281. Beckmann Fragmentation and Rearrangement. Part VI Thian-3-one oximes

Fragmentation Reactions No. 26

by **Cyril A. Grob** and **Junya Ide**

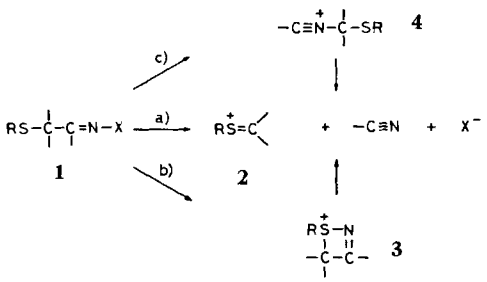
Institute of Organic Chemistry, University of Basel

(16. X. 74)

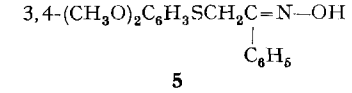
Summary. In 70% aqueous dioxane thian-3-one *anti*-oxime *p*-toluenesulfonate (tosylate) (**8b**) undergoes concerted fragmentation to the methylidenesulfonium ion **14**, part of which recyclizes to 1,3-thiazepin-4-one (**11**). With the *syn*-isomer **8b** rearrangement to 1,4-thiazepin-3-one (**10**) and fragmentation to **14** occur in the ratio 4:1. Analysis of the rate data in 80% ethanol shows that *anti* fragmentation is 142 times as fast as *syn* fragmentation, but only 26 times as fast as rearrangement of the 'homomorphous' thian-4-one oxime tosylate (**18b**). A comparison of the rates of cyclohexanone oxime tosylate **20**, thian-3- and -4-one oxime tosylates reveals the rate retarding influence of sulfur. – The configurations assigned to the stereoisomeric thian-3-one oximes (**8a**) in the literature have to be reversed in the light of present results.

Heterolytic fragmentation [1] of an α-alkylthio ketoxime derivative of the type **1** (X = nucleofuge) should lead to a methylidenesulfonium ion **2** and a nitrile (reaction a), (*Scheme 1*).

Scheme 1



A reaction of this kind was apparently first observed by *Vinkler & Autheried* [2] who reported in 1948 that one isomer of α-(3,4-dimethoxyphenylthio)-acetophenone oxime (**5**), presumably the *anti*-form[1]), was cleaved to benzonitrile upon reaction with benzenesulfonyl chloride in pyridine or with phosphorus pentachloride. The second isomer, however, underwent the *Beckmann* rearrangement to the amide **6**.



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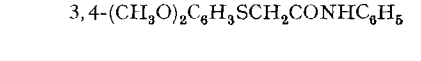

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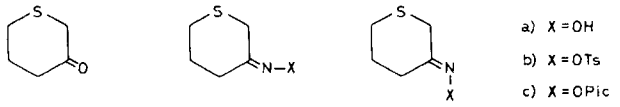
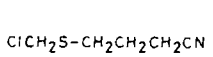
The fragmentation of α-alkylthio ketoximes was subsequently studied by *Autrey & Scullard* [3] and by *Ohno et al.* [4]. The former authors proposed an alternative path-

[1]) *Syn* or *anti* with respect to the hydroxy and α-alkylthio groups.

way for fragmentation involving the formation and subsequent cleavage of an intermediate 1,2-thiazetin-1-ium salt **3** (reaction b), *Scheme 1*). Recently *Hill & Cullison* [5] have sought to distinguish between these two routes by incorporating the sulfur atom in the ring of a cyclic α-alkylthio ketone, such as thian-3-one (**7**). Since both the *syn*- and *anti*-oximes **8a** of this ketone are unable to cyclize for structural reasons, fragmentation should not occur if a thiazetin-1-ium salt **3** were an obligatory intermediate.



7 *syn*-**8** *anti*-**8**



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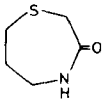

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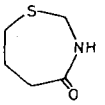

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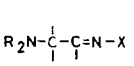
Treatment of an oxime of m.p. 96°, assumed by *Hill & Cullison* to be the pure *anti*-isomer **8a**, with thionyl chloride or with PCl_5 yielded the α-chloro thioether **9** in good yield. It was therefore concluded that fragmentation had occurred by pathway a). Treatment of the same oxime with *p*-toluenesulfonyl chloride and pyridine produced 11% of the rearranged lactam **10** besides fragmentation product. This result was surprising because *Beckmann* rearrangement of the *anti*-oxime tosylate **8b** should furnish the isomeric lactam **11**[2]). The authors therefore concluded that some *anti*/*syn* isomerization had taken place [5].

Prior to this report we had studied the rates and products of thian-3-one *syn*- and *anti*-oxime *p*-toluenesulfonates (tosylates) **8b** in aqueous solvents. This study was undertaken to determine the extent and mechanism of fragmentation of isomeric α-alkylthio ketoximes and, in particular, to distinguish between the concerted mechanism a), which applies to α-amino ketoximes (**12**) [7], and the rearrangement-fragmentation pathway c) (*Scheme 1*). The latter two-step mechanism can occur with oximes containing weakly electrofugal groups, such as *t*-butyl methyl *anti*-ketoxime (**13**) [8]. Acyclic α-alkylthio ketoximes **1** were included in this investigation in order to seek evidence for the cyclization mechanism b), as described in the following paper [9].



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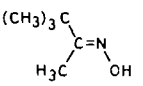

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Results. – Oximation of thian-3-one (**7**) led to a 7:3 mixture of oximes **8a** from which a pure isomer of m.p. 103–104° was isolated by recrystallisation. The NMR. spectrum of this oxime showed a singlet at δ 3.40 due to the C(2) methylene group.

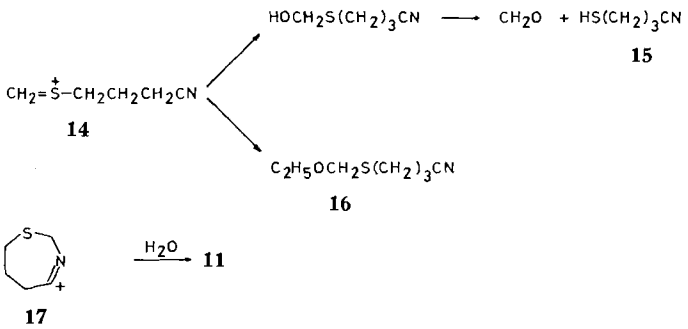
[2]) Migration of the carbon atom *anti* to the nucleofugal group X is well established in the *Beckmann* rearrangement [6].

The same δ value was reported by *Hill & Cullison* [5] for their oxime (m.p. 96°), which is undoubtedly identical despite the somewhat lower but uncorrected melting point. Attempts to isolate the isomeric oxime failed, mixed crystals of m.p. 73–74° being invariably obtained. These contained *ca.* 66% of the second isomer, as determined by NMR. assay of the corresponding C(2) methylene singlet at δ 3.20.

However, an analysis of the NMR. spectra does not support the configurations assigned by the above authors [5], who based their conclusions on the shifts of the C(2) methylene singlets at δ 3.2 and 3.4 caused by the shift reagent tris(dipivalomethanato)europium. Since a smaller downfield shift was observed with the oxime of m.p. 96° and with δ 3.4, it was assigned the *anti* configuration. Actually, *syn*-oximes produce smaller downfield shifts as recently shown by *Berlin & Rengaraju* [10][3]). The pure oxime of m.p. 96° (this work m.p. 104°) and with δ 3.4 is therefore the *syn*-isomer **8a**[4]). This is also borne out by the larger deshielding of the C(2) methylene protons caused by the neighbouring hydroxy group [11]. Our revised assignments are further supported by the rates and products of the isomeric oxime tosylates **8b**, as reported below.

The *syn*-oxime **8a** gave a crystalline *p*-toluenesulfonate (tosylate) **8b** and 2,4,6-trinitrophenyl ether (picryl ether) **8c**. Attempts to isolate the unstable tosylate **8b** of the *anti*-oxime failed. A mixture of tosylates prepared *in situ* with butyllithium and tosyl chloride and containing 54.5% *anti*- and 45.5% *syn*-isomer[5]) was therefore used for the determination of the rates and products of the *anti*-oxime tosylate **8b** (see experimental section).

Scheme 2



Reaction of the pure *syn*-oxime tosylate **8b** in 70% aqueous dioxane buffered with triethylamine at 23° afforded the known lactam **10** as the major product in 81% yield, but none of the isomeric lactam **11**. In addition 18.5% of formaldehyde was isolated as the bis-dimedone derivative. Formaldehyde is formed together with γ-mercaptobutyronitrile (**15**) by hydrolysis of the fragmentation product, the methylidenesulfonium ion **14** (*Scheme 2*). The nitrile **15** was present in the reaction product (IR. band at 2260 cm^{-1}) but underwent further reaction[6]) when attempts to isolate it

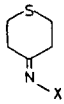
[3]) The authors suggest that coordination of the nitrogen lone pair brings about the shift.

[4]) This also follows from observed solvent shifts [5].

[5]) The original mixture of 34% *syn*- and 66% *anti*-oxime **8a** is isomerized by butyllithium (see experimental section).

[6]) Probably cyclization.

were made. However, when the *syn*-oxime tosylate **8b** was solvolyzed in ethanol, the stable ethoxy derivative **16** of the methylidenesulfonium ion **14** was obtained in 18.3% yield. Solvolysis of the *syn*-oxime tosylate **8b** therefore leads to *ca.* 82% rearrangement and *ca.* 18% fragmentation. This result was confirmed in an analogous reaction of the *syn*-oxime picryl ether **8c** in 70% dioxane.



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a) X = OH
b) X = OTs

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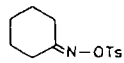

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As mentioned above, the *anti*-oxime tosylate **8b** was unstable and decomposed upon isolation. It was therefore prepared and reacted *in situ* as a mixture containing 45.5% of the *syn*-isomer. In 70% dioxane 72% of formaldehyde and 27% of lactam **11** were obtained from *anti*-**8b**, after correction for the known products from the *syn*-isomer. The lactam **11** could be formed by a *Beckmann* rearrangement of the *anti*-oxime tosylate **8b**. Alternatively, it could be produced by recyclization of the first formed methylidenesulfonium ion **14**, *i.e.* by fragmentation and recombination *via* the nitrilium ion **17** (*Scheme 2*). The latter route simulates a normal *Beckmann* rearrangement of the *anti*-oxime tosylate **8b** and has been observed previously in the fragmentation of cyclic α-amino ketoximes [7].

Table 1. *First order rate constants for cyclic ketoxime tosylates in 80 vol.% ethanol, c* = 10^{-3} M[a]). Mean deviation ±1,5%

oxime tosylate	*t* (°C)	$k \times 10^5$ (s^{-1})	$H^{\neq}$ kcal/mol	$S^{\neq}$ cal/mol degree
anti-**8b**	13.0	170.16[b])		
syn-**8b**	13.0[c])	6.55		
	22.9	23.16		
	23.0[c])	23.29	20.7	– 5.3
	33.0	74.54		
	43.0	229.38		
18b	13.0[c])	6.06		
	23.0	20.94	20.9	– 4.9
	33.0	76.35		
	43.0	209.51		
20	4.9	196.89		
	13.0	523.55		
	22.9	1617.9		
	23.0[c])	1635.0[d]	18.5	– 4.0

a) Determined conductometrically in the presence of two equiv. of triethylamine.
b) Calculated from the rate constant for the mixture of *syn*- and *anti*-oxime tosylates (see experimental section).
c) Extrapolated.
d) Previous value [8]: *k* (23°) 1660 × 10^{-5}.

The origin of the lactam **11** was clarified by reacting the *anti*-oxime tosylate **8b** in ethanol buffered with triethylamine, when 92% of the stable ethoxylated sulfide **16** and only 5.5% of the lactam **11** were formed. Clearly, the methylidenesulfonium ion **14** is first formed and subsequently trapped by the nucleophilic solvent. In 70% dioxane cyclization to **11** competes more successfully. Fragmentation is therefore the dominant, if not exclusive, reaction of the *anti*-oxime tosylate **8b**.

The rate constants for the *syn*- and *anti*-oxime tosylates **8b** in 80% ethanol are listed in Table 1. Included are the rate constants for the tosylate **18b** of the isomeric thian-4-one oxime (**18a**), and for cyclohexanone oxime tosylate (**20**). The latter compounds undergo normal *Beckmann* rearrangement to the lactam **19** and to caprolactam, respectively. They were required as standards to evaluate the polar and steric effects of sulfur on the ionization rates of the tosylates **8b**.

Discussion. – Thian-3-one *syn*-oxime tosylate **8b** undergoes competitive rearrangement and fragmentation in the ratio 82:18. On the other hand, the *anti*-isomer **8b** undergoes practically quantitative fragmentation followed by partial recombination of the methylidenesulfonium ion **14** to the lactam **11**. In addition, the configuration of the oxime tosylate markedly influences the reaction rate as shown in Table 2, which lists the relative rate constants for the tosylates **8b**, **18b** and **20**. Thus, *anti*-**8b** reacts 26 times as fast as *syn*-**8b**. However, the ratio of the rates of *anti* and *syn* fragmentation is much higher, namely 142. This ratio is obtained by partitioning the observed rate constant for *syn*-**8b** into the rate constants for rearrangement (81.5%) and fragmentation (18.5%) (Table 2).

Table 2. *Relative rate constants for the oxime tosylates* **8b** *and the homomorphous tosylates* **18b** *and* **20** *in 80 vol.% ethanol at 13°*

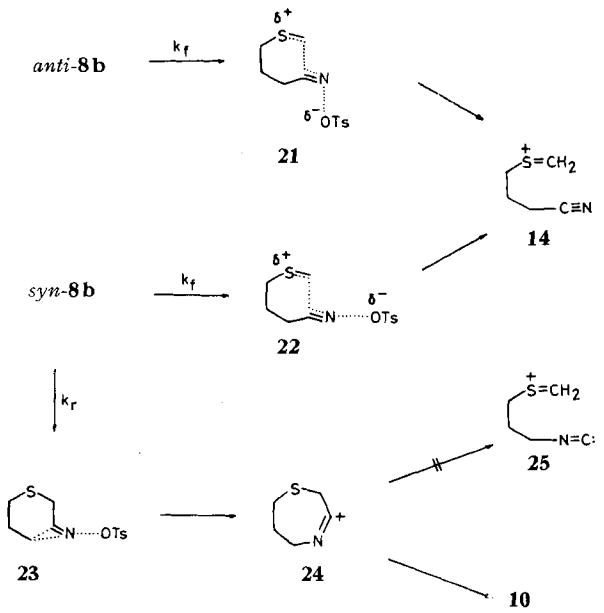
	$k_{obs} \times 10^5$	k_{obs}^{rel}	k_{frag}^{rel}	k_{rear}^{rel}
anti-**8b**	170.16	28.1	142	–
syn-**8b**	6.55[a]	1.1	1[b]	0.88[b]
18b	6.06	1	–	1
20	523.55	86	–	86

[a] Equal to the sum of k_{frag} (1.20×10^{-5}) and k_{rear} (5.35×10^{-5}).
[b] Calc. from k_{obs} and the fragmentation to rearrangement ratio of 18.5:81.5.

A high *anti*/*syn* fragmentation rate ratio was anticipated on stereoelectronic grounds. In the case of stereo-isomeric α-amino ketoxime derivatives (**12**) the *anti*-forms react *ca.* 10^3 times as fast as the *syn*-forms [7], thus demonstrating the preference for *anti* fragmentation. The high relative rate and the practically quantitative formation of fragmentation product implicate a concerted mechanism for *anti*-**8b**, involving simultaneous cleavage of the C(2)–C(3) and N–OTs bonds in the transition state **21** (*Scheme 3*).

These findings exclude the alternative rearrangement-fragmentation pathway c) (*Scheme 1*). In this case an intermediate nitrilium ion **17** should be formed at a rate comparable or lower than the rate of rearrangement of *syn*-**8b** or of thian-4-one oxime tosylate **18b**.

Scheme 3



The formation of lactam **10** and fragmentation product **14** from the *syn*-oxime tosylate **8b** raises the question whether rearrangement and concerted fragmentation are competitive processes (k_f and k_r in *Scheme 3*) or whether they occur *via* a common intermediate. The intermediate for *Beckmann* rearrangement is the bent nitrilium ion **24** formed through the transition state **23** [8]. However, the ion **24** cannot be an intermediate in fragmentation, because its cleavage would lead to the isonitrile **25** or its hydrolysis products, none of which were detectable. Concerted *syn* fragmentation k_f therefore competes with rearrangement k_r in the ratio 18.5:81.5 (*Scheme 3*). Concerted *syn* fragmentation has been shown to occur in α-amino ketoxime derivates **12** and to be stereo-electronically much less favorable [7].

It is noteworthy that the rearrangement of thian-3-one *syn*-oxime tosylate (**8b**) is somewhat slower than that of thian-4-one oxime tosylate (**18b**) (column 4 in Table 2). In these reactions the migration of a methylene group γ or β to sulfur, respectively, is involved. A reversed rate order would be expected on the basis of the rate retarding effect of an electron-withdrawing substituent [6] such as sulfur. This follows from a comparison between the rates of these compounds and of cyclohexanone oxime tosylate (**20**) (Table 2) which rearranges approximately 10^2 times as fast. However, steric effects due to different ring geometry undoubtedly modify polar effects. Since relevant information concerning these factors is lacking, any conclusions are bound to be speculative.

Finally, the rate enhancement due to concerted fragmentation of the *anti*-oxime tosylate **8b** (frangomeric effect) is only 28 if the rate of thian-4-one oxime tosylate (**18b**) is taken as the standard of reference. By contrast, concerted fragmentation of α-amino *anti*-ketoxime derivatives (**12**) is of the order 10^6 times faster than rearrange-

ment of homomorphous ketoxime derivatives [7]. This large difference reflects the much greater tendency towards formation of an aminocarbenium ion $(R_2N{=}CH_2)^+$ as compared to a thiocarbenium ion $(RS{=}CH_2)^+$. This question will be discussed in the following paper.

This work was supported by a grant no. 2.320.70 from the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung.*

Experimental Part

Melting points (m.p.) were determined on a *Kofler* block and are corrected. Boiling points (b.p.) are not corrected. NMR. spectra were measured on a *Varian* A-60 or HA-100 spectrometer; chemical shifts are recorded in ppm relative to tetramethylsilane as an internal standard ($\delta = 0$). The IR. spectra (*Beckmann* IR-8) are recorded in cm^{-1}.

Thian-3-one (**7**) was prepared as described by *Leonard & Figueras* [12]: b.p. 67–68°/4 Torr (Lit. [12]: 101–102°/18 Torr).

syn- *and* anti-*Oximes* **8a**. A solution of 33.8 g (0.844 mol) of NaOH in 123 ml of water was added dropwise with stirring at 0° to a solution of 49 g (0.422 mol) ketone **7** and 59 g (0.844 mol) of hydroxylamine hydrochloride in 370 ml of 80% ethanol. After further stirring at 23° for 2 h the solution was concentrated *in vacuo*. After the addition of 150 ml water the mixture was extracted repeatedly with ether. The extracts were washed with a saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Ten recrystallizations of the solid residue (54.1 g) from 20% aqueous methanol afforded 8.2 g of pure *syn*-oxime **8a**, m.p. 103–104° (Lit. [5]: m.p. 96°). – IR. (CCl_4): 3600, 2600–3600, 1050, 888. – NMR. ($(CD_3)_2SO$): 1.8–2.4 (4H, *m*), $=C-CH_2CH_2-$; 2.72 (2H, *m*), CH_2S; 3.40 (2H, *s*), $=C-CH_2S$; 10.51 (1H, *s*), $=N-OH$.

C_5H_9NOS	Calc.	C 45.79	H 6.92	N 10.68	S 24.45%
(131.198)	Found	,, 45.86	,, 7.19	,, 10.88	,, 24.71%

Ten recrystallizations from 20% methanol of the residue from the first mother liquor gave 7.6 g of mixed crystals containing 33.7% *syn*- and 66.3% *anti*-oxime, m.p. 73–74°, as determined by integration of the singlets for the $=C-CH_2S$ protons at 3.40 (*syn*) and 3.20 (*anti*). IR. bands at 1035 and 904 are characteristic for the *anti*-oxime.

Isomerization of syn- *and* anti-*oximes* **8a**. A solution of 1.0 mol-equiv. of butyllithium in hexane was added at 0° under N_2 to a solution of 50 mg (0.38 mmol) of mixed crystals of **8b** containing 33.5% and 66.5% of the *syn*- and *anti*-forms, respectively, in 3 ml of dry tetrahydrofuran. After stirring at 0–5° for 1 h the lithium compounds were decomposed with 1 N HCl and the solvents removed *in vacuo*. The residue was taken up in benzene and washed with saturated aqueous NaCl solution and dried over Na_2SO_4. After evaporation of the solvent there remained 37 mg of a mixture of 45.5% *syn*- and 54.5% *anti*-oxime **8b**, as determined by integration of the $=C-CH_2S$ peaks at $\delta = 3.40$ and 3.20 ppm, respectively.

Thian-3-one syn-*oxime* p-*toluenesulfonate* (**8b**). To a solution of 150 mg (1.145 mmol) of *syn*-oxime **8a** in 10 ml of dry ether 1.145 mmol (1 equiv.) of butyllithium in hexane were added with a syringe with stirring under N_2 at $-15°$. The resulting suspension of the lithium salt was stirred a further hour at 0°. Then a solution of 219 mg (1.145 mmol) of *p*-toluenesulfonyl chloride in 5 ml of dry benzene was added at 0–5° and the reaction mixture stirred for 2 h at 5°. After removal of the deposited salt by filtration, the filtrate was evaporated *in vacuo* at 20°. The oily residue was taken up in 10 ml of benzene, the solution filtered and again evaporated to dryness. The residue was dissolved in 1.5 ml of chloroform, to which pentane was added until it became slightly cloudy. After standing at 5° for some hours, 230 mg (71%) of crystals deposited. After recrystallization from chloroform/pentane, m.p. 90.5–92°. – NMR. ($CDCl_3$): 2.0–2.5 (4 H, *m*), $=C-CH_2CH_2-$; 2.42 (3 H, *s*), $-CH_3$; 2.67 (2 H, *m*), CH_2S; 3.42 (2 H, *s*), $=C-CH_2S$.

$C_{12}H_{15}NO_3S_2$ (285.387) Calc. C 50.52 H 5.30 N 4.91% Found C 50.28 H 5.22 N 4.88%

Thian-3-one syn-*oxime 2,4,6-trinitrophenyl ether* (**8c**). To a solution of 131 mg (1 mmol) *syn*-oxime **8a** in 0.1 ml of dry pyridine and 0.5 ml of dry acetone a solution of 495 mg (1 mmol) of 2,4,6-trinitrochlorobenzene in 0.4 ml of dry acetone was added at 0°. The reaction mixture was

magnetically stirred for 4 h and the light-sensitive product precipitated by addition of 15 ml of dry methanol. Recrystallization of the solid (225 mg) by solution in a minimum of chloroform and addition of pentane afforded 216 mg (63%) of pale yellow crystals, m.p. 123–124°. – NMR. ($CDCl_3$): 3.55 (2 H, *s*), $=C-CH_2S$.

$C_{11}H_{10}N_4O_7S$ (342.293) Calc. C 38.60 H 2.95 N 16.37% Found C 38.70 H 2.70 N 16.56%

Thian-4-one oxime (**18a**) was prepared from the known ketone [13] by the procedure described for the oximes **8a** and recrystallized from hexane: fine needles, m.p. 84–85° (Lit. [14]: m.p. 84–85°).

C_5H_9NOS (131.198) Calc. C 45.79 H 6.92 N 10.68 S 24.45%
Found ,, 46.03 ,, 7.06 ,, 10.54 ,, 26.66%

Thian-4-one oxime *p*-toluenesulfonate (**18b**) was prepared from the oxime **18a** by the procedure described for the *syn*-oxime tosylate **8b**. The crude product was recrystallized by dissolving in dry ether, adding an equivalent amount of pentane and cooling, m.p. 81–83°.

$C_{12}H_{15}NO_3S_2$ (285.387) Calc. C 50.52 H 5.30 N 4.91% Found C 50.75 H 5.58 N 5.08%

Cyclohexanone oxime *p*-toluenesulfonate (**20**) was prepared from the oxime with one equivalent each of butyllithium and *p*-toluenesulfonyl chloride, as described for *syn*-**8b**. After recrystallization from benzene/pentane, m.p. 58–60° (Lit. [15]: m.p. 57–58°).

Preparative Solvolyses. – All runs were repeated at least once.

Thian-3-one syn-*oxime* p-*toluenesulfonate* **8b**. A solution of 140 mg (0.492 mmol) of *syn*-**8b**, 140 mg (1 mmol) of dimedone and 98 mg (0.98 mmol) of triethylamine in 10 ml of 70 vol.% dioxane was stirred at 23° for 10 h, then warmed to 60° for 15 min. To the cooled solution 120 ml of an aqueous buffer solution (prepared from 80 ml 1N sodium acetate and 40 ml 1N hydrochloric acid) were added. After standing for 2 h at 0° the deposited crystals were filtered onto a sintered glass funnel, washed with 10 ml of cold water and dried over P_2O_5 *in vacuo* for 3 h. 26.5 mg (18.4%) of the *bis-dimedone derivative* were obtained (average of several runs), m.p. 187–190°; after recrystallization from ethanol, m.p. 189–190°, which did not depress the m.p. of an authentic sample.

In a further run, 190 mg (0.666 mmol) of *syn*-**8b** and 135 mg (2 equiv.) of triethylamine were reacted in 70% dioxane for 10 h at 23°. The solution was concentrated *in vacuo* and, after addition of 0.5 ml of water, extracted with 10 ml of benzene. Evaporation of the dried benzene solution gave a solid, which was purified on a silica gel column by eluting with chloroform. From benzene 71 mg (81%) of the lactam *1,4-thiazepin-3-one* (**10**), m.p. 141–142° (Lit. [16]: m.p. 141–142.5°). – IR. (CCl_4): 3410 (free NH), 3100–3600 (assoc. NH), 1660 (NHCO). NMR. (CCl_4): 3.26 (2 H, *s*), $S-CH_2C=O$.

C_5H_9NOS (131.198) Calc. C 45.79 H 6.92 N 10.68 S 24.45%
Found ,, 46.03 ,, 7.18 ,, 10.58 ,, 24.13%

Thian-3-one syn-*oxime 2,4,6-trinitrophenyl ether* (**8c**). A solution of 261.3 mg (0.762 mmol) of picryl ether **8c**, 107 mg (0.762 mmol) of dimedone and 160 mg (1.54 mmol) of triethylamine in 10 ml of 70% dioxane was thermostated at 57° for 18 h. The coloured reaction mixture was buffered as described for *syn*-**8b** and cooled to 0° for 2.5 h. Yield 36 mg (16.16%) of the *bis-dimedone derivative*, m.p. 189–191°. The average yield in several runs was 16%.

Ethanolysis of syn-*oxime tosylate* **8b**. A solution of 457 mg (1.61 mmol) of *syn*-**8b** and 165 mg triethylamine in 50 ml dry ethanol was kept at 23° for 60 h. After evaporation of the solvent *in vacuo* 1.5 ml of water were added and the mixture extracted with five 10 ml portions of pentane. The extracts were dried over Na_2SO_4 and evaporated to dryness. The residue, 92 mg of oil, was chromatographed on 5 g of silica gel. Elution with benzene/ether 20:1 afforded 50 mg of the *ethoxy sulfide* **16**, which was identical with a sample from the *anti*-**8b** described below. Gas-chromatographic analysis of the product of an analogous reaction showed the presence of 18.3% ethoxy sulfide **16**.

Thian-3-one anti-*oxime* p-*toluenesulfonate* (**8b**). To a cooled solution of 100 mg (0.762 mmol) of a mixture (m.p. 73–74°) containing 66.3 mg *anti*- and 33.7 mg *syn*-oxime **8a** in 5 ml dry tetrahydrofuran were added 1.05 mol-equiv. of butyllithium in hexane with stirring under N_2. After further stirring for 2 h at 0° a solution of 152 mg (0.8 mmol) of *p*-toluenesulfonyl chloride in 8 ml tetrahydrofuran was added to the lithium oximate (this contained 54.5% *anti*- and 45.5% *syn*-isomer, as shown by the above isomerization experiment). Stirring was continued for 2 h at 0°

and the solvent evaporated *in vacuo* below 0°. The residue, consisting of *anti*- and *syn*-**8b**, was immediately dissolved in 10 ml of 70% dioxane, to which 224 mg (1.59 mmol) of dimedone and 18 mg of triethylamine had been added. After standing for 10 h at 23° and for 15 min at 60°, 120 ml of aqueous acetate buffer (see above) were added to the cooled solution. After 2 h at 0° the deposited crystals were filtered off, washed with cold water and dried over P_2O_5 *in vacuo* for 3 h. The amount of *bis-dimedone derivative*, 106.1 mg, m.p. 187–190°, corresponds to a yield of 72.5% formaldehyde from the *anti*-oxime tosylate and 18.4% from the *syn*-oxime tosylate.

In an analogous run 1.50 g of a mixture of *syn*- and *anti*-oximes **8a** were converted to the corresponding tosylates, which were reacted in 30 ml of 70% dioxane containing 1.8 g of triethylamine for 60 h at 23°. The solution was concentrated *in vacuo* to one tenth and extracted repeatedly with benzene/chloroform 5:1. The extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The residue, 514 mg, was chromatographed on 8 g of silica gel. Chloroform eluted 98% of a mixture of 81% lactam **11** and 19% of lactam **10**, as determined by gas-chromatography. Repeated chromatography on silica gel yielded 45 mg of the lactam *1,3-thiazepin-4-one* (**11**). Crystallization from benzene, m.p. 136–137.5°. – IR. ($CHCl_3$): 3420 (free NH), 3150–3360 (assoc. NH), 1660 (NHCO). – NMR. ($CDCl_3$): 2.02 (2 H, *m*), C—CH_2—C; 2.59 (2 H, *t*), CH_2CO; 2.94 (2 H, *t*), CH_2S; 4.33 (2 H, *d*, J = 4 Hz), SCH_2N; 6.70 (1 H, br.), NH. The doublet at 4.33 is replaced by a singlet when D_2O is added, which proves the partial structure —SCH_2NH— of **11**.

C_5H_9NOS	Calc.	C 45.79	H 6.92	N 10.68	S 24.45%
(131.198)	Found	,, 45.93	,, 6.75	,, 10.84	,, 24.62%

Direct analysis of the reaction mixture by gas-chromatography, employing an authentic sample of **11** for calibration, showed the yield of the lactam to be 28.3%.

Ethanolysis of thian-3-one anti-*oxime* p-*toluenesulfonate* **8b**. 250 mg of a mixture containing 55.3% *anti*- and 44.7% *syn*-oxime **8a** were converted by butyllithium to a mixture of 51.5% lithium *anti*- and 48.5% *syn*-oximates. This was treated with 400 mg of *p*-toluenesulfonyl chloride in 7 ml of dry tetrahydrofuran, and the resulting tosylates **8b** reacted in 50 ml of dry ethanol containing 197 mg of triethylamine for 16 h at 23° and 8 h at 50°. After evaporation of the solvent *in vacuo* 2.5 ml of water were added and the mixture extracted repeatedly with pentane. Evaporation of the dried extracts left 288 mg of an oil which was chromatographed on 8 g of silica gel. Benzene/ether 10:1 eluted 129 mg (92%) of the *ethoxy sulfide* **16**, which was distilled at 15 Torr and a bath temperature of 155–165°. A pure sample was obtained by preparative gas-chromatography. – IR. (CCl_4): 2160 (CN), 1085 (C—O—C). NMR. (CCl_4): 1.18 (3 H, *t*, J = 7.0 Hz) and 3.52 (2 H, *q*, J = 7.0 Hz), OCH_2CH_3; 4.55 (2 H, *s*), OCH_2S.

$C_7H_{13}NOS$ (159.254) Calc. C 52.81 H 8.23 N 8.80% Found C 53.07 H 8.39 N 9.04%

Besides the ethoxy sulfide **16**, 5.5% of the lactam **11** were detected by quantitative gas-chromatography, employing an authentic sample for calibration.

Thian-4-one oxime p-*toluenesulfonate* (**18b**). To the lithium salt, prepared from 500 mg (3.81 mmol) of the oxime **18a** and 1.05 equiv. of butyllithium in 20 ml dry ether, was added a solution of 763 mg (4.0 mmol) of *p*-toluenesulfonyl chloride in 20 ml ether at 0°. The mixture was stirred for 4 h and evaporated *in vacuo*. The residue was treated in 15 ml of 70% dioxane containing 570 mg of triethylamine for 15 h at 23°. The solvent was evaporated *in vacuo*, 5 ml of water added and the mixture repeatedly extracted with benzene. The extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated. The solid residue of *1,4-thiazepin-5-one* (**19**) (yield 98%) was recrystallized from benzene, m.p. 116–117° (Lit. [17]: m.p. 117–118°). – IR. ($CHCl_3$): 3415 (free NH), 3150–3400 (assoc. NH), 1655 (NHCO).

C_5H_9NOS	Calc.	C 45.79	H 6.92	N 10.68	S 24.45%
(131.198)	Found	,, 46.07	,, 6.79	,, 10.74	,, 24.29%

Kinetic measurements. – The reaction rates for *syn*- and *anti*-**8b**, **18b** and **20** were measured by the previously described conductometric method [18]. The rate constant for *anti*-**8b** was determined with a known mixture of *anti*- and *syn*-**8b** prepared *in situ*. Since the conductivity change due to the pure *syn*-isomer and the total change are directly measured, the change due to the *anti*-isomer is obtainable by substraction [19].

Elemental analyses by Mr. *E. Thommen*, NMR. spectra by Mr. *K. Aegerter*.

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282. *Beckmann* Fragmentation and Rearrangement. Part VII. Fragmentation and Cyclization of α-Methylthio-Ketoximes

Fragmentation Reactions No. 27

by **Cyril A. Grob** and **Junya Ide**

Institute of Organic Chemistry, University of Basle

(16. X. 74)

Summary. α-Methylthio-propiophenone *anti*-oxime *p*-toluenesulfonate (tosylate) (**12b**) fragments quantitatively in 80% ethanol yielding benzonitrile and a methylidenesulfonium ion **15**. The *syn*-isomer, however, undergoes a *Beckmann* rearrangement. The fragmentation of α-methylthio-isobutyrophenone *anti*-oxime tosylate (**13b**) is accompanied by cyclization to the 1,2-thiazetin-1-ium ion **27**, which is hydrolyzed *via* the sulfimine **29** to the keto sulfide **20** and the keto sulfoxide **30**. A comparison of the rates of the α-alkylthio *anti*-ketoxime tosylates **12b** and **13b** and of the homomorphous oxime tosylates **16b** and **17b** shows that fragmentation and cyclization are strongly assisted by the sulfur atom. Whereas both the *anti*- and *syn*-isomers of α-amino ketoxime derivatives fragment quantitatively, only the *anti*-isomers of α-alkylthio ketoxime derivatives undergo facile fragmentation.

In Part VI [1] three pathways were considered for the nitrile forming fragmentation [2] of α-alkylthio ketoxime derivatives **1** (*Scheme 1*, X = nucleofugal group), *i.e.* a) a concerted process; b) rearrangement to a nitrilium ion **2** followed by cleavage to a methylidenesulfonium ion **3** and a nitrile, and c) cyclization to a 1,2-thiazetin-1-ium ion **4** which also leads to fragmentation products.