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THE PYROLYTIC ELIMINATION OF ALDEHYDES FROM N-ALKYLOXY LACTAMS AND THIOLACTAMS

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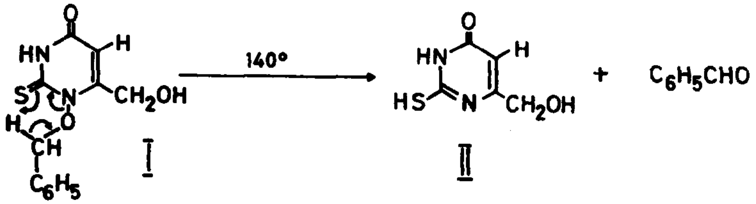
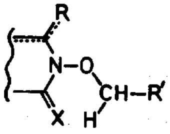
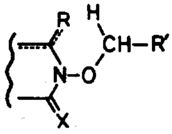
In two initially unrelated investigations we have observed the very ready loss of formaldehyde or benzaldehyde on mild pyrolysis of certain N-methoxy or N-benzyloxy lactams or thiolactams. Thus, the 2-thiouracil derivative (I) on heating in vacuo at 140° gave benzaldehyde and 6-hydroxymethyl-2-thiouracil (II); and attempts to synthesise mycelianamide dimethyl ether (XVII; R_6 = geranyl) have been frustrated by the ease with which substances of this type lose one mole of formaldehyde even at 65°.



We have examined some of the factors facilitating this reaction in the series of compounds (I-XVII) (1). Compounds were dissolved in d_6-dimethylsulphoxide (approx. 8% solutions) and heated in sealed n.m.r. sample tubes with vapour baths at 98°, 139° or 177°. Their decomposition was followed by n.m.r. spectrometry, by observing the disappearance of the benzylic protons of benzyloxy groups, or methoxyl protons of methoxy compounds, and by observing the appearance of the aldehydic proton of benzaldehyde. In all cases other proton-bearing groups provided suitable internal standards for integration of the spectra. Approximate half-lives for these decompositions are shown in the Table. The structural requirements for ready elimination are summarised by the generalised structure (III) below, and by the following observations:



IIIa



IIIb

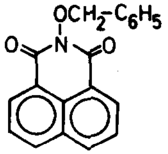
(i) The reaction is strongly facilitated by the presence of bulky substituents at R of (III). We consider that this is due to a relief of molecular overcrowding in the transition state for elimination of the alkoxyl group as aldehyde. Further, the population of the reactive planar conformation (IIIa) will be favoured with respect to the unreactive conformation (IIIb) when the size of the group R is increased. If this interpretation is correct, then the stereochemistry about the benzylidene double bond in mycelianamide and its very labile dimethyl ether must be as shown (XVII), as implied previously by Birch, Massy-Westropp, and Rickards (2). The related simple dioxopiperazine derivative (VIII) was stable in dioxan at 85° for 60 hr.

(ii) Decomposition is more rapid where X=S than where X=O (e.g., pairs of compounds XIII, IX and I, X), either because of greater nucleophilicity or greater size of the sulphur atom. This effect is also observed in the lower temperatures of decomposition of alkyl xanthates (ca. 200°) as compared with those of alkyl carboxylates (350-500°) (3). Methylation at N3 in the 2-thiouracil series (compound XIV) facilitates reaction, probably by increasing the nucleophilicity of the adjacent sulphur atom.

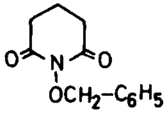
(iii) With the exception of the tetrahydropyranyl ether (VII; $T_{\frac{1}{2}}$ 0.9 hr./177°) the N-alkyloxy dicarboximides (4) (IV - VI) are stable under our most extreme conditions (d_6-DMSO/177°/20 hr.), despite the favourable statistical factor (two carbonyl groups) in this series. The nucleophilicity of X (Carbonyl oxygen) is probably lower in the compounds (IV - VI) than in the uracil derivatives (5) (IX - XII).

(iv) The benzyloxy compound (XVI) decomposed at a lower temperature than the corresponding methoxy compound (XV).

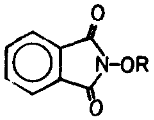
(v) The decomposition of the methoxy compound (XV was faster in the very polar solvent d_6-dimethylsulphoxide than in o-dichlorobenzene.



IV

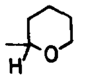


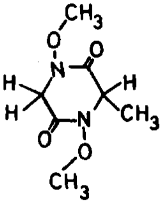
V



VI R = CH_2-C_6H_5

VII R =

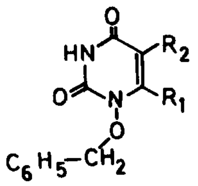
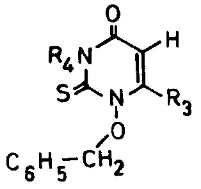
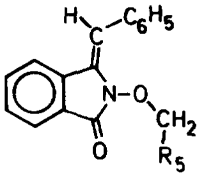
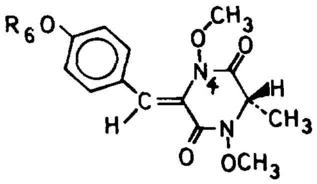




VIII

TABLE

Half-lives for Pyrolytic Elimination(a)

		R_1	R_2	t(°C)	$T_{\frac{1}{2}}$ (hr)
	IX	H	H	177	10.0
	X	CH_2OH	H	177	3.0
	XI	CH_3	CN	177	2.0
	XII	C_2H_5	CN	177	0.25
				139	30.0
		R_3	R_4	t(°C)	$T_{\frac{1}{2}}$ (hr)
	XIII	H	H	139	2.5
	XIV	CH_2OH	CH_3	139	0.1
	I	CH_2OH	H	139	0.33
				98	5.0
		R_5	R_6	t(°C)	$T_{\frac{1}{2}}$ (hr)
	XV	H	-	177	0.66
				177(d)	1.66
	XVI(c)	C_6H_5	-	139	1.2
	XVII(b,c)	-	Geranyl	65(e)	1.2

(a) Unless otherwise noted, the reactions were run in d_6-DMSO.

(b) Loss of the 4-methoxyl group is inferred from the behaviour of synthetic compounds in the mycelianamide series.

(c) Non-crystalline but characterised by satisfactory TLC behaviour, and by IR and NMR spectra.

(d) In o-dichlorobenzene.

(e) In benzene.

This elimination reaction is analogous to the thermal *cis*-eliminations of alkyl xanthates and carboxylates (3), and formally analogous to both Norrish Type II photochemical cleavage reactions of simple amides (6) and their mass spectral β-cleavage reactions with hydrogen transfer (7,8).

We have not found any clear parallel between ready thermal decomposition of these compounds and the occurrence of a strong [M - RCHO] peak in their 70 e.v. mass spectra. Thus the thermolabile compounds (IX), and (XIII), did show [M - RCHO] peaks, but compound (XV) did not.

Further synthetic work is in progress to define the scope of this reaction, and to duplicate the extreme lability of mycelianamide dimethyl ether. We thank Dr. C.S. Barnes (C.S.R. Research Laboratories) and Mr. E.A. Scribner (University of Sydney) for mass spectra and Mr. R.W. Rickards for a generous sample of mycelianamide.

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1. All crystalline compounds gave satisfactory analyses. Spectral data were in accord with assigned structures. Selected reactions were run on a preparative scale; benzaldehyde and formaldehyde were isolated as 2,4-DNP derivatives, and the lactam products identified by comparison with authentic samples.
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