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1,2-OXAZINE CHEMISTRY—I

SYNTHETIC APPROACHES TO TETRAHYDRO-1,2-OXAZINES

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Abstract—The synthesis of a series of N-carbethoxytetrahydro-1,2-oxazines, by the reaction of 1,4-dibromobutane derivatives with N-hydroxyurethane under basic conditions, and their reduction to N-Me derivatives is described. Stereochemical and mechanistic points of interest in these reactions are discussed.

INTRODUCTION

The tetrahydro-1,2-oxazine ring system is of considerable conformational interest. Firstly the ring contains an N—O bond and it is known[1-6] that preferred torsion angles about heteroatom–heteroatom bonds differ appreciably from those about C—C bonds. Secondly trialkylhydroxylamine systems are known to display slow nitrogen inversion processes in their NMR spectra.[7] Thirdly there are four different ring C atoms on which axial–equatorial equilibria may be observed each of which will be governed by a different set of non-bonded interactions. Finally the conformational equilibrium on nitrogen is of interest.[8] In order to study these effects we required to synthesise suitable derivatives. This paper outlines our synthetic work.

The first synthesis of a tetrahydro-1,2-oxazine was accomplished by King in 1942.[9] It had previously been shown[10] that alkyl halides react with N-hydroxyurethane (1) in the presence of strong bases to give O-alkylhydroxyurethanes. In an attempt to prepare 1,3-trimethylene- and 1,4-tetramethylene-bis-oxyurethane from 1,3-dibromopropane and 1, 4-dibromobutane, the cyclic N-carbethoxyisoxazolidine (2) and -tetrahydro-1,2-oxazine (3) were isolated. Hydrolysis with hydrochloric acid and subsequent basification yielded the free bases which showed typical amine behaviour with mineral acids, methyl iodide, dinitrobenzoyl chloride and picric acid.

Subsequent entries into this series have been made by hydrogenation of the 3,6-dihydro-oxazines obtained by Diels–Alder reactions of butadienes with nitroso compounds.[11]

The only other recorded synthesis of tetrahydro-1,2-oxazines involves the pyrolysis of certain N-oxides.[12]

Since we required a versatile synthetic route capable of giving fair yields of a variety of compounds in this series we chose to investigate King's method.

The dibromides required for this work were all readily available from the appropriate diols which were synthesised by standard methods. Apart from the hydroboration reaction used to give 2,3-dimethylbutane-1,4-diol these preliminaries do not require discussion. The main points of interest concern the stereochemical and mechanistic aspects of the cyclisation reaction, and the LAH reduction of the N-carbethoxy group to N-Me. Table 1 lists the tetrahydro-oxazines whose synthesis was either attempted or accomplished, together with physical data where appropriate.

The cyclisation reaction. Although King[9] quotes a yield of over 80% for the reaction of 1 mole of 1,4-dibromobutane with 2 moles of N-hydroxyurethane, his method only enabled us to achieve a 35% yield. In order to optimise this figure several experimental conditions were varied. Neither the time allowed for the reaction, the base used, nor the water content of the ethanol used as solvent significantly improved the yield. Addition of a trace of potassium iodide however increased the yield to 45% whilst the use of diiodobutane gave a 60% yield. The ditosylate of *cis*-hexahydrophthalyl alcohol gave no trace of **25**. Finally we found that a 3:1 molar ratio of urethane to dibromide gave consistent and acceptable yields of between 60 and 70%. This method, which is outlined in the experimental section was used in all subsequent preparations.

In several of the cyclisations studied two structurally different isomers can be formed, e.g. 1,4-dibromopentane gives both 3- and 6- methyl derivatives (**5** and **11**). The identity and relative amounts of the isomer pairs formed in the cyclisation step could readily be monitored by NMR and GLC studies.

The first point of interest in Table 2 concerns the conservation of the relative configuration at both asymmetric centres in the synthesis of the diastereoisomeric 3,6-dimethyl derivatives (**13** and **15**).

Table 1. Compounds synthesised or attempted to be synthesised

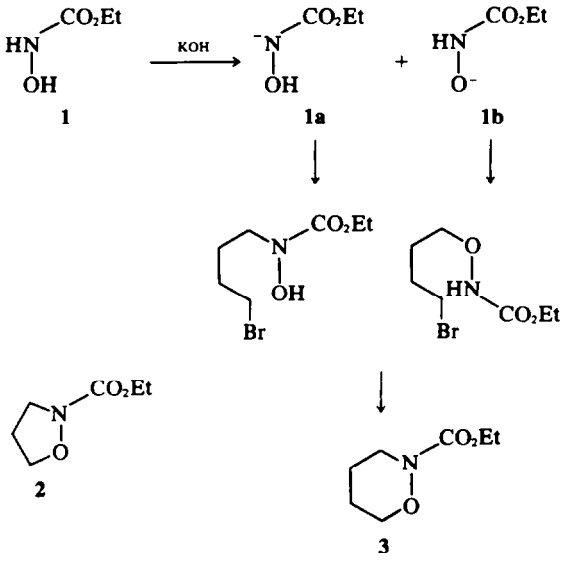
Compound	N substituent	Other substituents	Physical data	
			B.p.°	M.p. of picrate
3	CO_2Et	—	58–62/0·25 mm	
4	CH_3	—	94	
5	CO_2Et	3-Me	*a*	
6	CH_3	3-Me	104–105	177
7	CO_2Et	4-Me	—	
8[i]	CH_3	4-Me	119–120	110–113
9	CO_2Et	5-Me	—	
10[i]	CH_3	5-Me	119–120	110–113
11	CO_2Et	6-Me	*a*	
12	CH_3	6-Me	104–105	
13	CO_2Et	c3,6-diMe	—	
14	CH_3	c3,6-diMe	138–140	147–149
15	CO_2Et	t3,6-diMe	—	
16	CH_3	t3,6-diMe	128	133–134
17[ii]	CO_2Et	3,3-diMe	122/4 mm	
18	CH_3	3,3-diMe	—	
19[ii]	CO_2Et	6,6-diMe	122/4 mm	
20	CH_3	6,6-diMe	—	
21[iii]	CO_2Et	c4,5-diMe	135/2 mm	
22	CH_3	c4,5-diMe	143[b]	154–155
23[iii]	CO_2Et	t4,5-diMe	135/2 mm	
24	CH_3	t4,5-diMe	138[b]	135–136
25	CO_2Et	c-4,5-fused cyclohexyl	114/1·5 mm	
26	CH_3	c-4,5-fused cyclohexyl	68/5 mm	134
27	CO_2Et	3,3-diCO_2Et	185/6 mm	
28	CO_2Et	3,3,6,6-tetraMe	—[c]	
29	CO_2Et	t3,5-diMe	94/3·5 mm[b]	
30	CH_3	t,3,5-diMe	*a*	

[i] Mixture of **8** and **10** not separated
[ii] Mixture of **17** and **19** not separated
[iii] Mixture of **21** and **23** not separated
[a] Separated from isomer by GLC
[b] Purified by spinning band distillation
[c] Not obtained

The stereochemistry of the initial meso or racemic bromide is conserved to give the *cis*- or *trans*- products respectively. The small amount of apparent loss of configuration (< 10%) could arise from incomplete separation of the two dibromides. It is probable in the strongly basic conditions employed, that N-hydroxyurethane should lose a proton from either nitrogen or oxygen to give the tautomeric anions (**1a** and **1b**). The ring formation should now proceed by initial nucleophilic attack of either oxygen or nitrogen on the alkyl halide, reionisation at the other ionisable site and ring closure (Scheme 1). The conservation of relative configuration in 3,6-dimethyl cases implies that an S_N2 mechanism is valid for secondary centres, in this reaction. Since it is widely accepted that secondary halides react more slowly than primary halides under S_N2 conditions,[13] the 3:1 bias between **5** and **11**, suggests that the initial step in ring formation is the attack of oxygen of tautomer **1b** at the primary centre. It is not possible, on our data, to decide whether the lesser isomer is formed by slower attack of oxygen at the secondary centre or initial attack by nitrogen at the primary centre.

Several pieces of evidence from the literature corroborate the picture outlined above. It has been shown that only O-alkylated products are obtained when alkyl monhalides react with N-hydroxyurethane.[10] Swidler and Steinberg,[14] who studied the dissociation of benzohydroxamic acid found approximately equal quantities of the two expected anions, but noted that the oxyanion was the stronger nucleophile.

The 7:1 product ratio between the 3,3- and 6,6-dimethyl cases (Table 2; 17, 19) also supports the suggested mechanism which here would involve in-



SCHEME 1

Table 2. Ratios of isomeric products

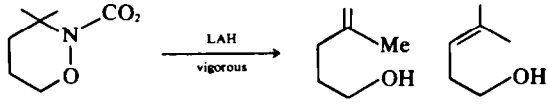
Dibromide	Isomers formed	Ratio
1,4-Dibromopentane	5,11	3:1
2 Methyl-1,4-dibromobutane	7,9	3:2
Meso-2,5-dibromohexane	13,15	>10:1
Racemic 2,5-dibromohexane	15,13	>10:1
4-Methyl-1,4-dibromopentane	17,19	7:1

itial attack of oxygen at the primary centre followed by slower S_N1 attack of nitrogen at the tertiary centre. The small bias of 3:2 noted for compounds **7** and **9** could arise from a β substituent effect in the initial step.

Steric hindrance appears to play a role in these reactions, because repeated attempts to prepare **28** from 2,5-dimethyl-2,5- dibromohexane were unsuccessful.

Lithium aluminium hydride reductions. With the exception of compounds **17** and **19** reduction of the N-carbethoxy compounds with LAH proceeded smoothly giving about 60% yields of the N-Me derivatives.

Reduction under the standard conditions (see Experimental) of the 7:1 mixture of 3,3- and 6,6-dimethyl compounds gave a very low yield of N-Me compounds presumed to be **18** and **20**, but not characterised, in a 1:5 ratio. Steric hindrance of the carbethoxy group in **18** by the adjacent *gem*-dimethyl group presumably only allows the reduction to proceed satisfactorily in the other isomer (**19**). When more vigorous reductive conditions were employed the alkenols (**31** and **32**)[15] were isolated showing cleavage of the N—O bond (Scheme 2).

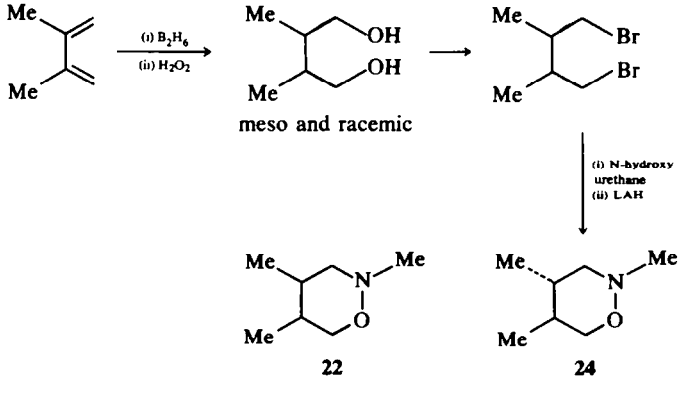


SCHEME 2

Hydroboration of 2,3-dimethylbuta-1,3-diene. A convenient route to the 2,3-dimethylbutane-1,4-diol required for the synthesis of **21** and **23** is by hydroboration of 2,3-dimethylbuta-1,3-diene (Scheme 3). Brown[16] suggested that only the *meso*-diol is formed in this reaction but in our hands the diol formed by this method eventually gave a 3:2 mixture of the N-methyloxazines (**22** and **24**) suggesting that both *meso* and *racemic* diols are formed.

EXPERIMENTAL

Cyclisation procedure illustrated by the reaction of N-hydroxyurethane with 1,4-dibromobutane. N-hydroxyurethane (63 g, 0·6 mol),[17] KOH (33·6 g, 0·6 mol) and 1,4-dibromobutane (43·2 g, 0·2 mol) in abs EtOH (300 ml)



SCHEME 3

Table 3. Analytical data on Picrates of N-methyloxazines

Compound	Formula of picrate	Found C	Found H	Found N	Required C	Required H	Required N
6	$C_{12}H_{16}N_4O_8$	41·85	4·65	16·21	41·86	4·68	16·27
8 and 10*	$C_{12}H_{16}N_4O_8$	41·70	4·50	16·31	41·86	4·68	16·27
14	$C_{13}H_{18}N_4O_8$	43·68	5·05	15·80	43·57	5·07	15·63
16	$C_{13}H_{18}N_4O_8$	43·42	5·07	15·78	43·57	5·07	15·63
22	$C_{13}H_{18}N_4O_8$	43·71	5·06	15·75	43·57	5·07	15·63
24	$C_{13}H_{18}N_4O_8$	43·70	5·08	15·82	43·57	5·07	15·63
26	$C_{15}H_{20}N_4O_8$	46·72	5·20	14·40	46·88	5·25	14·58

*Analysed as mixture

were heated under reflux on a water bath for 6 hr. The soln was decanted from the pale yellow residue, which was washed with EtOH (3 × 50 ml) and the combined extracts were evaporated to leave a mixture of N-hydroxyurethane and product. This oil was shaken vigorously with an equal volume of water. The resulting two layers were separated and the aqueous layer washed with an equal volume of ether. The *combined* organic layers were dried over $MgSO_4$ and distilled. N-carbethoxytetrahydro-1,2-oxazine boiled at 58–62°/0·25 mm (lit. 113–116/12 mm), yield 23 g, 0·14 mole (72%).

Lithium aluminium hydride reductions. The following general procedure illustrated by the reduction of **23** was finally adopted. The N-carbethoxyoxazine **23** (7 g, 0·03 mol) in dry ether (10 ml) was added cautiously to a soln of LAH (2·7 g, 0·07 mol) in dry ether (20 ml). After stirring for 1 hr, water (3 ml), 50% NaOH aq (3 ml), and finally water (10 ml) were added, and the ether decanted. The residual sludge was washed with ether (3 × 30 ml) and the extracts were combined and dried ($Mg SO_4$). The ether and a small amount of EtOH were removed by distillation through a 25 cm Vigreux column and the residue yielded on distillation **26** 3·0 g, 0·019 mole (64%) b.p. 68°/5 mm.

Gas chromatography. Analytical chromatograms were run on a Perkin–Elmer F11, and preparative chromatograms were done on a Varian Aerograph 700. A carbowax 20 M plus KOH on chromosorb W column was found suitable for the separation of N-methyltetrahydro-1,2-oxazines, and both a 1½% fluoroscilicone oil on AW DMCS chromosorb W column and a 15% silicone grease on chromosorb P column were used for the N-carbethoxy derivatives.

Product characterisation. The products were characterised by analysis of the picrates of the N-methyltetrahydro-1,2-oxazines (Table 3) and by their NMR spectra.[18]

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