Kinetics and Mechanism of the Alkaline Release of Phenyl(mercapto)tetrazoles from α-Oximes

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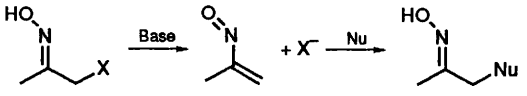
Compounds such as α-phenyl(mercapto)tetrazole (PMT) oxime (**9**) undergo rapid elimination of the PMT anion in base *via* a nitrosoene intermediate. Solution kinetics and HPLC analysis of reaction products are consistent with the mechanism shown in Scheme 2. For open chain oximes such as **4**, substitution α to the oxime increases the rate of release of PMT and is attributed to the relief of strain when a crowded reactant is converted to a less-crowded product. For cyclic oximes, the six-membered ring compounds are more reactive than the corresponding five-membered compounds. A linear isokinetic relationship between the entropy and enthalpy of activation was found with β = 346 ± 51 K. Entropies of activation were found to range from −7 to +24 c.u. (1 c.u. = 4.184 J mol^{-1} K^{-1}) and support the proposed mechanism.

Nitrosoenes have long been postulated as intermediates in the reaction of α-halo oximes with nucleophilic bases (Scheme 1).[1] Many research groups have made synthetic use of this nitrosoene intermediate for the replacement of the halide with nucleophiles[2,3] while others have employed the nitrosoene in cycloaddition reactions.[4]



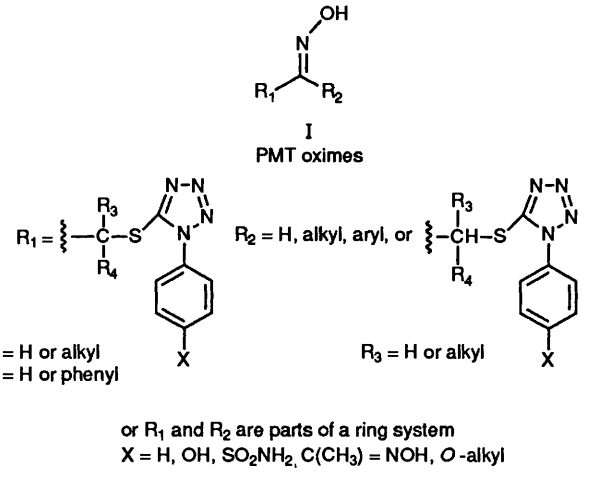
Scheme 1

Nitroso intermediates[5] are also observed when α,β-epoxy oximes react with cuprates to furnish α-alkylated β-hydroxy ketones. Kinetic and stereochemical investigation of the solvolysis of *E* and *Z* α-halo acetophenone oximes in aqueous media has been reported by Kaiser.[6] Our interest in base-labile protective groups for heterocyclic thiols and other photographically useful heterocycles led us to investigate the chemistry of α-mercapto tetrazole oximes.[7] We found the α-mercapto tetrazole oxime to be an effective means of releasing phenyl(mercapto)-tetrazole (PMT) with base and report here our results on the kinetics and mechanism of the base-catalysed release of mercaptotetrazole from α-substituted oximes.

Results and Discussion

When a latent image in a silver emulsion is developed in a photographic system, invariably some silver which has not been struck by light is reduced. This is known as fog and is not advantageous. One method of controlling fog is to release phenyl(mercapto)tetrazole (PMT) at an appropriate time.[8] We therefore undertook a kinetic investigation of α-substituted oximes (**1**–**25**) of the general formula **I**. The oximes were prepared by literature procedures. The stereochemical assignment and purity of each oxime sample used in this study was evaluated by ^{1}H and ^{13}C NMR spectroscopy.†

The reaction of the PMT oximes with 0.25 mol dm^{-3} KOH in 30% acetonitrile–water follows a pseudo-first-order rate law. A typical absorbance *vs.* time curve and the corresponding rate plot are shown in Figs. 1(*a*) and (*b*). Table 1 lists the rate constants determined for the release of PMT from the oximes as studied at 22 °C.



For the open-chain oximes, substitution at the position α to the oxime group increases the rate of release of PMT, *e.g.*, **4** *vs.* **5** and **12**; **6** *vs.* **7**; **1** *vs.* **3**.‡ We attribute this order of reactivity to the relief of steric strain when a crowded reactant is converted into a less-crowded product. This is illustrated by the very high reactivity of **12** compared to **4**. In addition to the large steric effects, a rather small effect on rate was observed with electron-withdrawing and electron-donating substitutents. Introduction of a second PMT (electron withdrawing) group has an accelerating effect on the rate of release of the PMT *E* to the oxime, *e.g.*, **4** and **6**.

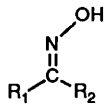
Substitution at the *para*-position on the PMT influences the reactivity of the compound. An electron-donating *para*-hydroxy group decreases the rate of reaction (**1** *vs.***2**; **6** *vs.* **9**; **15** *vs.* **16**; **19** *vs.* **20**) whereas the electron-withdrawing *p*-SO_2NH_2 group increases the rate (**15** *vs.* **17**; **19** *vs.* **21**). Even though these groups are somewhat remote from the reaction centre, the slight differences in rate are most likely an example of an inductive effect. Long-chain ether and $-C(CH_3)=NOH$ groups at the *para*-position have no significant effect on the release rates.

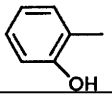
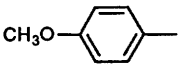
† Steric compression by the oxime results in substantial upfield shifts for *Z* α carbons. For a leading reference using ^{13}C NMR to assign the stereochemistry of oximes, see C. A. Bunnell, and P. L. Fuchs, *J. Org. Chem.*, 1977, **42**, 2614.

‡ See Table 1 for details of structures **1**–**25**.

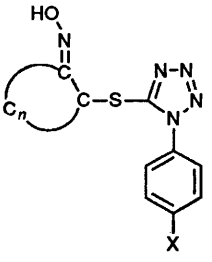
Table 1 Reaction of substituted oximes with 0.25 mol dm^{-3} KOH in 30% acetonitrile–water at 22 °C

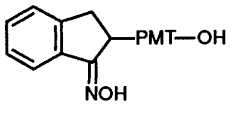
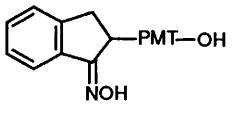
(*a*) Open-chain compounds



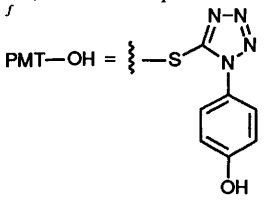
Substrate	R_1	R_2	k_{obs}/s^{-1}
1	PMT–CH_2	H	1.41×10^{-2} [a] 5.42×10^{-4} [b]
2	*p*-OH–PMT–CH_2	H	5.33×10^{-3} [a] 1.49×10^{-3} [b]
3	PMT(CH_3)(Ph)C	H	4.17×10^{-1} [a,c]
4	PMT–CH_2	CH_3	3.73×10^{-2} [a]
5	PMT(CH_3)CH	CH_3	3.15 [a]
6	PMT–CH_2	PMT–CH_2	7.62×10^{-2} [a] 2.26×10^{-4} [d]
7	PMT(CH_3)CH	PMT(CH_3)CH	10.0 [a] 2.56×10^{-2} [d]
8	*p*-CH_3–C(=NOH)–PMT–CH_2	*p*-CH_3–C(=NOH)–PMT–CH_2	6.19×10^{-2} [a]
9	*p*-OH–PMT–CH_2	*p*-OH–PMT–CH_2	1.36×10^{-2} [a]
10	PMT–CH_2		1.03×10^{-2} [a] 2.0×10^{-4} [b]
11	PMT–CH_2		1.62×10^{-1} [a]
12	PMT(Ph)CH	CH_3	20.4 [a]
13	*p*-OC_6H_{13}–PMT–CH_2	CH_3	3.22×10^{-2} [a]
14	*p*-$OC_{12}H_{25}$–PMT–CH_2	CH_3	4.17×10^{-2} [e]

(*b*) Cyclic compounds



Substrate	*n*	X	k_{obs}/s^{-1}
15	3	H	5.78×10^{-1} [a]
16	3	OH	1.14×10^{-1} [a]
17	3	SO_2NH_2	1.05 [a]
18	3	C(=NOH)–CH_3	~3.03×10^{-1} [a] (insol.)
19	4	H	12.8 [a]
20	4	OH	3.15 [a]
21	4	SO_2NH_2	23.1 [a]
22	4	C(=NOH)–CH_3	11.2 [a]
23	4	OC_6H_{13}	11.4 [a]
24			3.15×10^{-1} [a,f] 3.27×10^{-2} [b,f]
25			2.86×10^{-2} [b,f]

[a] PMT release from *E*-isomer. *Z* refers to the hydroxy group on the same side as the substituent R_1 and *E* refers to the hydroxy group on the opposite side of R_1. [b] The slower rate is likely to be PMT release from *Z*-isomer, since the samples were known to be mixtures of *Z*- and *E*-isomers. [c] In 0.0025 mol dm^{-3} KOH. [d] Second PMT release. [e] In 0.05 mol dm^{-3} KOH. [f]



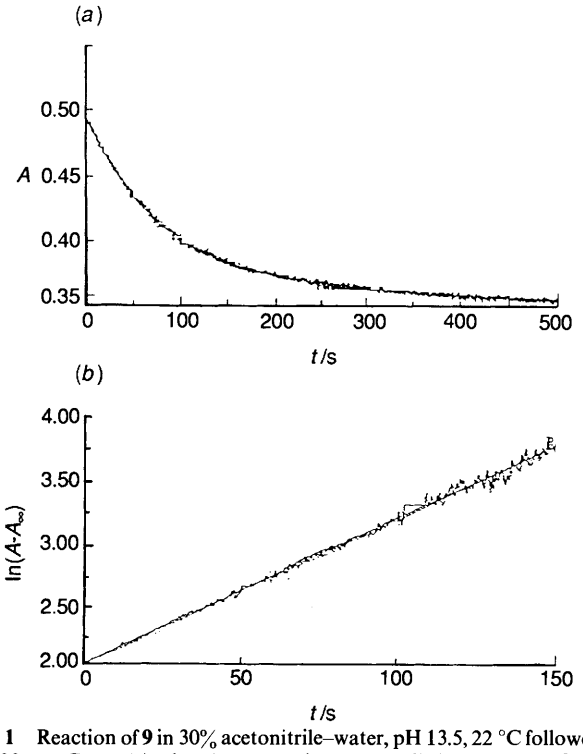


Fig. 1 Reaction of **9** in 30% acetonitrile–water, pH 13.5, 22 °C followed at 300 nm. Curve (*a*), absorbance *vs.* time; curve (*b*), least-squares fit to pseudo-first-order over three half-lives.

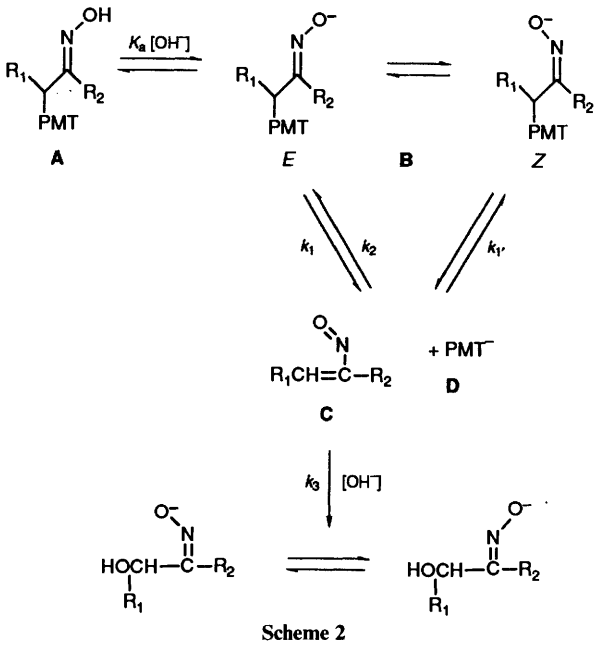
For cyclic compounds, the six-membered ring compounds are found to be more reactive than the corresponding five-membered ring compounds (**19** *vs.* **15**; **20** *vs.* **16**; **21** *vs.* **17**; **25** *vs.* **24**). It is likely that the higher steric strain introduced during the formation of the nitrosocyclopentene intermediate compared to the formation of nitrosocyclohexene intermediate in the transition state accounts for the rate difference.

As shown in Table 1, we have found that the *E*-isomers are more reactive than the *Z*-isomers. This is expected for heterolytic fragmentation reactions where the reaction centre is not a part of a ring system.[9] A similar difference in rate is observed when bromide is the leaving group.[10]

As part of our kinetic study we undertook an analysis of the reaction products. Table 2 lists the amounts of PMT or *p*-hydroxy-PMT released after the apparent completion of reaction for the oximes **6**, **7** and **9** in 0.25 mol dm^{-3} KOH in 30% acetonitrile–water. It is apparent that for **6** and **7** both PMTs are released from the substrate. The PMT *E* to the oxime is released at the faster rate. The second PMT is released much more slowly, either with the PMT *Z* to the oxime or as a result of the mono-PMT nitrosoalkene intermediate rotating and being captured by OH^- such that the resulting oxime anion is now *E* to the remaining PMT group. The oxime **9** released only one equivalent of *p*-hydroxy-PMT. This is in agreement with the results of kinetic studies * where only one rate of reaction is observed for **9**, *i.e.*, the release of the *E p*-hydroxy-PMT.

We also studied the pH dependence of the reaction of the oxime **9** with alkali in 30% acetonitrile–water. At high pH (11.5–13.5) the pseudo-first-order rate plot gives a straight line over at least three half-lives of the reaction. However, on lowering the pH of the system, deviation from pseudo-first-order kinetics was observed. Using a well-known kinetic analysis [11] for a series of first-order reactions, we were able to determine two observed

* Silver titration under similar experimental conditions by J. Poppenhouse (Polaroid Corporation) show the rate of release of the second *p*-hydroxy-PMT molecule from **9** to be slow.



Scheme 2

rate constants. Based upon the proposed reaction mechanism shown in Scheme 2, the pH *vs.* k_{obs} data were fitted to eqn. (1). Fig. 2 shows a typical fit.

$$k_{obs} = k_1K_a/([H^+] + K_a) \quad (1)$$

Table 3 gives the pK_a values and the unimolecular rate constants (k_1) for oximes **4**, **6**, **9** and **20** determined from a least-squares best fit to eqn. (1). It is important to note the agreement between the pK_a for **4** and that known for acetoxime,[12] *i.e.* 12.2.

The deviation from pseudo-first-order reaction at lower pH can be explained by the difference in the relative rates of reaction of **C** (Scheme 2) with OH^-, **D** or other nucleophiles present in the buffered systems. The reactivity of an ion with the intermediate **C** is expected to depend on the nucleophilicity of the ion. From the data on the nucleophilicity constants [12] ionized *p*-hydroxy-PMT is expected to be a better nucleophile than hydroxide ion, which is better than phosphate or carbonate.

At high pH the reaction of **C** with OH^- is fast because of the high concentration of OH^-, resulting in rapid removal of **C** and consequent prevention of its reaction with any other nucleophile. In this case the observed rate is the cleavage of **B**. As the pH is lowered, the reaction of **C** with **D** becomes comparable to the reaction of **B** with OH^-. During the latter stages of the reaction, the increasing concentration of **D** shifts the equilibrium away from **C** and hence slows the rate of formation of products. The conversion of **9** to the product when the reaction mixture was quenched to pH 2.5 was only *ca.* 80 mole %, which can be attributed to the back-addition of PMT anion to the intermediate nitrosoalkene **C**. Acetate ions, present in the buffers, have low nucleophilicity and no significant reactivity toward **C**, as shown by the comparison of rates in phosphate and mixtures 0.02 mol dm^{-3} each of phosphate, acetate and borate at the same pH.

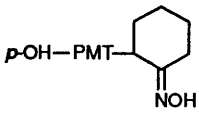
This hypothesis was further tested by adding *p*-hydroxy-PMT to the reaction mixture and following the reaction at a pH where the pseudo-first-order plots deviate from linearity. With the addition of *p*-hydroxy-PMT (*p*-hydroxy-PMT:**9** = 0.55:1) a retardation due to the presence of the added *p*-hydroxy-PMT is observed, as expected.

Using a kinetic simulation program [13] to model Scheme 2, rate constants (Table 4) were determined from the best fit to data from HPLC analysis of reaction mixtures. The rate

Table 2 Release of PMT and *p*-hydroxy-PMT from oximes

Substrate	Structure	Substrate/ mmol	Released/ mmol	Released (%)
4	$CH_3-\overset{\overset{NOH}{\|\|}}{C}-CH_2-PMT$	0.11	0.10	91
6	$PMT-CH_2-\overset{\overset{NOH}{\|\|}}{C}-CH_2-PMT$	0.35	0.63	90
7	$PMT-(CH_3)CH-\overset{\overset{NOH}{\|\|}}{C}-CH(CH_3)-PMT$	0.15	0.27	90
9	$p\text{-OH-PMT-}CH_2-\overset{\overset{NOH}{\|\|}}{C}-CH_2-PMT-p\text{-OH}$	1.33	1.29	49

Table 3 Ionization constants determined from a least-squares fit to eqn. (1)

Substrate	Structure	pK_a	k_1/s^{-1}
4	$CH_3-\overset{\overset{NOH}{\|\|}}{C}-CH_2-PMT$	12.3[a]	0.011[a]
6	$PMT-CH_2-\overset{\overset{NOH}{\|\|}}{C}-CH_2-PMT$	12.7 11.5[b]	0.038 0.000 21[b]
9	$p\text{-OH-PMT-}CH_2-\overset{\overset{NOH}{\|\|}}{C}-CH_2-PMT-p\text{-OH}$	11.9	0.011
20		12.9	3.15

[a] Measured in water containing 1% acetonitrile. [b] The second number in each column for **6** refers to the release of the second mole of PMT.

Table 4 Equilibrium and rate constants calculated for reaction in Scheme 2

Constant	Value
K_a	2.45×10^{-12} [a]
k_1	0.010 s^{-1}
k_2	20.8 dm^3 mol^{-1} s^{-1}
k_3	0.72 dm^3 mol^{-1} s^{-1}

[a] pK_a = 11.6

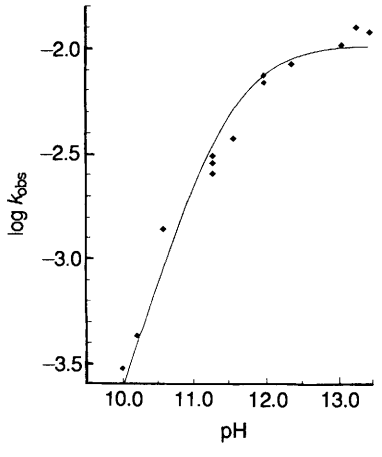


Fig. 2 pH–rate profile for the reaction of **9** in 30% acetonitrile–water at 22 °C. The line is a least-squares fit to eqn. (1).

constants determined in this way show excellent agreement with the rate data determined from stopped-flow experiments (*cf.* **9** in Table 3).

The high value of k_2 explains the retardation of the reaction when k_3[OH] $\ll k_2$[C][D], which is the situation at lower pH and k_2[C][D] $\gg k_1$[B] when a build up of **D** occurs.

In another experiment an excess of free *p*-hydroxy-PMT was added to the reaction mixture at pH 10.9. The experimental data from HPLC analysis of a reaction mixture are compared with the curve calculated using the rate constants given in Table 4. Again, the good fit observed is consistent with the proposed Scheme 2.

It was observed that at high pH and large concentrations of **9**, pseudo-first-order stopped-flow curves showed deviation from linearity. Using the kinetic simulation program of Scheme 2, similar deviations were observed and further support the proposed mechanism.

The activation parameters for several compounds were determined and the results listed in Table 5. From the Arrhenius plot shown in Fig. 3 for compound **4**, $\Delta H^{\ddagger}$ = 26.0 kcal mol^{-1}. In the photographic process, it is often desirable to employ reactions with high activation energies. Since many chemical reactions in solution at room temperature have $\Delta H^{\ddagger} \approx$ 12 kcal mol^{-1}, the high activation energy for **4** led us to find that this reaction series follows an isokinetic relationship.[13] A plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$, Fig. 4, gave a good fit to a straight line with a slope, β = 346 ± 51 K. As further verification of this relationship, we applied a statistical method[14] for kinetic measurements at several corresponding temperatures. A slightly higher value, β = 396 ± 2 K, was obtained. Table 5 also shows that the entropies determined range from − 7 to +24 e.u. According to

Table 5 Activation parameters for the reaction of oximes in 0.25 mol dm^3 KOH, 30% acetonitrile–water

Substrate	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/e.u.
4	26.0[a]	20.4[a]
6	20.8	6.4
	26.4[b]	24.2[b]
9	21.3	4.62
11	21.3	12.8
15	20.7	9.36
16	16.5	−4.47
19	19.5	13.2
20	14.5	−7.16

[a] Measured in water containing 1% acetonitrile–water. [b] Release of second molecule of PMT.

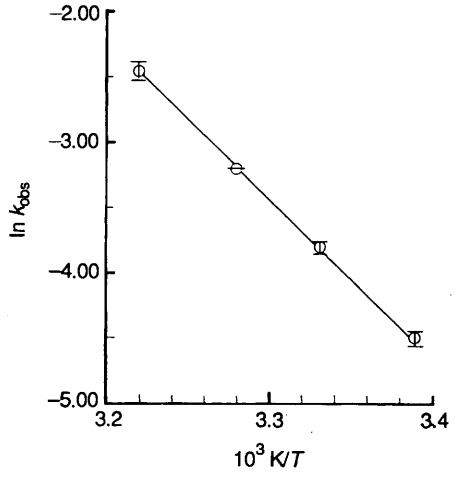


Fig. 3 Arrhenius plot for the reaction of **4** with 0.25 mol dm^{-3} KOH in 30% acetonitrile–water

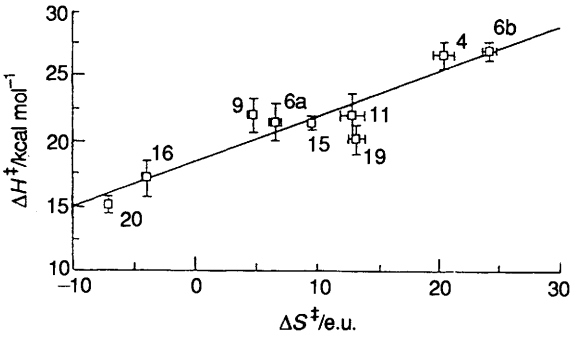


Fig. 4 Plot of $\Delta H^{\ddagger}$ *vs.* $\Delta S^{\ddagger}$ for the elimination of PMT from oximes. The slope, β, of the line is 346 ± 51 K

Espenson,[15] values close to zero or positive are indicative of the rate-determining step being an E1 elimination as proposed in Scheme 2.

In conclusion, results from stopped-flow kinetics, the HPLC analysis of reaction mixtures, and the kinetic simulations of the reaction are presented and all support the proposed mechanism in Scheme 2. Not only do the activation parameters support this mechanism but these parameters also show an interesting isokinetic relationship that is useful in the photographic application of these materials.

Experimental

Kinetics and Product Study.—The rates of hydrolysis of the substrates at different temperatures in 30% acetonitrile–water containing buffers of varying pH were determined spectroscopically. Potassium hydroxide solutions were used for maintaining pH 12 and above and buffers containing 0.02 mol dm^{-3} of each of acetate, borate and phosphate ions were used for reactions below pH 12. Sodium hydrogencarbonate, 0.025 mol dm^{-3} was used for a buffer of pH 11.27. The ionic strength was maintained at 0.25 mol dm^{-3} for all the reactions by adding potassium chloride. The final pH of all solutions was measured using an Orion 611 pH meter and a Ross combination pH electrode. The faster reactions were followed by a Dionex Stopped-Flow apparatus and the slower reactions were followed by a Perkin-Elmer 330 spectrophotometer at 280–300 nm. The kinetic measurements were made at least in triplicate and gave standard deviations that did not exceed 10%. The activation parameters were determined measuring the rates at five temperatures from 15–35 °C.

A typical absorbance *vs.* time curve for the reaction of **9** with 0.25 mol dm^{-3} KOH in 30% acetonitrile–water at 25 °C, obtained from Stopped-Flow apparatus, and the corresponding pseudo-first-order plot are shown in Figs. 1(*a*) and (*b*), respectively.

The products of reaction of the substrates with OH^- were analysed by HPLC using a HP1090A Liquid Chromatograph and Hewlett-Packard RP-18 columns. The reaction mixtures containing the substrates and KOH in 30% acetonitrile–water were allowed to stand at 22 °C for definite periods of time. The mixtures were quenched with hydrochloric acid and were analysed. The products were identified by their retention times as well as by coinjection with known samples.

Materials.—Phenyl 5-mercapto(1*H*)tetrazole and its sodium salt were obtained from Eastman Kodak. 1-(4-Hydroxyphenyl)-5-mercapto(1*H*)tetrazole, 1-(4-acetylphenyl)-5-mercapto(1*H*)tetrazole and 1-(4-sulfamoylphenyl)-5-mercapto(1*H*)tetrazole were prepared according to literature procedures.[16–18]

1-(4-Hexyloxyphenyl)-5-mercapto(1*H*)tetrazole and 1-(4-dodecyloxyphenyl)-5-mercapto(1*H*)tetrazole were prepared through standard sodium azide cyclization of the corresponding phenyl isothiocyanates. α-Haloaldehyde acetals and α-haloketones were either available from commercial sources or prepared according to literature procedures.

General Procedure for the Preparation of α-Substituted Oximes.—The α-oximes reported in this study were prepared by one of the two general methods: (A) The appropriate phenyl(mercapto)tetrazole was treated with the appropriate α-haloaldehyde acetal or α-haloketone to provide an intermediate which, upon formation of oxime under standard conditions, furnished the desired oxime or (B) the α-haloketone was converted to its oxime and subsequent reaction with the appropriate phenyl(mercapto)tetrazole gave the desired α-substituted oxime.*

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*acetaldehyde oxime* (**2**). A mixture of 1-(4-hydroxyphenyl)-5-mercapto(1*H*)-tetrazole (20.4 g, 0.105 mol), bromoacetaldehyde diethyl acetal (19.7 g, 0.1 mol) and sodium hydrogencarbonate (8.82 g, 0.105 mol) in acetonitrile (150 cm^3, dried over molecular sieve, 4 Å) was heated at reflux under nitrogen for 6 h. The reaction mixture was cooled to room temperature and the salts were filtered off using fresh acetonitrile for washing. The filtrate was stripped of solvent and the residue extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogencar-

* Compound numbers suffixed **A**, e.g. **4A**, refer to the free carbonyl compound; those without refer to the oxime (see Table 1 for structural details).

bonate followed by water and brine and dried over Na_2SO_4. Removal of solvent on a rotary evaporator gave 13.08 g of syrupy residue which was homogeneous by TLC (Whatman K5F silica gel, CH_3OH–$CHCl_3$, 10:90) and was used directly in the formation of the desired oxime.

A mixture of the above syrup (12.4 g, 0.04 mol) and hydroxylamine hydrochloride (3.5 g, 0.05 mol) in ethanol (75 cm^3) and water (25 cm^3) was heated at reflux for 4 h. Sodium acetate trihydrate (6.9 g, 0.05 mol) was added and refluxing continued for 2 h. The solvent was removed and the residue diluted with ice–water. Cooling and scratching gave an off-white solid, which was filtered, washed with water and dried to provide 11.0 g of the oxime, m.p. 132–134 °C. Recrystallization from ethyl acetate–hexane (charcoal) gave a homogeneous material (single spot by TLC; CH_3OH–$CHCl_3$, 10:90), m.p. 133–135 °C; ^1H NMR ([$^2H_6$]DMSO) δ_H 11.5–10.95 (1 H), 10.2 (1 H), 7.7–6.85 (5 H) and 4.25–3.98 (2 H); MS, *m/z* 252 (MH^+).

1-[1-*Phenyl*-5(1H)-*tetrazolylthio*]*propan*-2-*one* (**4A**). A mixture of 1-phenyl-5-mercapto-(1*H*)tetrazole (8.91 g, 0.05 mol), chloroacetone [4.63 g (90% pure), 0.045 mol] and sodium hydrogencarbonate (4.2 g, 0.05 mol) was stirred in dry acetonitrile (100 cm^3) under nitrogen at ambient temperature for 66 h. The reaction mixture was filtered and the salts washed with fresh acetonitrile. The combined filtrates were stripped of solvent on a rotary evaporator and the residual off-white solid was slurried with water, filtered and crystallized from methanol. After being vacuum dried at ambient temperature, 8.92 g (76% yield) of white crystals, m.p. 77–78 °C were obtained, IR(KBr) ν/cm^{-1} 1735; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 201.1, 153.9, 133.1, 130.7, 130.1, 124.4, 43.5 and 28.7.

1-[1-*Phenyl*-5(1H)-*tetrazolylthio*]*propan*-2-*one oxime* (**4**). A mixture of the ketone (**4A**) (4.69 g, 0.02 mol), hydroxylamine hydrochloride (1.5 g) and sodium acetate (1.72 g, 0.02 mol) in ethanol (100 cm^3) was stirred at ambient temperature for one week. The resulting colourless crystals were recovered by filtration, washed with ethanol and dried in a vacuum oven at ambient temperature to provide 4.34 g of a colourless solid. Recrystallization of 4.0 g from CH_3OH–H_2O gave 2.3 g of colourless needles, m.p. 141–142 °C. ^{13}C NMR ([$^2H_6$]DMSO) δ_C 153.7, 150.5, 133.1, 130.6, 130.0, 124.7, 31.7 and 12.9; MS, *m/z* 250 (MH^+).

1,3-*Bis*[1-*phenyl*-5(1H)-*tetrazolylthio*]*propan*-2-*one* (**6A**). A solution of 1-phenyl-5-mercapto(1*H*)tetrazole (37.42 g, 0.21 mmol) in dry acetone (250 cm^3) was stirred under nitrogen with sodium hydrogencarbonate (17.64 g, 0.21 mol) for 15 min. 1,3-Dichloropropan-2-one (12.7 g, 0.1 mol) was added and the reaction mixture was heated under reflux for 5 h. The reaction mixture was cooled in an ice bath, and the salts were filtered and washed with fresh acetone. The filtrate was stripped of solvent on a rotary evaporator and the residual solid was stirred with aqueous sodium hydrogencarbonate for 20 min. The solid was filtered, washed with water and dried in a vacuum oven at 55 °C to provide 39.0 g (95% yield) of solid, m.p. 152–154 °C. ^{13}C NMR ([$^2H_6$]DMSO) δ_C 197.7, 154.5, 134.0, 131.7, 131.1, 125.4 and 42.8; MS *m/z* 410.47.

1,3-*Bis*[1-*phenyl*-5-(1H)-*tetrazolylthio*]*propan*-2-*one oxime* (**6**). A mixture of ketone **6A** (12.3 g, 0.03 mol), hydroxylamine hydrochloride (2.3 g, 0.033 mol), potassium acetate (3.24 g, 0.033 mol), tetrahydrofuran (200 cm^3), methanol (50 cm^3) and water (20 cm^3) was heated under reflux with stirring for 20 h. Solvents were removed on a rotary evaporator and the syrupy residue was dissolved in methanol (20 cm^3). Gradual dilution with water (100 cm^3) with efficient stirring resulted in the separation of crystalline solid which was filtered, washed with water and dried in a vacuum oven, first at ambient temperature and then at 50 °C. A homogeneous solid (12.35 g, single spot on TLC; Whatman K5F Silica Gel, EtOAc–$CHCl_3$, 5:95), m.p. 145–147 °C was obtained. ^{13}C NMR ([$^2H_6$]DMSO) δ_C 154.9, 154.4, 149.9, 134.0, 131.6, 130.9, 125.6, 36.6 and 28.3; MS, *m/z* 426 (MH^+).

2-[1-*Phenyl*-5(1H)-*tetrazolylthio*]*cyclohexanone* (**19A**). 1-Phenyl-1*H*-tetrazole-5-thiol sodium salt (216.20 g, 1.08 mol), 2-chlorocyclohexanone (143.2 g, 1.08 mol) and sodium hydrogencarbonate (4.2 g, 0.05 mol) were slurried in 1.2 dm^3 of dry acetonitrile and heated under reflux with stirring under nitrogen for 45 h. After being cooled to room temperature, the salts were filtered and washed with a small volume of fresh acetonitrile. The combined filtrates were stripped of solvent on a rotary evaporator. The oily residue was taken up in 0.6 dm^3 of dichloromethane and washed twice with aqueous sodium hydrogencarbonate. After being dried (sodium sulfate), the solvent was removed on a rotary to provide 291.7 g (98% yield) of a pale yellow solid which was crystallizable from ethanol. ^{13}C NMR ([$^2H_6$]DMSO) δ_C 205.0, 153.2, 133.5, 130.2, 129.8, 123.9, 58.3, 41.7, 35.6, 27.5 and 25. 2; MS, *m/z* 273.

2-[1-*Phenyl*-5(1H)-*tetrazolylthio*]*cyclohexanone oxime* (**19**). The ketone **19A** (291.7 g, 1.06 mol) was dissolved in 1.5 dm^3 of warm EtOH under argon in a dry 2 dm^3 three-neck flask with mechanical stirring. NH_2OH·HCl (75.2 g, 1.08 mol), followed by NaOAc·$3H_2O$ (147.2 g, 1.08 mol) were added as solids and the slurry was allowed to stir for 18 h at room temperature. The reaction slurry was extremely thick at this point and was chased from the flask with fresh EtOH. The white solids were collected by filtration, air-dried overnight, and then slurried exhaustively with water. This gave 182 g of crude oxime. The EtOH filtrate from the reaction was concentrated and placed in the freezer to provide an additional 47 g of oxime. The combined oximes were crystallized from EtOH to provide 209 g (68% yield) of a white solid: m.p. 104–105 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 154.9, 153.5, 133.1, 130.6, 129.9, 124.7, 50.2, 34.5, 25.0, 24.0 and 23.3; MS, *m/z* 288.

2-[*Phenyl*-5(1H)-*tetrazolylthio*]*acetaldehyde oxime* (**1**). A mixture of *Z* and *E* by ^{13}C NMR; m.p. 84–85 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 153.7, 153.2, 145.9, 145.8, 133.4, 130.42, 130.38, 129.9, 123.8, 123.7, 31.4 (*E*) and 25.0 (*Z*); MS, *m/z* 235.

2-*Phenyl*-2-[1-*phenyl*-5(1H)-*tetrazolylthio*]*propanal oxime* (**3**). M.p. 125–126 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 150.7, 150.7, 140.2, 133.0, 130.6, 129.5, 128.6, 128.1, 126.4, 125.4, 58.4 and 25.4; MS, *m/z* 325.

3-[1-*Phenyl*-5(1H)-*tetrazolylthio*]*butan*-2-*one oxime* (**5**). White gum; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 154.0, 153.0, 133.2, 130.5, 129.8, 124.8, 48.3, 19.1 and 11.5; MS, *m/z* 263.

1,3-*Bis*[1-(4-*acetylphenyl*)-5(1H)-*tetrazolylthio*]*propan*-2-*one* (**8A**). M.p. 155–156 °C; IR (KBr) ν/cm^{-1} 1695 and 1735; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 197.1, 196.8, 153.8, 138.0, 136.3, 130.0, 124.5, 42.1 and 27.0.

1,3-*Bis*[1-(4-*acetylphenyl*)-5(1H)-*tetrazolylthio*]*propan*-2-*one trioxime* (**8**). M.p. 170–171.5 °C; ^1H NMR ([$^2H_6$]DMSO) δ_H 11.2 (1 H), 11.6 (2 H), 8.2–7.6 (8 H), 4.4–4.2 (4 H) and 2.2 (6 H); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 154.0, 153.5, 152.0, 149.0, 138.9, 132.9, 126.9, 124.5, 124.5, 35.6, 27.4 and 11.5; MS, *m/z* 540 (MH^+).

1,3-*Bis*[1-(4-*hydroxyphenyl*)-5(1H)-*tetrazolylthio*)*propan*-2-*one* (**9A**). M.p. 124–125 °C (decomp.) ^{13}C NMR ([$^2H_6$]DMSO) δ_C 197.0, 159.4, 153.8, 126.4, 124.2, 116.4, 41.8, 39.1, 38.8; MS, *m/z* 443 (MH^+).

1,3-*Bis*[1-(4-*hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*propan*-2-*one oxime* (**9**). M.p. 183–185 °C (decomp.); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 159.2, 154.0, 153.4, 149.0, 126.3, 124.0, 116.1, 40.3 and 38.6; MS, *m/z* 458 (MH^+).

2-[1-*Phenyl*-5(1H)-*tetrazolylthioacetyl*]*phenol* (**10A**). M.p. 135–137 °C; ^1H NMR ($CDCl_3$) δ_H 11.6 (1 H), 8.2–7.0 (9 H) and 5.2 (2 H); MS, *m/z* 313 (MH^+).

2-[1-*Phenyl*-5(1H)-*tetrazolylthioacetyl*]*phenol oxime* (**10**). M.p. 165–167 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 197.3, 162.5,

153.2, 137.7, 133.4, 130.4, 123.8, 119.6, 118.8, 118.1, 77.5, 77.1, 76.7 and 41.7; MS, *m/z* 328 (MH^+).

α-[1-*Phenyl*-5-(1-H)-*tetrazolylthio*]-4-*methoxyacetophenone oxime* (**11**). M.p. 152–154°C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 159.7, 153.7, 148.6, 133.1, 130.5, 130.2, 129.9, 124.5, 123.6, 113.4, 55.3 and 37.0; MS, *m/z* 341.

1-*Phenyl*-1-[1-*phenyl*-5(1H)-*tetrazolylthio*]*propan*-2-*one oxime* (**12**). White gum; ^{13}C NMR ($CDCl_3$) δ_C 154.8, 152.9, 136.0, 133.2, 130.1, 129.6, 128.8, 128.7, 128.5, 124.0, 56.0 and 13.5; MS, *m/z* 325.

1-[1-(4-*Heptyloxyphenyl*)-5(1H)-*tetrazolylthio*]*propan*-2-*one oxime* (**13**). M.p. 54–56 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 160.4, 153.6, 152.7, 125.8, 125.4, 115.3, 68.4, 37.3, 31.6, 29.0, 28.8, 25.8, 22.4, 13.9 and 13.1; MS, *m/z* 364 (MH^+).

1-[1-(4-*Dodecyloxyphenyl*)-5(1H)-*tetrazolylthio*]*propan*-2-*one oxime* (**14**). M.p. 88 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 160.5, 153.7, 153.0, 125.9, 125.5, 115.4, 68.6, 31.8, 29.6, 29.3, 29.1, 26.0, 22.6, 14.1 and 13.1; MS, *m/z* 434 (MH^+).

2-[1-*Phenyl*-5(1H)-*tetrazolylthio*)*cyclopentanone oxime* (**15**). M.p. 148–149 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 160.9, 153.0, 133.1, 130.4, 129.8, 124.6, 48.1, 33.0, 26.0 and 21.8; MS, *m/z* 275.

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*cyclopentanone* (**16A**). M.p. 130–132 °C; ^1H NMR ([$^2H_6$]DMSO) δ_H 10.2 (1 H), 7.5–6.8 (4 H), 4.5–4.2 (1 H) and 2.8–1.8 (6 H).

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*cyclopentanone oxime* (**16**). M.p. 160–161 °C (decomp.); ^{13}C NMR ([$^2H_6$]-DMSO) δ_C 161.0, 159.2, 153.1, 126.4, 124.3, 116.1, 48.0, 40.1, 33.0, 26.0 and 21.8; MS, *m/z* 292 (MH^+).

2-[1-(4-*Sulfonamidophenyl*)-5(1H)-*tetrazolylthio*]*cyclopentanone* (**17A**). M.p. 150–152 °C; ^1H NMR ([$^2H_6$]DMSO) δ_H 8.2–7.7 (4 H), 7.5 (2 H), 4.5–4.3 (1 H) and 1.7 (6 H); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 211.8, 153.0, 145.8, 135.4, 127.5, 125.3, 51.8, 36.1, 29.7 and 20.1.

2-[1-(4-*Sulfonamidophenyl*)-5(1H)-*tetrazolylthio*]*cyclopentanone oxime* (**17**). M.p. 207 °C (decomp.); ^1H NMR ([$^2H_6$]-DMSO) δ_H 10.9 (1 H), 8.82–7.8 (4 H), 7.6 (2 H), 4.8–4.6 (1 H) and 2.6–2.2 (6 H); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 161.0, 153.4, 145.9, 135.5, 127.3, 125.4, 48.4, 33.0, 26.1 and 21.8; MS, *m/z* 355 (MH^+).

2-{1-[4-(1-*Hydroxyiminoethyl*)*phenyl*]-5(1H)-*tetrazolylthio*}-*cyclopentanone* (**18A**). m.p. 135–136 °C; ^1H NMR ([$^2H_6$]-DMSO) δ_H 11.6 (1 H), 8.1–7.6 (4 H), 4.6–4.3 (1 H) and 2.7–1.8 (9 H).

2-[1-(4-*Acetylphenyl*)-5(1H)-*tetrazolylthio*]*cyclopentanone dioxime* (**18**). M.p. 192 °C; ^1H NMR ([$^2H_6$]DMSO) δ_H 11.6 (1 H), 11.0 (1 H), 8.8–7.7 (4 H), 4.8–4.6 (1 H) and 2.6–1.6 (9 H); MS, *m/z* 333 (MH^+).

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*cyclohexanone* (**20A**). M.p. 85–87 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 205.1, 159.2, 153.1, 126.4, 124.1, 116.1, 57.4, 41.0, 34.9, 26.8 and 24.5; MS, *m/z* 290.

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*cyclohexanone oxime* (**20**). M.p. 168–169 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 160.0, 155.8, 154.4, 127.4, 125.2, 117.4, 51.1, 35.6, 26.1, 25.1 and 24.4; MS, *m/z* 305.

2-[1-(4-*Sulfonamidophenyl*)-5(1*H*)-*tetrazolylthio*]*cyclohexanone* (**21A**). M.p. 180–181 °C (decomp.); ^1H NMR ([$^2H_6$]DMSO) δ_H 8.2–7.9 (4 H), 7.6 (2 H), 5.1–4.8 (1 H) and 2.8–1.0 (8 H).

2-[1-(4-*Sulfonamidophenyl*)-5(1H)-*tetrazolylthio*]*cyclohexanone oxime* (**21**). M.p. 198 °C (decomp.); ^1H NMR ([$^2H_6$]-DMSO) δ_H 10.9 (1 H), 8.82–7.8 (4 H), 7.6 (2 H), 4.7–4.5 (1 H) and 3.0–1.2 (8 H); MS, *m/z* 369 (MH^+).

2-[1-(4-*Acetylphenyl*)-5(1H)-*tetrazolylthio*]*cyclohexanone dioxime* (**22**). M.p. 182 °C (decomp.); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 154.9, 153.4, 152.0, 138.9, 133.0, 126.8, 124.6, 50.2, 34.4, 24.9, 24.0, 23.3 and 11.4; MS, *m/z* 346.

2-[1-(4-*Hexyloxyphenyl*)-5(1H)-*tetrazolylthio*]*cyclohexanone* (**23A**). M.p. 87–89 °C; IR (KBr) ν/cm^{-1} 1738.

2-[1-(4-*Hexyloxyphenyl*)-5(1H)-*tetrazolylthio*]*cyclohexanone oxime* (**23**). M.p. 113—114 °C; MS, *m/z* 389.

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*indan*-1-*one* (**24A**). M.p. 200–201 °C; ^{13}C NMR ([$^2H_6$]DMSO) δ_C 200.2, 160.2, 153.6, 152.9, 136.4, 135.9, 128.8, 127.6, 127.3, 125.1, 124.6, 117.2, 50.0 and 35.1; MS, *m/z* 324.

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]*indan*-1-*one oxime* (**24**). Mixture of 56% *Z* and 44% *E* by NMR (±5%); m.p. 182–185 °C (decomp.); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 159.2, 156.4, 155.4, 153.3, 153.2, 145.1, 144.4, 134.5, 131.8, 131.2, 130.4, 128.3, 127.5, 127.2, 126.4, 125.8, 125.6, 124.2, 120.9, 116.1, 46.2 (*E*); 42.4 (*Z*), 38.7 and 37.9; MS, *m/z* 339.

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]-α-*tetralone* (**25A**). M.p. 165–166 °C (decomp.); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 193.0, 160.1, 153.9, 144.8, 135.1, 132.1, 129.9, 128.0, 127.8, 127.4, 125.1, 117.2, 50.8, 31.5 and 29.7; MS, *m/z* 338.

2-[1-(4-*Hydroxyphenyl*)-5(1H)-*tetrazolylthio*]-α-*tetralone oxime* (**25**). M.p. 190 °C (decomp.); ^{13}C NMR ([$^2H_6$]DMSO) δ_C 159.2, 152.8, 148.8, 136.9, 129.2, 129.1, 128.7, 126.5, 126.4, 124.2, 123.5, 116.1, 39.0, 26.1 and 24.4; MS, *m/z* 353.

IR spectra were recorded on a Perkin-Elmer 727B IR spectrometer and ^1H and ^{13}C NMR spectra were recorded on EM-390, CFT-20 and XL-300 Varian spectrometers.

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