Structure–Activity Relations. Part 6.[1] The Alkaline Hydrolysis of 3-Methyl-5-methylidene- and 3,5-Dimethylthiazolidine-2,4-diones. The Addition of Thiols to 3-Methyl-5-methylidenethiazolidine-2,4-dione

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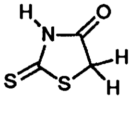
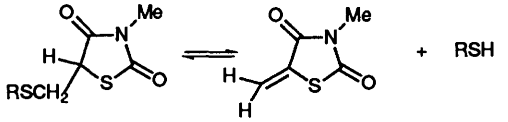
The rate-coefficients for the alkaline hydrolysis of 3-methyl-5-methylidene- and 3,5-dimethylthiazolidine-2,4-diones in water at 25.0 °C have been measured. The reaction of the 5-methylidene substrate is first order in both substrate and hydroxide ion. The reaction of the 5-methyl substrate is two-phase. The first and more rapid reaction of this substrate is 1.4 times faster than the only observed reaction of the former substrate. The second reaction is the hydrolysis of an intermediate, which is first order in substrate and has two components, one first and the other second order in hydroxide ion. The rate coefficients for the addition of a series of thiols to the 5-methylidene substrate in water at pH 7.40 have been measured. A Brønsted coefficient of *ca.* 0.37 has been found. The detailed reaction pathway and relation to Marcus and related theories are discussed.

A number of compounds containing the keto vinyl group have been shown to possess antibacterial activity.[2] Their biological activity has been considered to arise from their reaction with groups such as thiols[3] and model reactions for such systems have been studied.[1] Many derivatives of rhodanine **1** have been shown to have antibacterial and related biological activities.[4,5]



1

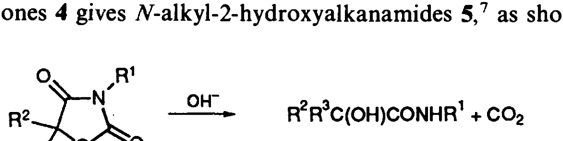
The antibacterial activities of 3-methyl-5-thioalkoxythiazolidine-2,4-diones **2** have been found to be very similar, despite variation in the alkyl group, and the activity has been considered to arise from reaction (1).[6] 3-Methyl-5-methylidenethiazolidine-2,4-dione **3** could react with nucleophilic thiol groups essential to enzyme functions.



(1)

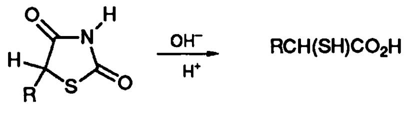
2 **3**

The alkaline hydrolysis of 3,5,5-trialkyloxazolidine-2,4-diones **4** gives *N*-alkyl-2-hydroxyalkanamides **5**,[7] as shown in reaction (2). Primary fission occurs between the 2-carbonyl group and both the oxygen and nitrogen, with the former predominating. The products of alkaline hydrolysis of 5-alkylthiazoline-2,4-diones **6** are the 2-mercaptoalkanoic acids **7**,[8] as shown in reaction (3). Further, the alkaline hydrolysis of 5-arylidene- or -alkylidene-rhodanines **8** gives the tautomeric products **9a**,**b**,[8] as shown in reaction (4). The alkaline hydrolysis of 3-methyl-1,3-thiazoline-2,4-dione **10a** has been fully investigated by Machacek *et al.*[9] and shown to proceed by two base-catalysed steps, with primary attack at the 4-carbonyl group.



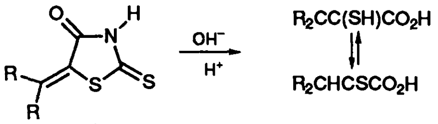
(2)

4 **5**



(3)

6 **7**

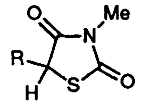


9a
9b

(4)

8

In the present study, the alkaline hydrolysis of 3,5-dimethyl and 3-methyl-5-methylidenethiazalidine-2,4-diones **10b** and **3** have been investigated. The addition of a series of thiols to the 5-methylidene substrate has been studied and the reactivity related to the nucleophilic addition process.



10 a R = H
10 b R = Me

Results and Discussion

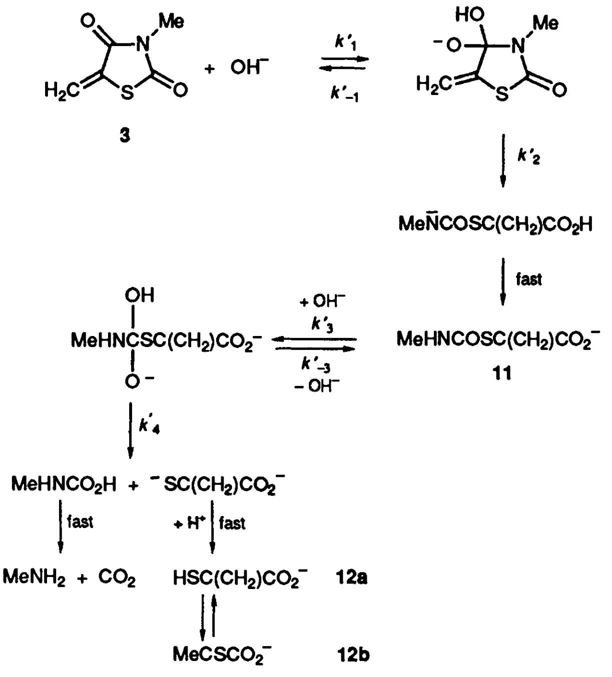
Alkaline Hydrolysis of 5-Substituted 3-Methylthiazolidine-2,4-diones.—The two 5-substituted 3-methylthiazolidine-2,4-diones are both hydrolysed in aqueous solution at alkaline pH. The product of this reaction for the 5-methylidene substrate appears to be the tautomeric 2-thiopyruvic acid **12** (see Experimental). A reaction path is shown in Scheme 1. The alkaline hydrolysis of this substrate is first order in both the substrate and hydroxide, with the observed first- and second-order rate coefficients shown in Table 1. The solvent kinetic isotope effect, $k_2^{H_2O}/k_2^{D_2O}$ = 0.80 and is very similar to the

Table 1 Rate coefficients (k_1 and k_2) for the alkaline hydrolysis of 3-methyl-5-methylidenethiazolidine-2,4-dione in water (μ = 1.0) at 25.0 °C.[a]

pH	$k_1/10^{-5}$ s^{-1}	k_2/dm^3 mol^{-1} s^{-1} [b]
8.70	3.10	6.20
8.98	6.00	6.25
9.60	23.2	5.81
9.96	56.0	6.13
10.60	278	6.97
10.97	648	6.93
11.45	2300	[8.16]

[a] The rate coefficients are reproducible to ±5%. [b] k_2 = 6.38 (±0.38) dm^3 mol^{-1} s^{-1} in water, 8.01 (±0.51) dm^3 mol^{-1} s^{-1} in deuterium oxide (see Experimental).

values observed for alkaline ester hydrolyses.[10] The rate-determining step would thus appear to be k'_1 in Scheme 1.



Scheme 1

The 5-methyl substrate has a two-phase alkaline hydrolysis reaction. A reaction path is shown in Scheme 2. The first and faster reaction produces the anion of the thiocarbamate **13**, *cf.* ref. 9. This reaction is first order both in substrate and hydroxide, with the observed first- and second-order rate coefficients shown in Table 2. The rate of the methyl substrate is *ca.* 1.4 times faster than that of the methylene substrate. This effect appears to arise from the conjugation effects in the ring which are sustained by the unsaturated 5-substituent. The small differences in the polar and steric substituent effects would be expected to operate in the opposite direction.[11] The second and slower reaction produces 2-mercaptopropanoic acid. This reaction is first order in substrate and has components which are first and second order in hydroxide, with the observed first, second and third order rate coefficients shown in Table 3. This type of behaviour has been observed previously for several *N*-methyl anilides.[12,13] However, the ratio k_3/k_2 observed in this study of *ca.* 2 × 10^3 is much greater than those previously observed[12] for other substrates. The rate-determining steps appear to be k_4' and k_5' in Scheme 2. The anion of the thiocarbamate **11** would appear to be significantly more stable to alkaline hydrolysis than **13**. This probably arises from the better leaving group in **11**.

Table 2 Rate coefficients (k_1 and k_2) for the alkaline hydrolysis of 3,5-dimethylthiazolidine-2,4-dione in water (μ = 1.0) at 25.0 °C.[a]

pH	$k_1/10^{-5}$ s^{-1}	k_2/dm^3 mol^{-1} s^{-1} [b]
10.06	109	9.48
10.50	340	10.7
11.02	965	9.19
11.46	3490	12.1

[a] See Table 1. [b] k_2 = 10.4 (±1.0) dm^3 mol^{-1} s^{-1} in water.

Table 3 Rate coefficients (k_1, k_2 and k_3) for the alkaline hydrolysis of **13** in water (μ = 1.0) at 25.0 °C.[a]

pH	$k_1/10^{-5}$ s^{-1}	$k_1[\mathrm{OH}^-]^{-1}$/dm^3 mol^{-1} s^{-1} [b]
10.90	15.0	0.188
11.42	118	0.447
11.72	437	0.831
12.00	1500	1.50

[a] See Table 1. [b] $k_1[\mathrm{OH}^-]^{-1} = k_2 + k_3[\mathrm{OH}^-]$ giving k_2 and k_3 = 0.074 (±0.004) dm^3 mol^{-1} s^{-1} and 143 (±8) dm^6 mol^{-2} s^{-1}.

Addition of Thiols to 3-Methyl-5-methylidenethiazolidine-2,4-dione.—The addition reaction is first order in both substrate and thiols. Table 4 shows the rate coefficients for the addition of the thiols in water at pH 7.40 and at 25.0 °C, together with the known pK_a values of the thiols.[14] Under these conditions the substrate is not hydrolysed by hydroxide and the thiols do not cause ring fission. This selectivity must arise from hard–soft acid–base factors. Scheme 3 shows the suggested mechanistic pathway. The effect of structural changes on kinetic basicities and nucleophilicities can be correlated by means of the Brønsted eqn. (1). The factor β has been interpreted as a

$$\log k_b = \beta \log K_b + \log G_b \qquad (1)$$

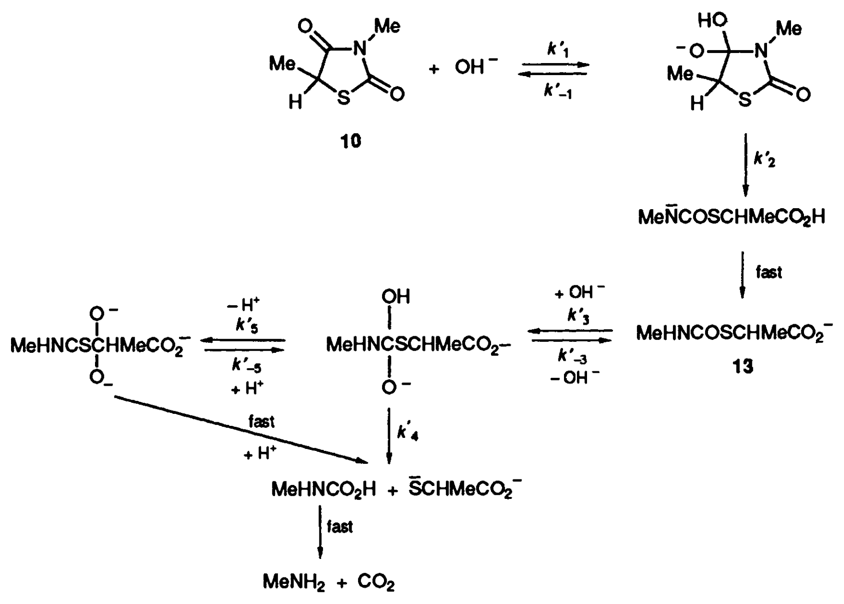
parameter which measures the extent to which the transition state resembles reactants and products.[15] Values of *ca.* unity indicate a transition state resembling the products and *ca.* zero resembling the reactants. However, values >1 and <0 have been reported.[16,17] It has been suggested[17] that the Brønsted coefficients should be regarded only as a 'rough' qualitative guide to transition state structure. The relation between log k_2 for the addition and the pK_a values of the thiols are shown in Fig. 1. The Brønsted equation correlation, excluding the thiols 1 and 11, Table 4, is given in eqn. (2). Thus, the β value

$$\log k_2 = 0.367 \log K_a - 1.946 \qquad (2)$$
$$n = 10, s = 0.051, r = 0.922$$

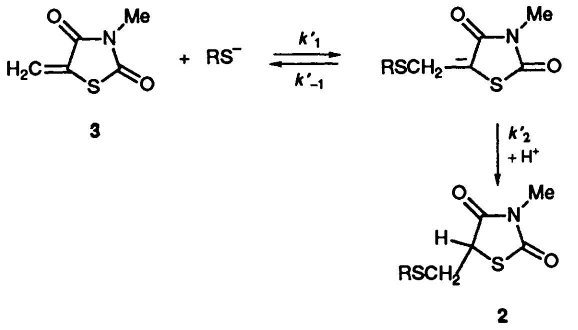
of *ca.* 0.3 indicates an 'early' transition state with the carbanion only partially developed. The large negative deviations observed for 2-mercaptopropanoic (as the carboxylate anion) and mercaptosuccinic acid (as the carboxylate dianion) appear to be related to extra electrostatic and/or steric effects present in the transition state, similar to related effects noted in vinyl ether hydrolyses.[18] Bernasconi[19] has suggested an approach based on the formalisation provided by Marcus theory. Eqn. (3) below

$$\log k_0 = \log k_1 - \beta \log K_1 \qquad (3)$$

relates the intrinsic rate coefficient, k_0, to the forward rate coefficient for addition k_1, for the situation where $\Delta G° = 0$, *i.e.* $K_1 = 1$. Basing the calculation here on 3-methyl-5-methyl-



Scheme 2



Scheme 3

Table 4 Rate coefficients (k_2) for the addition of thiols to 3-methyl-5-methylidenethiazolidine-2,4-dione in water at pH 7.40 (μ = 1.0) at 25.0 °C.[a]

Thiol	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}	pK_a[b]
1 2-Mercaptopropanoic acid	14.8	10.20
2 n-Butyl hydrosulphide	165.$_5$	10.66
3 2-Mercaptoethanol	32.8	9.61
4 *N*-Acetyl-L-cysteine	26.3	9.52
5 3-Mercaptopropionic acid	37.1	10.20
6 Ethyl hydrosulphide	125	10.61
7 Benzyl hydrosulphide	39.8$_5$	9.43
8 Mercaptoacetic acid	48.7$_5$	10.25
9 L-Cysteine	12.5$_5$	8.32
10 Glutathione	12.3	8.56
11 Mercaptosuccinic acid	8.17$_5$	10.22
12 Methyl thioglycolate	10.6$_5$	7.68

[a] See Table 1. [b] Lit.,[14] values.

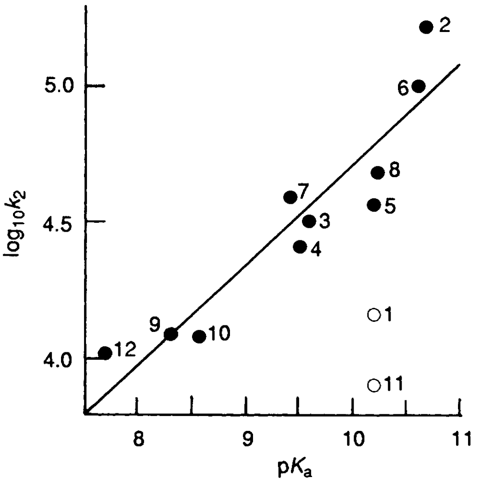
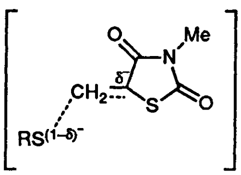


Fig. 1 Relation between log k_2 for the addition of thiols to 3-methyl-5-methylidenethiazalidine-2,4-dione and their pK_a values in water at 25.0 °C

idenethiazolidine-2,4-dione and benzyl hydrosulphide, log k_0 can be estimated as *ca.* 6, *cf.* ref. 20. This high intrinsic barrier[19] in water as solvent is associated with a lack of synchronisation between events such as bond formation/cleavage, development of resonance interactions, solvation/desolvation, *etc.* In the present case it would appear to be very much a function of the addition being of a thiol, as well as a lack of development of resonance interactions. The rate-determining step appears to be k'_1 in Scheme 3 and the transition state is shown as **13** below.



13

Experimental

Materials.—3,5-Dimethyl and 3-methyl-5-methylidenethiazolidine-2,4-dione were kindly donated by Dr. C. Smith of Rhone-Poulenc Ltd, Dagenham Research Centre. The thiols were obtained commercially and were recrystallised or redistilled until their physical properties were in satisfactory agreement with literature values. Inorganic salts were of analytical grade and were used without further purification.

Measurements.—Rate measurements of the hydrolyses and addition of thiols were performed by observing the changes in absorbance of the reaction solution using a Pye-Unicam SP8000 UV-VIS spectrophotometer or SF-3A stopped-flow spectrophotometer MKIV. The former was used for 'slow' reactions and the cell temperature was controlled to ± 0.05 °C by means of a Churchill thermocirculator. The reaction solvents were aqueous phosphate (pH 7.0–8.0) and borate (pH 7.8–10.6) buffers and sodium hydroxide (pH 10.5–12.0), adjusted to μ = 1.0 with NaCl. The pD values were obtained by adding 0.40 to the pH meter reading.[21] The solution (3 cm^3) in 1 cm cell fitted with a silicone rubber serum cap was flushed with oxygen-free nitrogen *via* inlet and outlet syringe needles. The substrate, dissolved in ethanol (spectroscopic grade, 3 mm^3) was injected into the cell with a Hamilton syringe such that the final concentration in the cell was *ca.* 1×10^{-4} mol dm^{-3}. The substrates hydrolysed very slowly > pH 8.50. The hydrolysis reactions were monitored at 280 nm (5-methylidene), 230 nm (5-methyl, primary reaction), and 240 nm (5-methyl, secondary reaction). Absorbance was displayed as a function of time at constant wavelength on a Unicam AR25 recorder and reactions were regarded as complete after ten half-lives. Good first order behaviour in substrate was found and the rate coefficients were evaluated as described previously.[22] The rates of addition were measured using both spectrophotometers, using the stopped-flow spectrophotometer half-lives < 8 s. At pH 7.40 the substrate does not undergo significant hydrolysis. The substrate was added as before and the thiol dissolved similarly (5–30 mm^3 of 0.1 mol dm^{-3}) was injected into the thermostatted cell. On completion of the kinetic runs the spectra indicated complete conversion of the substrate to product of addition by comparison with that of the product studied under identical conditions. The addition reactions were monitored at 280 or 284 nm for *N*-acetyl-L-cysteine. The first-order rate coefficients were obtained as before and good plots were obtained up to 80% reaction. The reaction was found to be first order in thiol. The second-order rate coefficients were calculated by dividing the first-order rate coefficient by the fraction, α, of thiols in their anionic form. The fraction is obtained from the known pH and pK_a values using the Henderson–Hasselbalch eqn. (4). The

$$\mathrm{pH} = \mathrm{p}K_a + \log \frac{\alpha}{1 - \alpha} \qquad (4)$$

second-order rate coefficients were checked by the method devised by Corbett,[23] which can be applied even if the excess used is only twofold.

Product Analysis.—The final product of the alkaline hydrolysis of the 5-methyl substrate was shown to be 2-mercaptopropanoic acid. The alkaline solution was acidified with concentrated hydrochloric acid at 0 °C and then subjected to freeze-drying. Extraction with dichloromethane gave the acid which was shown to be identical with an authentic sample characterised by m.p., ^1H and ^{13}C NMR and IR spectroscopy. It was not possible to isolate the pure intermediate product.

The product of the alkaline hydrolysis of the 5-methylene substrate was found to be impossible to isolate in pure form. The alkaline solution was acidified as above and then extracted with dichloromethane. The pale yellow oil isolated appeared to be composed of two components by TLC but could not be resolved. The product gave a positive result with Ellman's reagent and was studied by ^1H and ^{13}C NMR and IR spectroscopy. Comparison of these spectra with those of the starting material and pyruvic acid indicated the product to be a mixture of 2-thiopyruvic acid (or the ene thiol form) and the disulphide derived from the latter, 2-mercaptoacrylic acid. The latter appears to be derived by oxidation from the ene thiol form of the 2-thiopyruvic acid,[8] despite conducting the reaction under nitrogen.

The products of thiol addition to 3-methyl-5-methylidenethiazolidine-2,4-dione have been found to be the 3-methyl-5-thioalkoxythiazolidine-2,4-diones in quantitative yield.[6]

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