relatively high, nitrile formation from the *syn* oxime O-acetate might proceed *via* the *anti*-form. The experimental results, however, show a constant ratio of nitrile to oxime for the alkaline decomposition within the whole pH range studied. This fact requires the rate of isomerisation to be improbably high ($t_{\frac{1}{2}} = 0·05$ sec., as calculated from the run in 0·1N-NaOH).

As a comparison, it may be noted that Vassian and Murmann[6] found the rate of isomerisation of phenyl-2-pyridyl ketoxime in 1N-acid and base to be very slow ($t_{\frac{1}{2}} > 4000$ min.).

[5] C. R. Hauser, E. Jordan, and R. O'Connor, *J. Amer. Chem. Soc.*, 1935, **57**, 2456.
[6] E. G. Vassian and R. K. Murmann, *J. Org. Chem.*, 1962, **27**, 4309.

As the O-acetyloxime derivatives previously studied are assigned the *syn*-configuration,[3] reactions (III) and (IV) (Scheme 1) may be neglected.

A determining factor in the rate of elimination is the positive character of the aldehyde hydrogen, which is dependent on resonance in the conjugated system. As for oxime formation, an analogous relationship between the second-order rate constant and the pK of the parent oxime is expected (see Figure 2). The theoretical rate constants for the decomposition of 2-PAM-O-Ac, which we have been unable to prepare, may thus be extrapolated from Figure 2: k_2 (oxime formation) $= 200$ l. mole^{-1} sec.$^{-1}$, k_2 (nitrile formation) $= 300$ l. mole^{-1} sec.$^{-1}$, and k_2 (reaction with water, oxime formation) $= 5 \times 10^{-7}$ l. mole^{-1} sec.$^{-1}$.

Assuming a field effect corresponding to that in the decomposition of 2-MPAM-O-Ac, the extrapolated rate constants will be minimum values.