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CYCLISATION VERSUS ELIMINATION REACTIONS IN A NEIGHBOURING GROUP SYSTEM

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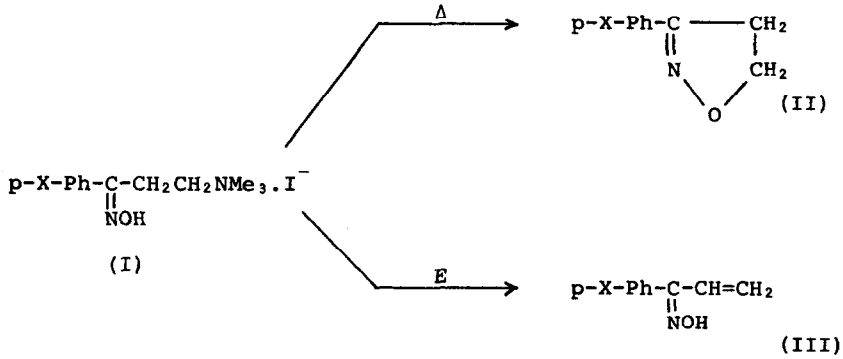
Oximate anion can be powerfully anchimeric towards saturated carbon.[1] While we have used this effect to prepare optically active isoxazolines[2] its broader synthetic use depends upon the extent to which the anchimeric process dominates over other competing processes such as elimination reactions. We report herein how this balance between cyclisation (Δ) and elimination (E) reactions in oxime systems changes with variation in leaving group, ring and side-chain substitutions and lyate ion. To our knowledge this is the first such general study of Δ vs. E processes in a neighbouring group situation and the patterns we observed may have wide application.



Scheme 1, X = MeO, H, Br, NO_2.

With $H_2O/^-OH$ as the solvent/lyate ion pair we examined how the reaction pattern* varied with the para-substituent (X) in the aryl ring of the parent ketoximes (I). The main reaction observed throughout was elimination, the vinyl ketoxime (III) being isolated in from 61% (X=NO_2) to 98% (X=H) yields, the minor product the isoxazoline (II) being detected in such amounts as 1.5% (X=H) to 18% (X=NO_2). In EtOH/EtO^- the reaction pattern was inverted, cyclisation being the major process in all five cases, in approximately 60 ±5% yields, with elimination occurring to 30 ±5%. With t-BuOH/t-BuO^- as the base system the Δ/E ratio was increased even further, yields of (II) being generally 90% and of (III) 10%. Within any lyate ion/solvent pair

*The reaction conditions which we used in general involved keeping the substrates (I) in solution with three equivalents of base (0.1M) at 45° for 2 hours. All reaction products were separated chromatographically.

the effect of specific ring substitution on the reactions observed was unpredictable i.e. it did not show a simple relationship with e.g. the σ of the substituent X.

The effect of lyate ion variation is best illustrated with the parent compound (I, X=H) (Table 1). While undoubtedly the solvent effects are many-sided, one observable correlation is that as solvent polarity is progressively decreased, cyclisation predominates. Only with the parent compound (I, X=H) was this lyate ion effect so pronounced.

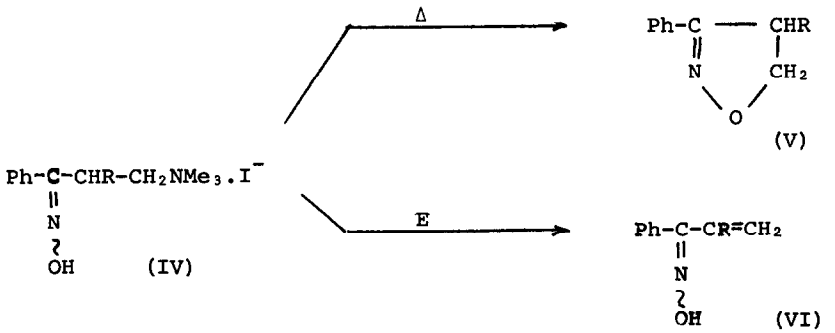
Table 1

Cyclisation/Elimination Patterns with Solvent/Base Variation					
Lyate ion	HO^-	MeO^-	EtO^-	$iPrO^-$	$tBuO^-$
Isoxazoline (II)(Δ)%	1.5[a]	21	71	90	97
Vinyl ketoxime (III)(E)%[b]	98	67	26	6	2.7[a]

[a]Very careful workup of the reaction mixtures enabled us to intercept those small quantities of the minor products. We recorded these in an earlier report.[1]

[b]Configurational studes[3] show the oxime group in both substrate and product is *anti* to the phenyl group.

Two kinds of side-chain substitution were examined. First, (Scheme 2) involved substitution at C-2 (compound IV). In the substrates here configurational factors became involved. Thus compound (IVa) as normally prepared[2] is a mixture of *syn-anti* isomers* in a ratio of 3 : 1 (^{1}H n.m.r.). Oximation in



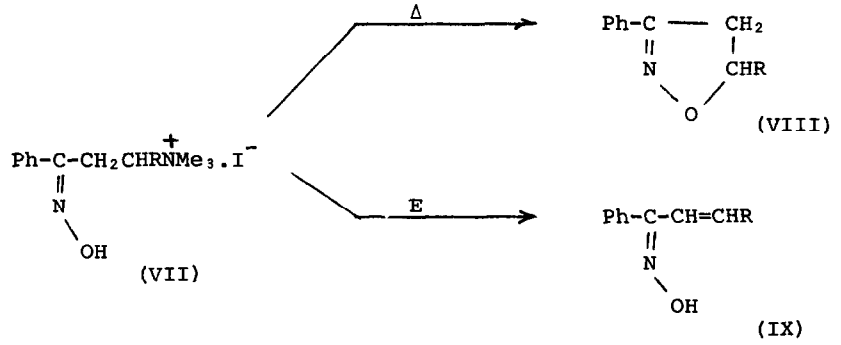
Scheme 2, a, R=Me; b, R=Ph.

*The terms *syn* and *anti* refer to the relationship between the 1-phenyl group and the oxime -OH.

pyridine[4] gave a *syn-anti* ratio of 2 : 3, which could not be further separated. When this mixture was submitted to our lyate ion gamut (H_2O/ HO^-, EtOH/ EtO^-, t-BuOH/t-BuO^-) the reaction products ratio was insensitive to the medium variation, the isoxazoline (V) being isolated in 51 ±2% yield, the elimination product (VI) in 25 ±5%. If one assumes that cyclisation arises from the *anti* isomer (present in 60%) and elimination from the *syn* (present in 40%)[5] then the Δ/E ratio encountered suggests that with the 2-methyl compound (IVa) cyclisation is almost complete even in aqueous base (unlike the behaviour of compound I, X = H).

With the 2-phenyl compound (IVb) the results were sharply different. While in the preparation of IVb from the parent ketone oximation conditions were critical, our normal procedure[3] leading to pure *syn* product, with oximation in pyridine[4] leading to mostly *anti* oxime. When the pure *anti*-form of (IVb) was submitted to our trio of lyate ion changes it also proved insensitive to such variation, (Vb) being isolated in only small yields (16 ±2%) whereas elimination predominates (76 ± 1%). Clearly steric factors played a major role. The *syn* 2-Ph compound (IVb) as expected gave only *syn* vinyl ketoxime (VIb) in all three solvent-lyate ion systems (Vb) being undetected (< 1%).

With the Mannich bases substituted at C-3 (V, Scheme 3) oximation[2] gave *anti*-isomers. When these materials (as methiodides VII) were subjected to our standard base solvent trio, cyclisation (compared to I, X = H) was favoured. Thus with the 3-Me substrate (VIIa), in HO^-, Δ was 10% (VIIIa) and in EtO^- and t-BuO^- it was 74%, E (IXa) being 78, 9 and 2% respectively. With the 3-Ph compound (VIIb), Δ was ≥ 98% in all three solvent/lyate ion-pairs.[6]



Scheme 3, a, R=Me; b, R=Ph.

Finally leaving group variation was examined, a range of materials of type $Ph\text{-}C(=NOH)CH_2CH_2\overset{+}{N}R_2Me.I^-$ (X) being prepared. Reaction of these in H_2O/HO^- revealed a major leaving group effect (Table 2) a decrease in pKa of the leaving group greatly favouring cyclisation.

Table 2

Cyclisation/Elimination Variation with change in Leaving Group, Compounds X in H_2O,HO^-.					
Compound X, NR_2 =	Piperidino	NMe_2	$NMeCH_2Ph$	morpholino	NMePh
Isoxazoline (II), Δ %	0.5	1.5	8	33	97
Vinyl ketoxime (III) E, %	98	98	85	60	1
Leaving Group (HNR_2) pKa	10	9.7	8.9	7.4	5.1

These studies have shown that by selection of suitable molecular frameworks and variation in reaction conditions, competition between cyclisation and elimination in model oxime systems may be directed as desired.

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4. K. Kotera, Y. Takano, A. Matsuura and K. Kitahonaki, Tetrahedron, 26, 539 (1970).
5. The pure *syn*-form of (IVa) was prepared by addition of dimethylamine to the corresponding *syn*-form of the vinyl ketoxime (VIa). This *syn*-material after quaternisation (CH_3I) was submitted to our lyate ion gamut and yielded largely ±90% elimination product (VIa).
6. This dramatic effect may be due to the Thorpe-Ingold effect {cf. e.g. C. K. Ingold and J. F. Thorpe, J. Chem. Soc., 1318 (1928)} and/or the presence of the benzylic type electrophilic centre (compare e.g. D. L. Coffen and D. G. Korzan, J. Org. Chem., 36, 390 (1971)).