Cleavage of Oxime Esters. A Concerted Reaction Proceeding Faster in Nonpolar Solvents

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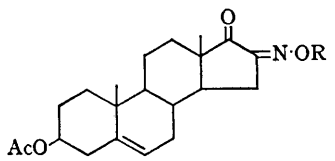
THE feasibility of fragmentation or cleavage in certain oximes under Beckmann rearrangement conditions has recently been recognised and has attracted considerable attention.[1-6] The cleavage of esters of α-keto-oximes (IV; X=Ac) occurs under even milder conditions, *i.e.* upon standing with aqueous solvents and alcohols,[5] and is of interest mechanistically and as a synthetic path to polyfunctional compounds.

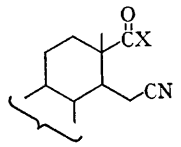
Whereas Ferris *et al.*[7] reported that compounds of type (IV) do not yield amides when treated with amines in alcohol, we can now show that (I) is readily cleaved by primary amines at 25° into amido-nitriles (IIIe–g) in 50–60% yield. Even amino-alcohols yield amides (IIIh–i) rather than esters. Concomitant hydrolysis to (II) accompanies the cleavage to the extent of 20%.

Increasing the steric requirements of the amines slows down the cleavage to the extent that even pyrrolidine or morpholine gives mainly hydrolysis of (I) to (II).

Of the three major paths (*a*, *b*, and *c*) that come into consideration for these cleavage reactions, the acylium ion path (*a*), favoured by other workers,[2,4,7] is unlikely on the basis of steric effects with amines and with alcohols. Thus, whereas at 25° complete cleavage of (I) takes place in methanol or ethanol within 24 hr., in isopropyl or t-butyl alcohol (I) is largely unaffected even after several days. On the other hand the more nucleophilic t-butoxide ion does



(I); R=Ac
(II); R=H

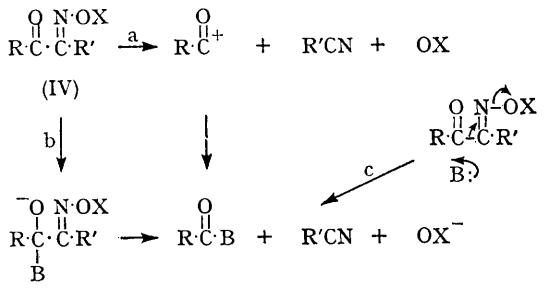


(III)

a; X=OMe
b; X=OEt
c; X=$OCMe_3$
d; X=SBu^n
e; X=$NH{\cdot}CH_2Ph$
f; X=$NHPr^n$
g; X=$NHBu^n$
h; X=$NH{\cdot}[CH_2]_2{\cdot}OH$
i; X=$NH{\cdot}[CH_2]_3{\cdot}OH$

[1] R. K. Hill, *J. Org. Chem.*, 1962, **27**, 29, and references cited.
[2] C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenzi, *Helv. Chim. Acta*, 1964, **47**, 1003, and references cited.
[3] G. H. Whitham, *Proc. Chem. Soc.*, 1959, 271.
[4] R. T. Conley, *J. Org. Chem.*, 1963, **28**, 278.
[5] A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, 1962, **27**, 1760.
[6] A. Hassner, A. W. Wentworth, and I. H. Pomerantz, *J. Org. Chem.*, 1963, **28**, 304.
[7] A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, 1960, **25**, 496.

cleave (I) to (IIIc) with concomitant hydrolysis to (II). Sodium butyl mercaptide readily gives (IIId) in 75% yield.



Reversible formation of an intermediate such as (V) is unlikely on the basis that (I) is unaffected by potassium propionate in acetonitrile and on the basis of solvent effects on the cleavage (see below).

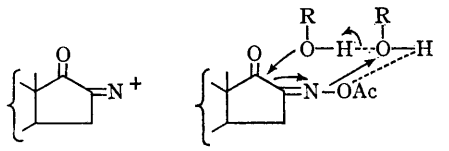
The effect of solvent polarity on the rates of conversion of (I) *into* (IIIa) *at* 25°

Solvent	*Z* Value*	Dielectric const.	Time (min.) per 1% conversion
Benzene	62·3	2·27	17
Chloroform	63·2	4·8	84
Dichloroethane ..	64·4	2	183
Dioxan	—	2·2	208
Acetonitrile	71·3	37·5	525
Acetone	65·7	21·2	9200
Dimethylformamide ..	68·5	37·6	17,500
Dimethyl sulphoxide	71·1	45	30,000

* see E. M. Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253.

The rates of conversion of α-keto-acetoxime (I) into nitrile ester (IIIa) with a 20-fold excess of methanol in a number of solvents emphasise the importance of a concerted process (path *c*) in this reaction. The cleavage is generally much slower in solvents of increased dielectric constant or ionising power, as shown in Table I.[8] An opposite trend would be expected for a solvolysis path involving a charged intermediate (path *a*), as well as for path *b*.

The solvent effect can be explained as a relief of interactions between the dipoles at C-16 and C-17 in (I) upon passing into the transition state; polar solvents can stabilise starting material (I) better than non-polar solvents. On the other hand the large rate differences can be accommodated by a concerted process as indicated by (VI) in which no net charges are developed in the transition state. In benzene the reaction is of first order in acetoxime (I) and the order in methanol is variable but approximately of second order.[8]



(V) (VI)

It appears that the cleavage of (I) with methanol belongs to an interesting class of solvent-assisted reactions which are speeded up in solvents of low polarity. This type of reaction might be of significance in biological processes.

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[8] The rates were followed by the appearance of the ester methyl peak in (IIIa) at τ6.3 and by the disappearance of the acetoxime methyl peak in (I) at τ7.7 in the n.m.r. spectrum.