536. *Transformations of 2-Methyl-Δ²-oxazoline in Aqueous Solution.*

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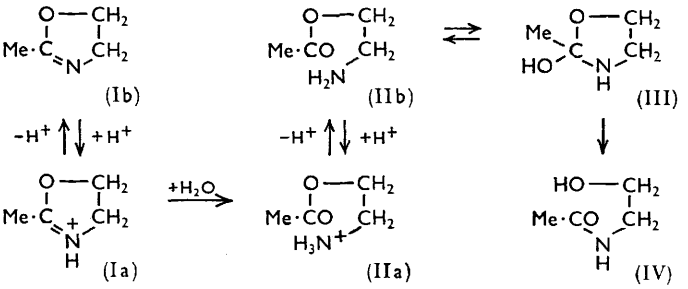
The pH of partially neutralised solutions of 2-methyl-Δ²-oxazoline changes with time, an initial rapid rise being followed by a slower fall; these changes are shown to be due to conversion into, first, *O*-acetylethanolamine, and then into *N*-acetylethanolamine. On the basis of the rates of the reactions involved it is concluded that 2-methyl-Δ²-oxazoline is not an intermediate in the conversion of *O*- into *N*-acetylethanolamine in aqueous solution.

Requiring, for another purpose,[1] to know the basic strength of 2-methyl-Δ²-oxazoline (I*b*), we attempted to determine this by the usual procedure of measuring the pH of partially neutralised aqueous solutions of the base. It was noticed that the pH of such solutions changed rapidly with time and, although pK_a was satisfactorily evaluated by extrapolation of the observed pH values to zero time, the phenomenon of an acid solution that became alkaline and then acid again with the mere passage of time seemed to warrant investigation.

As shown in Fig. 1, the pH of partially neutralised solutions of 2-methyl-Δ²-oxazoline rises rapidly during the first few hours to a maximum value and then falls more slowly, during several days, to a constant value. We are here concerned with a rapid change of a weak base into a stronger one, followed by a slower change of the stronger base into another weak one. The nature of these changes was revealed by paper chromatography. After three hours, the ninhydrin-positive *O*-acetylethanolamine (II), R_F 0·35, was the only detectable component of the solutions, whereas after three days this was accompanied by the ninhydrin-negative *N*-acetylethanolamine (IV), R_F 0·65. 2-Methyl-Δ²-oxazoline is too volatile to be detected on paper chromatograms, but its presence in the solutions for the first day or two was apparent from its characteristic odour. Clearly, the initial rapid rise of pH is due to conversion of 2-methyl-Δ²-oxazoline (pK_a 5·5) into the stronger *O*-acetylethanolamine (pK_a 8·6) which, in its turn, is converted into *N*-acetylethanolamine

[1] Porter, Rydon, and Schofield, *Nature*, 1958, **182**, 927.

($pK_a < 1$). The latter isomerisation was studied separately; the pH of a half-neutralised solution of *O*-acetylethanolamine falls, in three days, from an initial value of 8·6 to a final value of 5·2; paper chromatography showed the final solution to contain both the *O*- and the *N*-acetyl compound but the odour of the oxazoline was never detectable.



These transformations are best interpreted on the basis of the annexed reaction scheme, which is similar to, but differs in detail from, schemes which have been proposed by others.[2] The irreversibility of the migration (II) ⟶ (IV) in dilute aqueous acid (pH 1·2) was confirmed in a separate experiment.

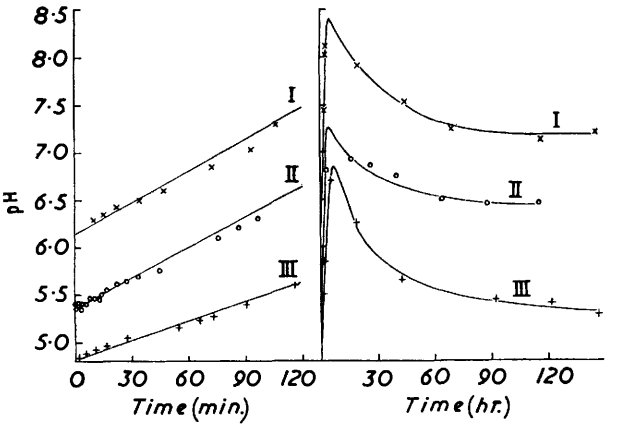


FIG. 1. *Change with time of* pH *of partially neutralised solutions of* 2-*methyl*-Δ^2-*oxazoline.*

I, 20% *neutralised*; II, 50% *neutralised*; III, 80% *neutralised.*

Since *O*-acetylethanolamine (II) is a much stronger base than the oxazoline (I), the pH during the initial part of the hydration of the latter compound to the former will be determined almost entirely by the dissociation of the cation (Ia). It may readily be shown that, in such a system, the pH at any time is a measure of the logarithm of the concentration of the cation (Ia). Let $[I]_0$ be the initial total concentration of the oxazoline (I) and y the number of equivalents of hydrogen ion added to the solution; then, adopting the usual symbolism, we have

$$[I_a]_0 = y[I]_0 \text{ and } [I_b]_0 = (1 - y)[I]_0$$

and, after a fraction, x, of the oxazoline has reacted,

$$[I_a] = (y - x)[I]_0 \text{ and } [I_b] = (1 - y)[I]_0$$

It follows that

$$\begin{aligned} \text{pH} &= pK_{a\text{I}} - \log [I_a]/[I_b] \\ &= pK_{a\text{I}} + \log [I]_0 + \log (1 - y) - \log [I_a] \\ &= \text{Constant} - \log [I_a] \end{aligned}$$

since, in any experiment, $pK_{a\text{I}}$, $\log [I]_0$, and y are constant.

[2] Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200; Elliott, *J.*, 1949, 589; Fry, *J. Org. Chem.*, 1950, **15**, 802; Konstas, Photaki, and Zervas, *Chem. Ber.*, 1959, **92**, 1288.

It will be seen from Fig. 1 that, for the first two hours, the pH rises approximately linearly with time; the slope of this straight line is $-k_1/2{\cdot}303$ where k_1 is the first-order velocity constant for the hydration of the cation (Ia). Velocity constants so calculated (mean value, $20{\cdot}5 \times 10^{-3}$ min.$^{-1}$) are collected in the Table (p. 2690); since no attempt was made to control the temperature in these experiments, the agreement between the individual values of k_1 is satisfactory. Extrapolation of the pH readings to zero time enables pK_a for 2-methyl-Δ^2-oxazoline to be calculated in the usual way; the individual values (mean, 5·51) from six experiments are also collected in the Table.

Considering now the isomerisation of the *O*-acetyl compound (II) into the *N*-acetyl compound (IV), (IIa) $\rightleftarrows$ (IIb) $\longrightarrow$ (IV), and applying reasoning similar to that used in the previous case, it can be shown that, at any time during the early part of the isomerisation,

$$\begin{aligned} \text{pH} &= \text{p}K_{a\text{II}} - y \log [\text{II}]_0 + \log [\text{IIb}] \\ &= \text{Constant} + \log [\text{IIb}] \end{aligned}$$

The pH is thus a measure of the logarithm of the concentration of unchanged (IIb) and the slope of the pH–time curve is $k_1/2{\cdot}303$, where k_1 is the first-order velocity constant for the isomerisation of (IIb). The course of this reaction, during the first two hours, plotted

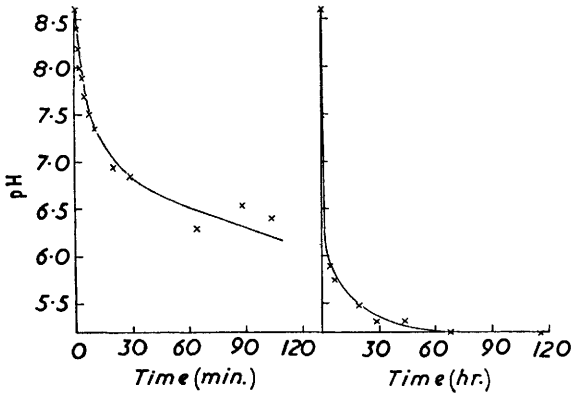


FIG. 2. *Change with time of* pH *of a half-neutralised solution of* O-*acetylethanolamine.*

in Fig. 2, shows that its apparent first-order velocity constant decreases steadily, with decreasing pH, from an initial value of 460×10^{-3} min.$^{-1}$ (pH 8·6—8·0), having an average value of 86×10^{-3} min.$^{-1}$ over the pH range 7·5—7·0 and 27×10^{-3} min.$^{-1}$ over the pH range 7·0—6·5. This slowing down of the isomerisation with decreasing pH is in accord with the generally accepted view that such *O* $\longrightarrow$ *N*-acyl migrations are catalysed by hydroxyl ions.[3]

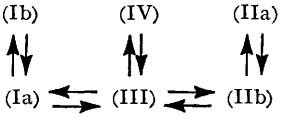
Although it is generally accepted that some form of cyclic intermediate must intervene in the isomerisation of an *O*-acyl compound, such as (II), to an *N*-acyl compound, such as (IV), there is not general agreement [3] concerning the nature of this intermediate. It may be the oxazoline, as (I), or the hydroxyoxazolidine, as (III); the intervention of the latter compound was first suggested by Bergmann, Brand, and Weinmann [4] and is strongly supported by stereochemical evidence.[5] Our results seem finally to exclude the intervention of the oxazoline in such isomerisations in weakly alkaline or weakly acid solution. For, if the isomerisation does indeed take the course (II) $\rightleftarrows$ (I) $\longrightarrow$ (IV), then the *O*-acyl compound (II) can only accumulate appreciably in the system, as we have shown it to do, if the forward reaction from (I) to (IV) is much slower than the back reaction from (I) to (II). Our finding is, however, that the formation of *N*-acetylethanolamine

[3] See Wiley and Bennett, *Chem. Rev.*, 1949, **44**, 458, and ref. 2.
[4] Bergmann, Brand, and Weinmann, *Z. physiol. Chem.*, 1923, **131**, 1.
[5] Van Tamelen, *J. Amer. Chem. Soc.*, 1951, **73**, 5773; Fodor and Koczka, *J.*, 1952, 850; Fodor and Kiss, *J.*, 1952, 1589.

(IV) from the *O*-acetyl compound (II) is as fast as, or faster than, the formation of the *O*-acetyl compound (II) from the oxazoline (I); it follows that the last-named compound cannot be an intermediate in the isomerisation of *O*-acetylethanolamine (II). It remains possible, and indeed likely, that the oxazoline may be an intermediate in the reverse process of *N* ⟶ *O*-acyl migration which requires very different, and strongly acidic, conditions.

Returning now to the transformations of 2-methyl-Δ^2-oxazoline, it is clear that, until some of the *O*-acetyl compound (II) has been converted into the *N*-acetyl compound (IV), the amount of the free oxazoline (Ib) will remain constant at its initial value. As soon, however, as any *N*-acetyl compound has been formed, hydrogen ions will become available to convert the free oxazoline into its cation (Ia), which is then available for further hydration to (IIa). Eventually, the system will contain only *N*- and *O*-acetylethanolamine, the latter in an amount equivalent to that of acid originally added. The proposed reaction scheme provides a satisfactory explanation of the findings of, *inter alia*, Goldberg and Kelly [6] and Phillips and Baltzly [2] with 2-phenyl-Δ^2-oxazoline and of Elliott [2] with the Δ^2-oxazolines derived from benzoyl-serine and -threonine and is probably generally applicable to the transformations undergone by Δ^2-oxazolines in aqueous solution.

[*Addendum*]. After this paper had been submitted for publication we became aware of the work of Martin, Lowey, Elson, and Edsall [7] on the analogous transformations of 2-methyl-Δ^2-thiazoline. These authors interpret their results in terms of a reaction scheme analogous to:



If certain assumptions are made concerning the various rate constants, such a scheme would fit our results, although there is no compelling reason why the transformations of the oxazoline should follow the same pattern as those of the thiazoline and there are, indeed, considerable differences between the two systems. It is important that, whichever scheme is used for interpretation, the oxazoline (I) is excluded as an intermediate between the *O*-acetyl compound (II) and the *N*-acetyl compound (IV).

Experimental

Paper chromatograms (descending) were run overnight on Whatman No. 1 paper, with butan-1-ol–pyridine–water (39 : 21 : 39) as developing solvent. Spots were detected with ninhydrin and by chlorination.[7]

2-Methyl-Δ^2-oxazoline, prepared by Wenker's method [8] and repeatedly distilled from potassium hydroxide, had b. p. 108—110° (Found: equiv. by titration, 87·7. Calc. for C_4H_7ON: equiv., 85·0) and was characterised as the picrate, m. p. 161—162° (lit.,[8] m. p. 163°).

N-Acetylethanolamine [8] had b. p. 120°/0·03 mm., R_F 0·60.

O-Acetylethanolamine hydrochloride, prepared by Crane and Rydon's method,[9] had m. p. 127—128° (lit.,[9] m. p. 130°), R_F 0·35. The base, b. p. 118—120°/0·1 mm., n_D^{21} 1·4690, liberated from this salt with sodium ethoxide and believed by Crane and Rydon to be *O*-acetylethanolamine, is ninhydrin-negative and does not give a picrate; it is *N*-acetylethanolamine, from which it is chromatographically indistinguishable.

pH *Measurements.*—Measurements were made, at room temperature, with a Pye Miniature pH meter, by the use of glass and calomel electrodes.

(i) 2-*Methyl*-Δ^2-*oxazoline.* A weighed quantity of the base was treated with the appropriate amount of 0·1N-hydrochloric acid and the pH of the solution determined at intervals. The

[6] Goldberg and Kelly, *J.*, 1948, 1919.
[7] Martin, Lowey, Elson, and Edsall, *J. Amer. Chem. Soc.*, 1959, **81**, 5089.
[7] Rydon and Smith, *Nature*, 1952, **169**, 922.
[8] Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079.
[9] Crane and Rydon, *J.*, 1947, 527.

results are summarised in the Table; complete curves for experiments 1, 4, and 6 are given in Fig. 1.

TABLE

Expt. no.	Equiv. of HCl	10^3k_1 (min.$^{-1}$)	pK_a	Expt. no.	Equiv. of HCl	10^3k_1 (min.$^{-1}$)	pK_a
1	0·20	25·6	5·53	5	0·80	15·4	5·46
2	0·20	21·1	5·65	6	0·80	15·1	5·43
3	0·50	23·7	5·66				
4	0·50	22·1	5·36		Mean ± S.E.	20·5 ± 1·7	5·51 ± 0·05

In all cases chromatography after 3 hr. showed the presence of only *O*-acetylethanolamine (R_F 0·36; ninhydrin-positive); after 3 days, *N*-acetylethanolamine (R_F 0·65; ninhydrin-negative, chlorine-positive) was also present.

(ii) O-*Acetylethanolamine.* The hydrochloride (0·1332 g.) was treated with 0·1N-sodium hydroxide (4·78 ml., 0·50 equiv.) and the pH of the solution determined at intervals. The results are plotted in Fig. 2.

Chromatography of the final solution showed the presence of both *O*- (R_F 0·35) and *N*-acetylethanolamine (R_F 0·60).

(iii) N-*Acetylethanolamine.* The pH of a solution of the base in 0·1N-hydrochloric acid (0·50 equiv.) was 1·2 and remained constant for 48 hr.

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