Acta Chemica Scandinavica B 38 (1984) 101–108

Preparation and Stability of 1,4-Oxathian-2-ones

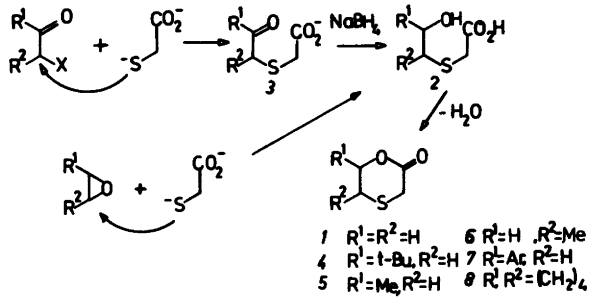
JORMA K. KOSKIMIES

Department of Chemistry, University of Helsinki, Vuorikatu 20, SF-00100 Helsinki 10, Finland

Several methods of preparation of various substituted 1,4-oxathian-2-ones are described, including the acid-catalyzed ring closure of δ-hydroxy acids, prepared *via* α-halo ketones or α-halo acids, and the base-catalyzed ring closure of β-haloethyl thioglycolate. 1,4-Oxathian-2-one is completely hydrolyzed in D_2O to the hydroxy acid at a rate comparable to the hydrolysis of δ-valerolactone. The rate of the lactonization is estimated to be *ca.* 100 times smaller in oxathianone than in valerolactone.

1,4-Oxathian-2-one (*1*), a rather obscure heterocyclic analogue of δ-valerolactone, is structurally interesting for the effect of the sulfur atom on the lactone ring.[1] A benzo derivative has been cited for physiological activity [2] and the 3-acetyl derivative has been reported to be a hydrolysis product of an oxathiene fungicide.[3] Few papers have been published on the synthesis of 1,4-oxathian-2-ones.[4,5] The lactone ring has been made by acid-catalyzed ring closure of 2-hydroxyethylthioacetic acid or its derivatives. This acid was obtained from an epoxide and thioglycolic acid[5–7] (Scheme 1) or by radical addition of thioglycolic acid to a vinyl ester followed by hydrolysis of the resulting ester.[4]

Since no suitable epoxides were at hand, another approach for the synthesis of 2-hydroxyethylthioacetic acids (*2*) was investigated. This new procedure starts from an appropriate α-bromo (or chloro) ketone which is readily available by direct bromination. Nucleophilic displacement of bromide by the thioglycolate dianion affords δ-keto acid *3*, which is then reduced with sodium borohydride to give the desired acid. The resulting δ-hydroxy acid *2* is converted to the lactone (*1*) by conventional acid-catalyzed esterification (Scheme 1). This procedure, which takes advantage of the increased S_N2-reactivity of α-halo ketones, can be conveniently carried out in one pot. Thus, for example, the reaction of α-bromopinacolone with thioglycolate dianion readily gives the keto acid (*3*: $R^1=(CH_3)_3C$-, $R^2=H$), which without isolation, was reduced by adding sodium borohydride to the ethanolic solution. The resulting crude hydroxy acid was then dissolved in benzene and heated in presence of a catalytic quantity of acid to afford lactone *4*. This method, which is useful in preparation of



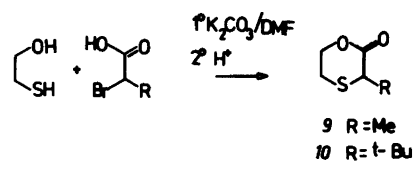
Scheme 1.

0302-4369/84 $2.50

6- and 5,6-substituted oxathianones, gives isomerically purer products than the epoxide method. For example, 6-methyl-1,4-oxathian-2-one (*5*), prepared from chloroacetone by the present method, is quite pure, whereas the compound made from propylene oxide contains a small amount of an isomeric impurity and requires tedious purification.[8] The preparation of oxathianones lacking substituents at the 6-position requires use of rather labile α-halo aldehydes and to avoid use of these materials other methods were employed: 5-Methyl-1,4-oxathian-2-one (*6*) was made from 1-propenyl acetate according to Baldwin[4] and the parent compound (*1*) from 2-chloroethanol and thioglycolic acid dianion.[9] The following oxathianones were prepared from α-halo ketones: 6-Methyl- (*5*), 6-*tert*-butyl- (*4*) and 6-*p*-bromophenyl-1,4-oxathian-2-one (*7*) as well as 2-oxa-5-thiabicyclo[4.4.0]decan-3-one (*8*). The bromo ketones were obtained by direct bromination of the appropriate ketones.

Oxathianones with substituents at the C(3) position were prepared from hydroxy acids (Scheme 2) available from α-bromo acids *via* novel nucleophilic displacement of bromide by 2-hydroxyethanethiolate. The substitution reaction was accomplished in *N,N*-dimethylformamide at 80 °C and gave a reasonable yield even in the case of the sterically hindered 2-bromo-3,3-dimethylbutanoic acid. Both 3-methyl- (*9*) and 3-*tert*-butyl-1,4-oxathian-2-one (*10*) were obtained in this way but the substitution reactions were not clean and the lactones had to be purified by column chromatography.

All oxathianones were characterized by the usual methods and new compounds were characterized by high resolution mass spectrometric analysis. The ^{1}H NMR spectra of known compounds were found to be similar to those reported in the literature. Preparation of 2-oxa-5-thiabicyclo[4.4.0]decan-2-one (*8*) gave a roughly 1:1 mixture of *cis* and *trans* isomers (*8c* and *8t*). The structural assignment of the *trans* lactone (*8t*), obtained in pure form by repeated crystallization, was based on the magnitude of the vicinal coupling constant (10.5 Hz) between the bridgehead protons that is typical for 1,2-diaxial protons in the cyclohexane ring.[10] This assignment was, moreover, confirmed by the chemical evidence: the same *trans* lactone was obtained from the reaction of cyclohexene oxide with thioglycolate dianion which is known to proceed *via trans*-ring opening.

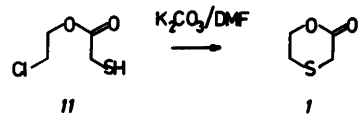


9 R=Me
10 R=t-Bu

Scheme 2.

Surprisingly, the lactonization of δ-hydroxy acids *2* proved difficult as it was complicated by a relatively fast intermolecular esterification leading to polymeric products. The ring closure was affected by *p*-toluenesulfonic acid catalyst in refluxing benzene or toluene with azeotropic removal of water and, not unexpectedly, a long reflux period and high dilution increased the yield of lactone. Nevertheless, the overall yields were often quite low (*ca.* 20 % for the parent compound *1*) because of the strong tendency of both the intermediate hydroxy acid and the lactone product to undergo polymerization. It was sometimes necessary to use chromatography for the separation of the lactone from polymeric by-products, since mere distillation often caused decomposition of the lactone and thus lowered the yield. The polymerization of 2-hydroxyethylthioacetic acid[4,11] and oxathianones[5] has been noted by other investigators. The substituted hydroxy acids are also known to polymerize but this reaction becomes less important with increasing steric bulk of the substituents, and some of these acids lactonize spontaneously rather than form intermolecular ester linkages. A similar trend is seen in polymerization/decomposition of pure liquid oxathianones: the parent compound deteriorates rapidly at room temperature while, for example, 6-*tert*-butyloxathianone (*4*) is stable. The polymerized lactones display a ^{1}H NMR spectrum which is compatible with a straight-chain ester, oligo- or polyester, containing variable amounts of free hydroxyl groups. Thus the polymerization is probably initiated by water (from air) or trace amounts of acid or base.

Since the preparative methods described above often gave lactones in low yields and of unsatisfactory purity, other means of ring closure were explored. The use of an acidic ion exchange resin[8] instead of a soluble acid catalyst was an improvement, because the catalyst could be easily removed from the product so that possible acid-induced decomposition of the lactone could

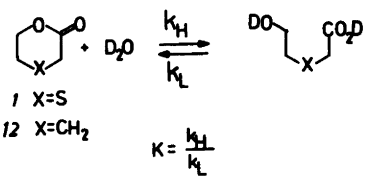


11 *1*

Scheme 3.

be avoided during the isolation stage. It was found that the lactonization could be affected under still milder conditions by stirring the acid in dichloromethane solution at room temperature with an ion-exchange resin and molecular sieves. Although this method gave product in nearly as high a yield as the azeotrope method, a considerable amount of polymeric material was formed. Due to the facile polymerization observed in the acid-catalyzed lactonization of the hydroxy acids, it was thought expedient to avoid this stage of synthesis altogether. Indeed, a product of excellent purity was obtained when the order of steps in the synthesis was reversed. Thus, 2-chloroethylthioglycolate (*11*) was converted to oxathiane *1* by anhydrous potassium carbonate in *N,N*-dimethylformamide at 80 °C (Scheme 3) and the isolated product was free of polymer. The low yield (27 %) may be due to the water solubility and the instability of the lactone (*1*) in water, which makes its separation from the solvent difficult. A mixture of 5- and 6-methyl lactones *6* and *5* was obtained from a mixture of corresponding chloropropyl esters in fair yield (56 %) when the work-up procedure was changed so that no water was employed. Use of other bases for the ring formation, such as potassium-*tert*-butoxide or triethylamine, gave poorer yields.

A quantitative measure of the stability of 1,4-oxathian-2-one compared to other six-membered lactones was obtained by comparison of its hydrolysis in deuterium oxide (studied by ^{1}H NMR spectroscopy (Scheme 4)) with that of δ-valerolactone (*12*). The hydrolysis probably



Scheme 4.

proceeds by an $A_{Ac}2$-mechanism with specific acid catalysis.[12,13] Since the pseudo-first order rate constant is dependent on the variable acid concentration[13] the reaction must be treated as a second-order autocatalytic reaction,[14] first order in lactone and first order in acid. The second-order rate constant was found to be k_H=0.19 l mol^{-1} min^{-1}. 10 % of acetone-d_6 was added to increase the solubility. This is likely to increase the rate constant k' by *ca.* 10 % compared to the value in pure D_2O.[15] The hydrolysis appears to go to completion and, based on the found limit of detection of the lactone in the ^{1}H NMR spectrum, the lower limit for the equilibrium constant, K=[acid]/[lactone], is estimated to be 100. From this estimate an upper limit on the rate of the reverse reaction (lactonization) is $k_L=1.9\times10^{-3}$ l mol^{-1} min^{-1}. For comparison, the hydrolysis of δ-valerolactone was investigated under the same conditions and was found to proceed at a rate of k_H=2.20 l mol^{-1} min^{-1} to an equilibrium mixture with K=8.8. The hydrolysis rate agrees well with that of Wheeler (2.2 in 0.02 N hydrochloric acid),[12] while the equilibrium constant, lower than that reported by the same author (16.2), agrees well with other figures reported in the literature.[16] The rate of lactonization to δ-valerolactone was found to be k_L=0.25 l mol^{-1} min^{-1}. Comparison of the results for the two substances shows that oxathianone *1* is kinetically more stable in water than valerolactone by a rate factor of about 10. Conversely, the rate of formation of oxathianone is much less than that of valerolactone by at least a factor 130 (0.25/0.0019). Thus the formation oxathianone is about as slow as lactonization to give ε-caprolactone.[17] This is clearly responsible for the slow intramolecular reaction observed during the synthesis of these compounds, allowing the intermolecular esterification to become important. The decreased rate probably reflects the increased angular strain in the cyclic transition state leading to the oxathianone ring, though an entropy effect caused by the longer chain cannot be excluded. During the preparation of oxathianones it was found that substituted oxathianones were often formed more readily from their hydroxy acid precursors than was the parent compound. A similar trend has been observed in methyl-substituted δ-valerolactones.[12]

The large equilibrium constant (K>100) in the hydrolysis of oxathianone confirms the suspected

instability of the ring system (for $K>100$ $\Delta G°$ becomes smaller than −11 kJ/mol). In other words, oxathianone is at least 6 kJ/mol less stable than δ-valerolactone with respect to ring opening. The reason behind this extra instability is evidently the angular strain in the ring arising from the incompatible geometric requirements exerted by the ester moiety (planarity) and the aliphatic sulfide chain (strongly puckered). The increased energy content of oxathianone may also be due to the unfavourable dipole–dipole interaction between the near-by ester and sulfide groups. The strain will probably affect the conformational situation in oxathianone. The carbocyclic valerolactone is known to prefer the half-chair form[18] with the other possible conformation, the classical boat, lying 2.5 kJ higher in energy.[19] The effect of the sulfur atom in oxathianone is to lower somewhat the energy of the boat (the eclipsing C–H interactions at C-5 and C-6 are absent) and to raise the energy level of the half-chair (deformed bond angles) so that the conformational equilibrium may be actually reversed. Indeed, in the solid state oxathianone 7 is known to assume the boat conformation.[20] The preference for a boat conformation would also serve to explain the slightly higher activation energy observed in the hydrolysis of oxathianone, since the transition state with boat-like conformation would be of higher energy than a more normal chair-like transition state.

The qualitatively observed fact, that the oxathianones become more stable as the number of substituents increases, has also been observed in δ-valerolactones[12,21] In the latter compounds this was shown to be due to the increased rate of lactonization.[12] Although the present compounds do not contain *gem*-dialkyl groups this phenomenon is similar to the *gem*-dimethyl effect[17, 22] which is thought to arise from a combination of a favourable enthalpy effect (the number of *gauche* interactions in the ring is less than in the open chain acid) and an entropy effect (resulting from the increased restriction of rotation in the acid form on chain branching or bulkier substituents). The order of magnitude of this effect in oxathianones seems to be about the same or even larger than in valerolactones. For example, bicyclic oxathianone *8* was found to form spontaneously to the extent of 50 % from the corresponding hydroxy acid (*i.e.* K≈1) which agrees well with the reported equilibrium constant of 0.89 for the lactone analogue.[21] Thus, variously substituted oxathianones are as stable as analogous valerolactones towards hydrolysis, even if there is a marked difference in stability between the parent compounds.

EXPERIMENTAL

Melting and boiling points are uncorrected. The ^{1}H NMR spectra were recorded with JEOL JMN PMX60 spectrometer (60 MHz). The sample concentrations varied between 5–20 % v/v and the standard was internal tetramethylsilane. IR spectra were recorded with Perkin Elmer 125 Grating Infrared Spectrometer as neat films between sodium chloride plates or as KBr pellets (solids). High resolution mass spectra (molecular weights) were run on a JEOL JMS-D 100 instrument.

The oxathianones were prepared according to the following general procedures.

Method A. Thioglycolic acid (0.10 mol) was neutralized with two equivalents of aqueous sodium hydroxide under a nitrogen atmosphere and the α-halo ketone in ethanol was added to the resulting solution. The keto acid thus formed was reduced by adding 0.05 mol of sodium borohydride. After stirring overnight, the solution was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated to afford the crude hydroxy acid, which was dissolved in 300–400 ml of benzene (or toluene) containing a catalytic quantity of acid. The contents of the flask, equipped with a Dean-Stark trap and a condenser, were heated at reflux for several days until lactone formation appeared to be complete (as detected by ^{1}H NMR). The acid catalyst was then neutralized by addition of potassium carbonate and the mixture was filtered. Removal of the solvent in a rotary evaporator gave the crude lactone, which was purified by distillation, recrystallization or chromatography (silica, benzene) as appropriate.

Method B. This is essentially the procedure of Kelstrup.[8]

Method C. N,N-Dimethylformamide (DMF, 100 ml) was dried by distillation with some added benzene (15 ml). The appropriate 2-haloethyl thioglycolate (0.15 ml) in DMF was added slowly to a stirred and heated (80–90 °C) mixture of 0.08 mol of anhydrous potassium carbonate in the DMF under nitrogen. Following complete addition, the solution was heated for an additional hour. The product was isolated by addition of ether followed by filtration of the mixture. The

Table 1. Preparative data on 1,4-oxathian-2-ones.

Compound	Method[a]	Starting material	Ring closure[b]	Yield %	Bp./Mp., °C/mmHg
4	A	α-Bromopinacolone[23]	TSA	45	81–85/0.04
8	A	2-Bromocyclohexanone[24]	TSA	83[c]	129–140/0.12
8t				20[d]	88–89
8t	B	Cyclohexene oxide	TSA	81	
7	A	*p*-Bromophenacylbromide[25]	Resin	70	132–132.5
5	A	Chloroacetone	Resin	51[e]	86–96/0.1 (lit.[8] 72/0.25)
	B	Propylene oxide	TSA	53[f]	
	A	Propylene oxide	Resin & molecular[g] sieves	35	
	C	1-Methyl-2-chloroethyl[h] thioglycolate	KO-*t*-Bu/*t*-BuOH	7[i]	
	C	1-Methyl-2-bromoethyl[j] thioglycolate	K_2CO_3/CH_3CH	11	
	C	1-Methyl-2-chloroethyl[h] thioglycolate	K_2CO_3/DMF	56[k]	
1	D	Chloroethanol	TSA	10	131/11 (lit.[5] 62–65/0.2
	E	Vinyl acetate	TSA	10	
	C	Chloroethyl thioglycolate	K_2CO_3/DMF	26	
	C	Chloroethyl thioglycolate	K_2CO_3/THF	18	
6	E	Propenyl acetate[4]	Resin	50	82/0.11 (lit.[4] 75/0.1
10	F	2-Bromo-3,3-dimethylbutanoic[26,l] acid	TSA	49[m]	170/10[n]
9	F	2-Bromopropanoic acid	TSA	83[m]	130–140/0.1[n] (lit.[5] 80–82/0.3)

[a] See text. [b] TSA=*p*-toluenesulfonic acid, refluxing benzene; resin=Dowex 50×8 acidic ion exchange resin, refluxing benzene. [c] *cis*/*trans* mixture (1:1). [d] Fractional crystallization from ether. [e] Isomerically pure product. [f] Contains an isomeric impurity, probably *6*. [g] Ring closure with resin and 4Å molecular sieves, CH_2Cl_2, room temperature; yield calculated from the hydroxy acid. [h] A mixture of isomers: 1-methyl-2-chloroethyl and 2-chloropropyl ester (3:2). [i] Starting material: lactone=2:1. [j] A mixture of isomers (see h) 2:1. [k] Lactones *5* and *6* in ratio 3:2. [l] Prepared by bromination[27] of 3,3-dimethylbutanoic acid.[28] [m] Slightly impure; analytical sample purified by TLC (silica, benzene). [n] Distillation carried out in a bulb-to-bulb distillation apparatus (Kugelrohr); the temperature refers to the outside bath temperature.

resulting filtrate was concentrated by removal of the solvents *in vacuo* (bath 40–50 °C, 0.3 mmHg) and the residue was distilled to afford pure oxathianone.

Method D. Aqueous sodium hydroxide (26 g, 0.65 mol) was added slowly to a solution of chloroethanol (25 ml, 0.37 mol) and 80 % aqueous thioglycolic acid (28 ml, 0.37 mol). After 2 d the mixture was acidified (HCl) and extracted continuously with ether. The resulting hydroxy acid was quickly lactonized as desribed in Method A.

Method E. The procedure of Baldwin *et al.*[4] was used.

Method F. The bromoacid (0.10 mol) in DMF was added slowly to a mixture of mercaptoethanol (0.14 mol) and potassium carbonate (0.20 mol) in DMF (*ca.* 100 ml) under nitrogen. The reaction mixture was heated in a water bath for 25 h. The resulting solution was diluted with water, acidified and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated on a rotary evaporator and finally on an oil pump (*ca.* 0.1 mm). The crude hydroxy acid residue was esterified as described in Method A.

The preparative data are listed in Table 1 and the spectral data in Table 2. The spectra of known compounds were found to correspond with the data reported in the literature.

Polymerization of 1,4-oxathian-2-one (1). On standing at room temperature lactone *1*, a vola-

Table 2. Spectral data for 1,4-oxathian-2-ones and precursors.

Compound	IR cm^{-1} (C=O)	NMR δ [a]	Exact mass
4	1745	1.04(9H, s), *ca.* 2.9(2H, m), 3.38(2H, AB, J=15 Hz), 4.10(1H, dd, J=10 Hz, J=4 Hz)	174.0706 obs. 174.0711 calc.
8t	1723	1.0–2.4(8H, m), 2.66–3.5(3H, m and AB, ν(AB)=3.47, J=14.8), 4.2(1H, dt, J=4.5 Hz, J=10 Hz).	172.0542 obs. 172.0555 calc.
8c [b]		1.0–2.4(m), 3.32(m), 3.37(AB, J=14.9 Hz) 4.62(m).	
7	1740(KBr) 1750($CHCl_3$)	3.0(2H, m), 3.38(2H, AB, J=14.8 Hz),5.4(1H, dd, J=6.5 Hz, J=7.5 Hz), 7.37 (4H, AB, J=8 Hz)	273.9472 obs 273.9486 calc.
10	1735	1.20(9H, s), 3.03(2H, m), 3.53(1H, s) 4.50(2H, m)	174.0722 obs. 174.0711 calc.
9	1735	1.47(3H, d, J=7 Hz), 2.93(2H, m), 3.51 (1H, q, J=7 Hz), 4.30(2H, m)	132.0223 obs. 132.0243 calc.
6,6-Dimethyl-5-oxo-3-thia-pentanoic acid		1.20(9H, s), 3.31(2H, s), 3.68(2H, s), 9.87(1H, s)	
5-*p*-Bromophenyl-5-hydroxy-3-thia-pentanoic acid		2.28(2H, t, J=4 Hz), 3.32(2H, s), 4.78(1H, dd, J=5 Hz, J=8 Hz), 6.67(1H, br. s), 7.33(4H, AB, J=8.8 Hz)	
2-*tert*-Butyl-5-hydroxy-3-thia-pentanoic acid		1.15(9H, s), 2.90(2H, t, J=4.5 Hz), 3.13(1H, s), 3.77(2H, t, J=6 Hz), 6.27(2H, br. s).	

[a] dd=doublet of doublets; dt=doublet of triplets. [b] Not obtained pure, impurity the *trans* compound.

tile liquid, is converted to a thick, high-boiling substance which may harden to a white solid. NMR($CDCl_3$) δ lactone: 3.00(2H, m), 3.40(2H, s), 4.53(2H, m); polymer: 2.95(2H,t, J=6.5 Hz), 3.37(2H, s), 4.37(2H, t, J=6.5 Hz), 5.50 (0.4 H, br. s).

Polymerization of 6-methyl-1,4-oxathian-2-one (5). When lactone *5*, a liquid, is stored at room temperature for long periods, it turns viscous and the NMR spectrum shows that the lactone has completely disappeared. A similar phenomenon is also observed in solutions of the lactone. NMR($CDCl_3$) δ lactone: 1.50(3H, d, J=6.5 Hz), 2.5–3.0(2H, m), 3.37(2H, AB, J=14.5 Hz), 4.60(1H, m); polymer: 1.37(3H, d, J=6 Hz), 2.85(2H, d, J=6 Hz), 3.32(2H, s), 5.17(1H, sextet), 5.78(0.8 H, br. s).

2-Chloroethyl thioglycolate (11) was prepared by acid-catalyzed esterification of chloroethanol and thioglycolic acid in 69 % yield; b.p. 110 °C/ 19 mmHg; NMR($CDCl_3$) δ 2.07(1H, t, J=8.5 Hz), 3.33 (2H, d, J=8.5 Hz), 3.71(2H, t, J=6 Hz), 4.38(2H, t, J=6 Hz).

Methyl-2-chloroethyl thioglycolate. Propylene chlorohydrin was made by adding propylene oxide (50 ml, 0.69 mol) to 150 ml of cold 37 % hydrochloric acid. This chlorohydrin was esterified with 65 ml (0.72 mol) of 80 % aqueous thioglycolic acid using *p*-toluenesulfonic acid catalyst and benzene for the azeotropic removal of water. The resulting ester solution was washed with brine and aqueous bicarbonate, dried ($MgSO_4$) and concentrated. Distillation gave 45 g (39 %) of the product which consisted of two isomeric esters in ratio 3:2, b.p. 108–114 °C/16 mmHg. NMR($CDCl_3$) δ major isomer: 1.36(3H, d, J=6.5 Hz), 2.04(1H, t, J=8 Hz), 3.33(2H, d, J=8 Hz), 3.60(2H, J=5 Hz), 5.12(1H, sextet, J=6 Hz).

Methyl-2-bromoethyl thioglycolate was prepared from propylene oxide, hydrobromic acid and thioglycolic acid in 54 % yield following a procedure similar to that described above, b.p. 112 °C/0.5 mmHg. NMR($CDCl_3$) δ major isomer: 1.38(3H, d, J=6.5 Hz), 2.15(1H, t, J=7.5 Hz), 3.33(2H, d, J=7.5 Hz), 3.55(2H, d, J=5.5 Hz), 5.05(1H, sextet, J=6 Hz). The product contained also 29 % of 2-chloropropyl thioglycolate as determined by NMR.

The reaction kinetics. About 200 mg of lactone was dissolved in D_2O in an NMR tube (in the case of oxathianone *ca.* 10 % v/v of acetone-d_6 was added for solubility). The appearance of the hydroxy acid was followed by ^1H NMR. The relative concentrations of the lactone and the hydroxy acid were calculated from the integral

signals of the protons at carbons 3 and 5. The rate equation can be formulated[13]

$$-\frac{d[\text{lactone}]}{dt} = \frac{d[\text{acid}]}{dt}$$
$$= k_H[\text{lactone}][H^+] - k_L[\text{acid}][H^+] \quad (1)$$

Setting $x=[\text{acid}]/\{[\text{acid}]+[\text{lactone}]\}$, $k_L=k_H/K$ and $[H^+]=\sqrt{K_a}x$ and intergrating gives

$$\ln\frac{(\sqrt{(1+1/K)}x+1)^2}{1-(1+1/K)x}$$
$$= \sqrt{(1+1/K)aK_a}\cdot k_H t \quad (2)$$

The rate constants were obtained by plotting the left-hand side of eqn. (2) against time and setting the slope equal to $\sqrt{(1+1/K)\,aK_a}\,k_H$, where K is the lactone ⇄ acid equilibrium constant in D_2O, x the fraction of acid in the reaction mixture, K_a the acidity constant of the hydroxy acid, a the initial concentration of the lactone and k_H the second order rate constant for the hydrolysis reaction. The pK_a for δ-hydroxyvaleric acid was taken to be 5.2 [based on the pK_a's for valeric acid 4.82 and for γ-hydroxyvaleric acid 4.69 from Ref. 29, corrected for less dissociation in D_2O (+0.45)[30]]. For (2-hydroxyethyl)thioacetic acid the pK_a value was estimated using the value of propylthioacetic acid[31] corrected for D_2O solvent[30] and added acetone(dissociation of acetic acid in 10 % acetone is decreased by *ca.* 0.12 pK_a-units):[32]) 3.77+0.45+0.12=4.34. The rate constants k_H 0.19±0.01 and 2.20±0.07 l mol^{-1} min^{-1} were obtained respectively for oxathianone and valerolactone. The uncertainties are derived from the estimated standard error of the slope in the least squares fit. The equilibrium constant for valerolactone was measured from the NMR spectrum to be 8.8±1.0 (the error refers to the precision of the measurement) and for oxathianone too large to be accurately determined. It was found that even 1 % of the lactone would still be visible in the NMR spectrum of the hydrolysis product so that K will be larger than 100. NMR(D_2O) δ 1,4-oxathian-2-one: 3.10(2H, m), 3.55(2H, s), 4.68(2H, m); 2-hydroxyethylthioacetic acid: 2.83(2H, t, J=6.5 Hz), 3.43(2H, s), 3.80(2H, t, J=6.5 Hz); δ-valerolactone: 1.90(4H, m), 2.50(2H, m), 4.40(2H, m); δ-hydroxyvaleric acid: 1.60(4H, m), 2.40 (2H, m), 3.58(2H, m), 4.83(O*H*).

Acknowledgements. The author is grateful to Mrs. E. Bernström for running several IR spectra and to Miss H. Kenttämaa for the high resolution mass spectra. This work was financially supported by Emil Aaltonen Foundation and Magnus Ehrnrooth Foundation.

REFERENCES

1. Jankowski, K. and Coulombe, R. *Tetrahedron Lett.* (1971) 991.
2. Greenwood, D. and Stevenson, H. A. *J. Chem. Soc.* (1953) 1514.
3. Suokas, E. and Kaltia, S. *Symposium in Synthetic Organic Chemistry,* Chemistry Days, Otaniemi, Finland 1971.
4. Davies, D. I., Hughes, L., Vankar, Y. D. and Baldwin, J. E. *J. Chem. Soc. Perkin Trans. 1* (1977) 2476.
5. Jankowski, K., Coulombe, R. and Berse, C. *Bull. Acad. Pol. Sci. Ser. Sci. Chim. 19* (1971) 661.
6. Black, D. K. *J. Chem. Soc. C.* (1966) 1708.
7. Kaufmann, H. P. and Schickel, R. *Fette, Seifen, Anstrichm. 65* (1963) 661.
8. Kelstrup, E. *J. Chem. Soc. Perkin Trans. 1* (1979) 1029.
9. Hellström, N. *Sven. Kem. Tidskr. 49* (1937) 201.
10. Jackman, L. M. and Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,* Pergamon, Oxford 1969, p. 288.
11. Reuterskiöld, J. A. *Diss.; Chem. Abstr. 34* (1940) 2791.
12. Wheeler, O. H. and Granell de Rodriquez, E. E. *J. Org. Chem. 29* (1964) 1227.
13. Frost, A. A. and Pearson, R. G. *Kinetics and Mechanism,* 2nd Ed., Wiley, New York 1961, p. 153.
14. Wiberg, K. B. *Physical Organic Chemistry,* Wiley, New York 1964, p. 320.
15. Tommila, E. and Hella, A. *Ann. Acad. Sci. Fenn. Ser. A2 53* (1953) 3.
16. Linstead, R. P. and Rydon, H. N. *J. Chem. Soc.* (1933) 580.
17. Illuminati, G. and Mandolini, L. *Acc. Chem. Res. 14* (1981) 95; Galli, D., Giovanelli, G., Illuminati, G. and Mandolini, L. *J. Org. Chem. 44* (1979) 1258.
18. Carroll, F. I., Mitchell, G. N., Blackwell, J. T., Sobti, A. and Meck, R. *J. Org. Chem. 39* (1974) 3890.
19. Philip, T., Cook, R. L., Malloy, T. B., Jr., Allinger, N. L., Chang, S. and Yuh, Y. *J. Am. Chem. Soc. 103* (1981) 2151.
20. Näsäkkälä, M. *Unpublished observation.*
21. Edward, J. T., Cooke, E. and Paradellis, T. C. *Can. J. Chem. 60* (1982) 2546.

22. Eliel, E. L., Allinger, N. L., Angyal, S. J. and Morrison, G. A. *Conformational Analysis,* Wiley, New York 1966, p. 191.
23. Boyer, J. H. and Straw, D. *J. Am. Chem. Soc. 74* (1957) 4506.
24. Houben-Weyl, *Methoden der Organischen Chemie,* Thieme, Stuttgart 1960, Vol/4, p. 180.
25. Vogel, A. I. *A Textbook of Practical Organic Chemistry,* 3rd Ed. Longman, Green, and Co, Ltd., London 1959, p. 960.
26. Gryszkiewicz-Trochimowski, E. and Gryszkiewicz-Trochimowski, O. *Bull. Soc. Chim. Fr.* (1951) 269.
27. Eck, J. C. and Marvel, C. S. *Org. Synth. Coll. Vol. 2* (1969) 74.
28. Wrede, F. and Rothaas, A. *Chem. Ber. 67* (1934) 739; *tert*-butylmalonic acid was made according to Eliel, E. L., Hutchins, R. O. and Sister M. Knoeber *Org. Synth. 50* (1970) 38.
29. Larsson, E. and Adell, B. *Z. Phys. Chem. A 156* (1931) 381 and *157* (1931) 342.
30. Schwartzenbach, G., Epprecht, A. and Erlenmeyer, H. *Helv. Chim. Acta 19* (1936) 1292.
31. Larsson, E. *Chem. Ber. 63* (1930) 1349
32. Fieser, L. F. *et al. J. Am. Chem. Soc. 70* (1948) 3151.

Received April 6, 1983,