The Reduction of 5,6-Dihydro-4*H*-1,3-oxazines to Tetrahydro-1,3-oxazines and the Formation of C-1 Deuteriated Aldehydes

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THE reduction of dihydro-4*H*-1,3-oxazines (I) to the tetrahydro-derivatives (II) has not been reported, perhaps because the ring opens too easily. As there are many routes[1] to compounds of type (I), a good reduction method would make the tetrahydro-oxazines (II) accessible, and so provide a new route to aldehydes from nitriles and carboxylic acids.[1] This method, utilizing the appropriate deuteriated reducing agent ($NaBD_4$) would also provide a convenient route to C-1 deuteriated aldehydes.[2] As part of a programme aimed at evaluating pH-controlled sodium borohydride reductions as a synthetic tool for sensitive groups,[3] we have investigated the reduction of the C=N linkage in dihydro-4*H*-1,3-oxazines (I) and obtained (at pH 7, −30°) good yields of the tetrahydro-1,3-oxazines (II) (see Table 1). Similar use of sodium borodeuteride gives comparable yields of the 2-deuterio-derivatives of (II). The effect of pH and temperature on this reaction was studied (Table 2) and the products vary from almost exclusive C=N reduction to almost exclusive ring cleavage to give the corresponding amino-alcohols (III). The extent of ring cleavage (to III) varies directly with the acidity of the medium, the amount of borohydride, and increasing temperatures. The ring cleavage need not necessarily occur *via* the tautomeric forms possible for (II) (A⇌B) since the *N*-methyl derivative, A (R′=Me) gave rise to the amino-alcohol, (V; R′=Me) upon treatment with sodium borohydride (pH 7, 0—5°). Since the *N*-methyl derivative

TABLE 1

2-*Substituted* 4,4,6-*trimethyltetrahydro*-1,3-*oxazines*

Cpd.	Yield (%)[a,b]	b.p. (torr)[d]	τ, 2-H
(IIa)	86[c]	68° (25)	5·9 (triplet)
(IIb)	78	82 (0·5)	5·4 (triplet)
(IIc)	88	93 (0·3)	5·6 (triplet)[e]
(IId)	85	96 (0·3)	4·8 (singlet)[e]
(IIe)	72	108 (0·3)	4·6 (singlet)

[a] The dihydro-1,3-oxazines (I), were prepared according to Ritter and Tillmans, *J. Org. Chem.*, 1957, **22**, 839; 1961, **26**, 218.

[b] Yields are for distilled products except where noted.

[c] Determined by quantitative gas chromatography. Distillation of (IIa) results in extensive polymerization; 57% was isolated after distillation.

[d] Correct elemental analyses were obtained for all compounds.

[e] Deuteriated compounds showed complete absence of these signals and the benzyl protons in (IIc) appeared as a singlet.

cannot exist as its open-chain tautomer, ring cleavage must occur by direct attack of the hydride species at C-2.† It is also quite likely that (V; R′=H) is formed directly from A (R′=H, R=alkyl) since there is no C=N stretch in the 6 μ region to suggest the presence of B.‡ For the 2-phenyl derivative (IId), the n.m.r. and i.r. spectra indicate that 30% of the open-chain tautomer, B, is indeed present. The 2-pyridyl derivative, (IIe), shows no evidence of the open-chain tautomer. The tetrahydro-1,3-oxazines (II) were hydrolyzed in 90% acetic acid (Table 3) to give the corresponding aldehydes, characterized as their 2,4-dinitrophenylhydrazones.

TABLE 2

Effect of temperature and pH upon the reduction of 2-substituted 4,4,6-trimethyl-5,6-dihydro-4H-1,3-oxazines (I)

Reaction temp.	pH	moles BH_4 / moles (I)	% (III)[a]	% (II)
		(Ia)		
0—5°	5	1	47	53
0—5	7	1	23	77
0—5	9	1	13	87
−15	7	1	14	86
−30	7	1	0	100
		(Id)		
0—5	7	1	10	90
0—5	3—5	5	100	0
−30	7	1	4	96

[a] Product composition determined by gas chromatography using a disc integrator.

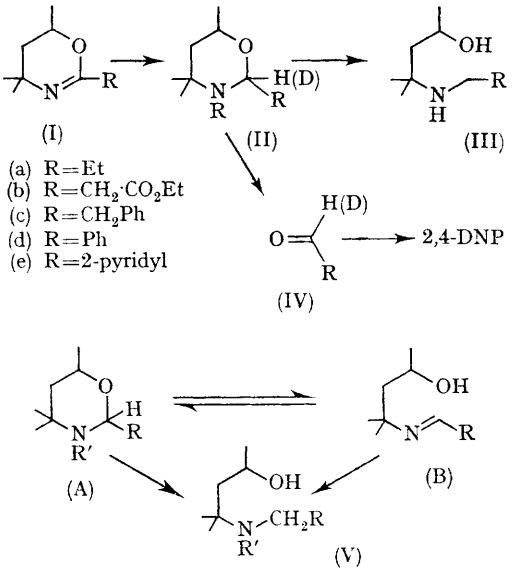
TABLE 3

Cleavage of tetrahydro-1,3-oxazines to aldehydes (IV)

Cpd. cleaved	Reaction conditions	Yield of 2,4-DNP %	m.p.°
(IIa)	90°, 1 hr.	79	147—150°
(IIc) (2-D)	90°, 5 min.	78[a]	118—120°
(IId) (2-D)	25°, 24 hr.	77[a]	240°

[a] Yield of deuteriated derivatives were comparable.

This procedure is typical for reducing (Ic) to (IIc): a solution of 10·85 g. of the dihydro-1,3-oxazine in 100 ml. of tetrahydrofuran–ethanol (1 : 1) was cooled to −30° in an open beaker equipped with electrodes attached to a pH meter. The pH of the solution was adjusted to 7 by the addition of 9N-hydrochloric acid followed by the dropwise addition of an aqueous solution of 1·2 g. sodium borohydride in 5 ml. water. The temperature was maintained at −30°, and the pH at 7, by simultaneous addition of 9N-hydrochloric acid. The solution was stirred at −30° for 1 hr. after addition of the reducing agent, then ether was added and the aqueous solution rendered alkaline. Separation of the organic layer and washing with saturated salt solution produced, after distillation of the concentrate, 9·7 g. (88%) of (IIc).



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† The amount of ring cleavage appears to depend upon the pH of the reduction. We are investigating this behaviour more fully.

‡ The C-2 proton in the n.m.r. spectrum integrates exactly to a single proton signal indicating that any open-chain tautomer would escape detection by this technique.

[1] Z. Eckstein and T. Urbanski, *Adv. Heterocyclic Chem.*, 1963, **4**, 311.

[2] A method for obtaining C-1 deuteriated benzaldehyde has recently been reported; D. Seebach, B. Erickson, and G. B. Singh, *J. Org. Chem.*, 1966, **31**, 4303.

[3] A. I. Meyers and J. M. Greene, *J. Org. Chem.*, 1966, **31**, 556; *J. Heterocyclic Chem.*, 1964, **1**, 300; A. I. Meyers and J. C. Sircar, *J. Org. Chem.*, 1967, **32**, in the press.