

CHEMISTRY OF 4-MEMBERED CYCLIC NITRONES (2,3-DIHYDROAZETE 1-OXIDES);
A NOVEL ONE-STEP SYNTHESIS OF *N*-ACETOXY β -LACTAMS

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Abstract: 2,3-Dihydroazete 1-oxide 1 reacts at room temperature with base, acid and lead tetraacetate to give the 5-hydroxyisoxazolidines 4a and 4b, the 6H-1,2-oxazin-6-one 7 and the *N*-acetoxy β -lactam 8, respectively; the reaction with lead tetraacetate represents a simple one-step conversion of a 4-membered cyclic nitronone into a β -lactam.

Recently we reported the first synthesis of 'stable' 4-membered cyclic nitrones (2,3-dihydroazete 1-oxides) by the reaction of nitroalkenes with ynaminnes (1-aminoacetylenes)¹. Since these 2,3-dihydroazete 1-oxides are isomeric with β -lactams we are now investigating routes to effect this isomerization. Because of the current interest in β -lactam antibiotics, a large number of synthetic routes have been developed for the preparation of β -lactams, but isomerization of 4-membered cyclic nitrones to β -lactams has not yet been reported. An attractive feature of such a synthetic route would be the stereochemistry of the resulting β -lactams. We have shown by X-ray analysis that the 2,3-dihydroazete 1-oxides are formed in a stereospecific manner, with the two most bulky substituents (at C-2 and C-3) at the same face of the 4-membered ring. Therefore, if isomerization of the nitronone moiety can be effected without changing this stereochemistry, such a synthesis of β -lactams would be stereospecific.

A large number of reactions are available for the conversion of nitrones into amides. In addition to photochemical rearrangement, aldonitrones have been converted into amides using a variety of chemical reagents such as acids, base, acetyl chloride and phosphorous halides². We wish to report here the preliminary results of a study of the reactivity of 4-membered cyclic nitrones towards such reagents. All the reactions were carried out with 2-(*N,N*-diethylcarbamoyl)-2-methyl-3-phenyl-2,3-dihydroazete 1-oxide (1) at room temperature³.

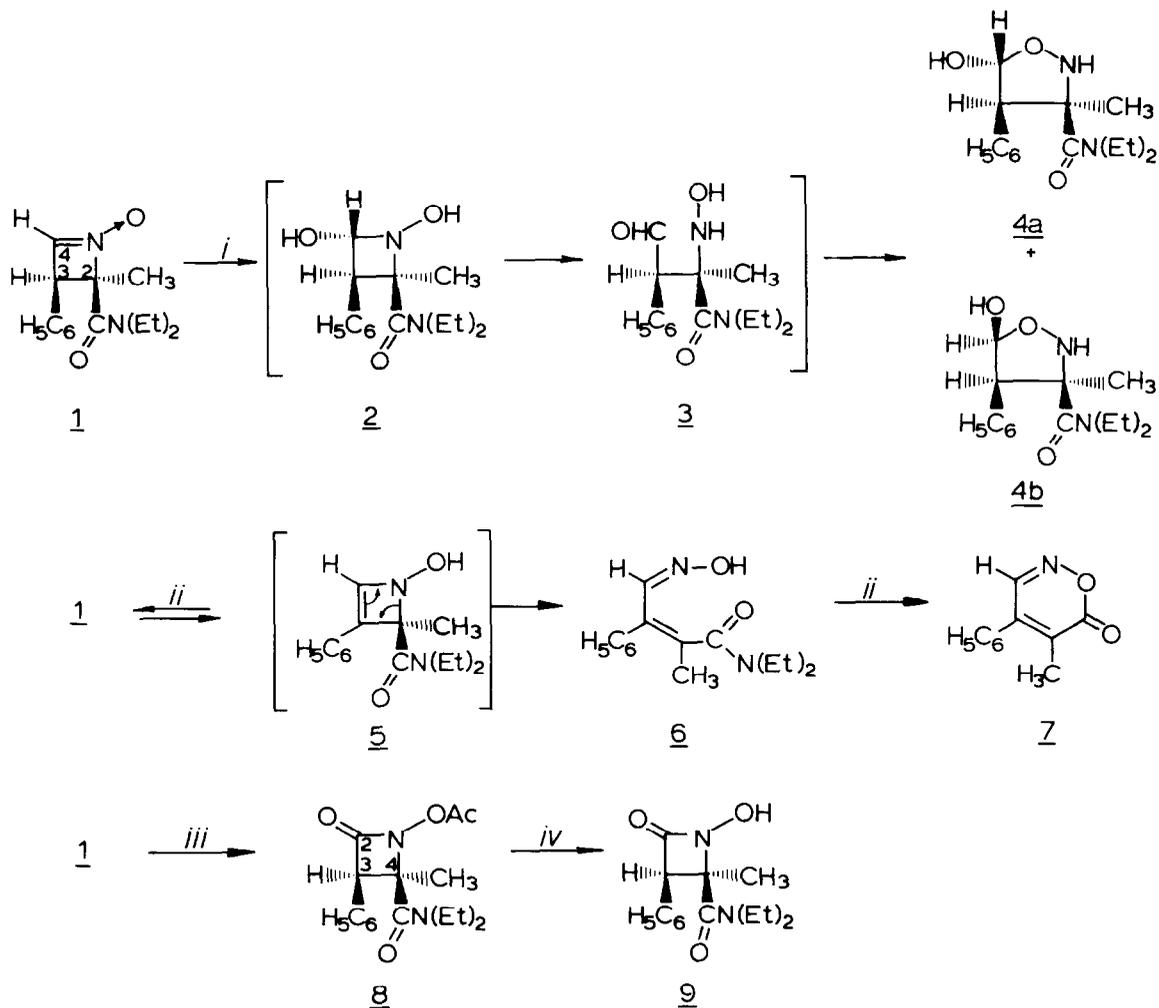
Reaction of 1 with six equivalents of sodium hydroxide in a mixture of methanol and water (2:1) for one hour yields the two isomeric 5-hydroxyisoxazolidines 4a and 4b (4:1) in a yield of 85%. Recrystallization from toluene/hexane did not affect the ratio of 4a and 4b (m.p. 124.5-125.5°C)⁴. The structures of 4a and 4b were proven by spectroscopic methods. MS: M^+ 278.16 (C₁₅H₂₂N₂O₃); due to hydrogen bonding, IR spectroscopy shows a sharp N-H absorption at 3210 cm⁻¹ and a shifted

amide absorption at 1615 cm^{-1} . Assuming that these mild reaction conditions have not affected the stereochemistry at C-3 and C-4, structure 4a was assigned to the predominant isomer on the basis of the smaller *trans* coupling ($J=1.0\text{ Hz}$) between the hydrogen atoms at C-4 and C-5, compared with the larger *cis* coupling ($J=6.0\text{ Hz}$) in the other isomer (4b); 4a: $^1\text{H NMR } \delta(\text{CDCl}_3)$: 1.86 (s, 3H, CH_3), 3.61 (d, $J\ 1\text{ Hz}$, 1H, H-4), 5.50 (d, $J\ 1\text{ Hz}$, 1H, H-5)ppm. $^{13}\text{C NMR } \delta(\text{CDCl}_3)$: 170.3 (s, C=O), 106.4 (d, C-5), 71.3 (s, C-3), 65.6 (d, C-4) 27.1 (q, CH_3)ppm. 4b: $^1\text{H NMR } \delta(\text{CDCl}_3)$: 1.70 (s, 3H, CH_3), 3.50 (d, $J\ 6\text{ Hz}$, 1H, H-4), 5.70 (d, $J\ 6\text{ Hz}$, 1H, H-5)ppm. $^{13}\text{C NMR } \delta(\text{CDCl}_3)$: 170.3 (s, C=O), 100.5 (d, C-5), 70.7 (s, C-3), 64.6 (d, C-4), 27.1 (q, CH_3)ppm. We assume that the first step in the formation of 4a and 4b involves hydration to give the azetidine 2. Subsequent opening of the ring will afford the aldehyde 3 which then rapidly cyclizes to give 4a and 4b (scheme). Recently Perronnet et al.⁵ have reported the cyclization of a similar ketone to a 5-hydroxyisoxazolidin-3-one.

When 1 was dissolved in dry acetic acid, after two hours the oxime 6 was isolated in a yield of 15%⁶ (m.p. $183\text{--}184^\circ\text{C}$, from chloroform/hexane). MS: M^+ 260.15 ($\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$). IR(KBr): 3180 cm^{-1} (OH), 1600 cm^{-1} (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$: 1.78 (s, 3H, CH_3), 7.90 (s, 1H, CH=N)ppm. $^{13}\text{C NMR } \delta(\text{CDCl}_3)$: 170.0 (s, C=O), 149.9 (d, C=N), 138.8 (s), 135.2 (s) and 132.5 (s) (C=C and Ph C-1)ppm. Prolonged reaction time or reaction of 6 in acetic acid for two hours resulted in the formation of a 6H-1,2-oxazin-6-one (7) (m.p. 97°C (dec)) in a yield of 65% starting from 6. Mass spectrometry showed the molecular ion (M^+ 187.06) which corresponds with $\text{C}_{11}\text{H}_9\text{NO}_2$, and a fragmentation pattern ($\text{M}^+ - \text{NO}$, $\text{M}^+ - \text{NO} - \text{CO}$) that is characteristic for 6H-1,2-oxazin-6-ones⁷. IR(KBr): 1715 cm^{-1} (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$: 2.20 (s, 3H, CH_3), 8.17 (s, 1H, CH=N)ppm. $^{13}\text{C NMR } \delta(\text{CDCl}_3)$: 165.5 (s, C=O), 147.2 (d, C=N), 138.9 (s), 132.7 (s) and 131.3 (s) (C=C and Ph C-1)ppm. The formation of the oxime 6 can be explained by an acid induced tautomerization of the nitron to the dihydroazete derivative 5⁸, which is thermally very unstable⁹ and immediately undergoes a ring opening reaction to give 6. Oxime 6 cyclizes in acetic acid medium to the oxazinone 7.

Since both base and acid failed to isomerize the 2,3-dihydroazete 1-oxide to a β -lactam and effected ring opening we decided to investigate the possibility of oxidative isomerization. Analogous oxidation of a 1-pyrroline 1-oxide to a 1-hydroxy-2-pyrrolidinone has been reported¹⁰. Lead tetraacetate reacted with 1 (two hours at 20°C) to yield the *N*-acetoxy β -lactam 8 in a yield of 51% (m.p. $113\text{--}115^\circ\text{C}$ (dec), from chloroform/hexane). The β -lactam structure is evident from the carbonyl absorption in the IR and $^{13}\text{C NMR}$ spectra, and from other spectroscopic data. MS: M^+ 318.15 ($\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4$). IR(KBr): 1820 cm^{-1} (OCOCH_3), 1780 cm^{-1} (C=O, lactam), 1630 cm^{-1} (C=O, amide). $^1\text{H NMR } \delta(\text{CDCl}_3)$: 1.82 (s, 3H, CH_3), 4.08 (s, 1H, H-3)ppm. $^{13}\text{C NMR } \delta(\text{CDCl}_3)$: 167.4 (s) and 167.1 (s) (O-C=O and C=O, amide), 162.7 (s, C=O, lactam), 74.3 (s, C-4), 63.1 (d, C-3), 21.0 (q, CH_3)ppm. Hydrolysis of the *N*-acetoxy group in 8 was achieved in a quantitative yield with aqueous sodium carbonate, and yielded the *N*-hydroxy β -lactam 9 (m.p. $186\text{--}189^\circ\text{C}$ (dec), from chloroform/hexane).

Scheme



All reactions were carried out at room temperature; *i*: NaOH in methanol-water (2:1); *ii*: acetic acid; *iii*: $\text{Pb}(\text{OAc})_4$ in benzene; *iv*: Na_2CO_3 in methanol-water (1:1).

MS: M^+ 276.14 ($\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_3$). IR(KBr): 3250 cm^{-1} (OH), 1775 cm^{-1} (C=O, lactam), 1625 cm^{-1} (C=O, amide). ^1H NMR δ (CDCl_3): 1.84 (s, 3H, CH_3), 3.97 (s, 1H, H-3) ppm. ^{13}C NMR δ (CDCl_3): 170.0 (s, C=O, amide), 162.7 (s, C=O, lactam), 72.3 (s, C-4), 63.4 (d, C-3), 20.0 (q, CH_3) ppm.

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References and Notes

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3. Nitron 1 slowly polymerizes in solution, even at room temperature.
4. Satisfactory elemental analyses were obtained for all new compounds (C,H,N \pm 0.3%).
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