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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 nitrone 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 ynamines (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 nitrone 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 halides[2]. 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 temperature[3].

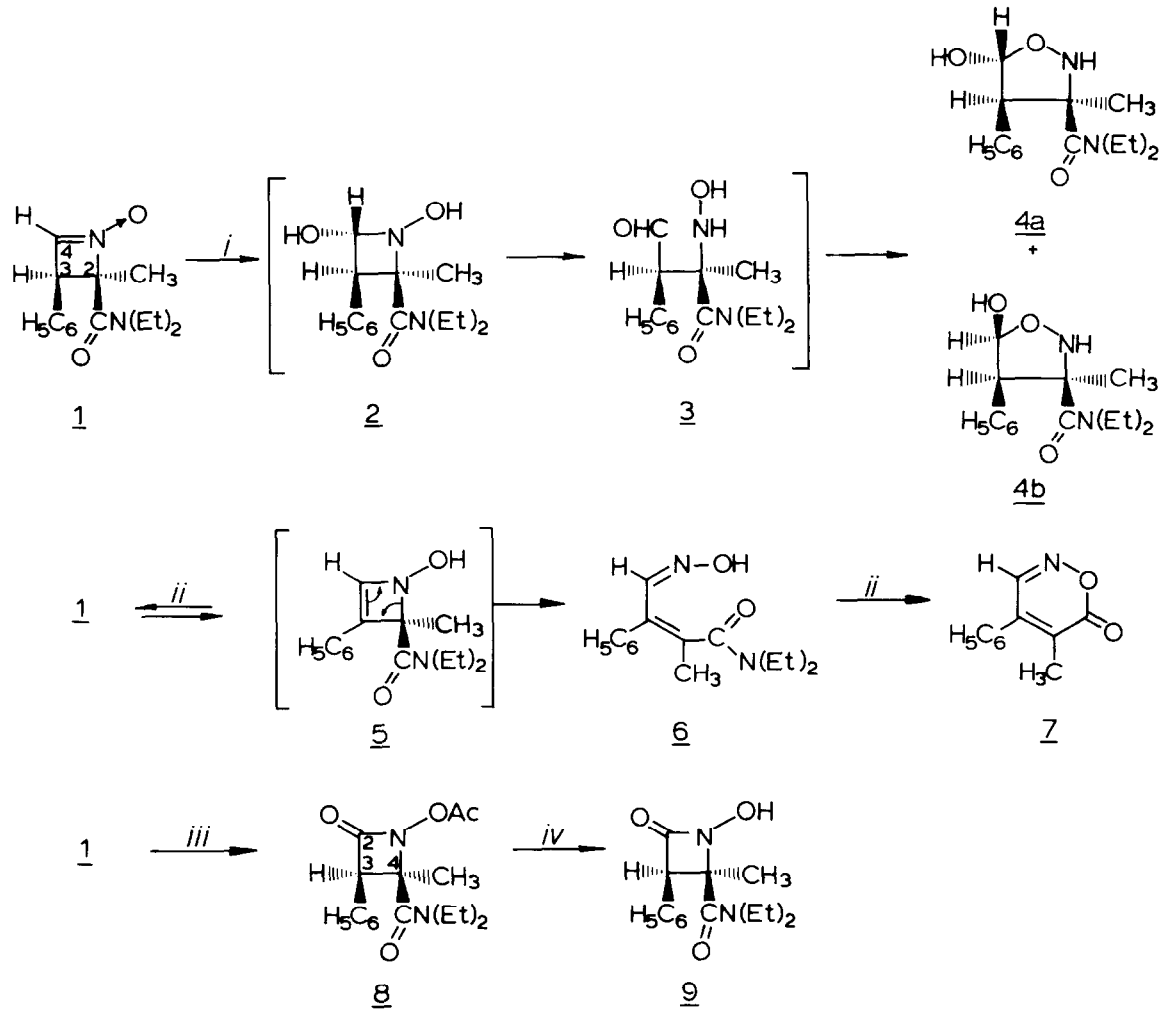
Reaction of 1 with six equivalents of sodium hydroxide in a mixture of methanol and water (2:1) for one hour yields the two isomeric 5-hydroxyisoxazolidines 4a and 4b (4:1) in a yield of 85%. Recrystallization from toluene/hexane did not affect the ratio of 4a and 4b (m.p. 124.5-125.5°C)[4]. The structures of 4a and 4b were proven by spectroscopic methods. MS: M^+ 278.16 ($C_{15}H_{22}N_2O_3$); 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 Hz) between the hydrogen atoms at C-4 and C-5, compared with the larger *cis* coupling (J = 6.0 Hz) in the other isomer (4b); 4a: ^{1}H NMR δ($CDCl_3$): 1.86 (s,3H,CH_3), 3.61 (d,J 1Hz,1H, H-4), 5.50 (d,J 1Hz,1H,H-5)ppm. ^{13}C NMR δ($CDCl_3$): 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}H NMR δ($CDCl_3$): 1.70 (s,3H,CH_3), 3.50 (d,J 6Hz,1H,H-4), 5.70(d,J 6Hz,1H,H-5)ppm. ^{13}C NMR δ($CDCl_3$): 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. 183-184°C, from chloroform/hexane). MS: M^+ 260.15 ($C_{15}H_{20}N_2O_2$). IR(KBr): 3180 cm^{-1} (OH), 1600 cm^{-1} (C=O). ^{1}H NMR δ($CDCl_3$): 1.78 (s, 3H,CH_3), 7.90 (s,1H,CH=N)ppm. ^{13}C NMR δ($CDCl_3$): 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 6*H*-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 $C_{11}H_9NO_2$, and a fragmentation pattern (M^+-NO,M^+-NO-CO) that is characteristic for 6*H*-1,2-oxazin-6-ones[7]. IR(KBr): 1715 cm^{-1} (C=O). ^{1}H NMR δ($CDCl_3$): 2.20 (s,3H,CH_3), 8.17 (s,1H,CH=N)ppm. ^{13}C NMR δ($CDCl_3$): 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 nitrone to the dihydroazete derivative 5[8], which is thermally very unstable[9] 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 reported[10]. 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. 113-115°C (dec), from chloroform/hexane). The β-lactam structure is evident from the carbonyl absorption in the IR and ^{13}C NMR spectra, and from other spectroscopic data. MS: M^+ 318.15 ($C_{17}H_{22}N_2O_4$). IR(KBr): 1820 cm^{-1} ($OCOCH_3$), 1780 cm^{-1} (C=O, lactam), 1630 cm^{-1} (C=O,amide). ^{1}H NMR δ($CDCl_3$): 1.82 (s,3H,CH_3), 4.08 (s,1H,H-3)ppm. ^{13}C NMR δ ($CDCl_3$): 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. 186-189°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: $Pb(OAc)_4$ in benzene; iv: Na_2CO_3 in methanol-water (1:1).

MS: M^+ 276.14 ($C_{15}H_{20}N_2O_3$). IR(KBr): 3250 cm^{-1} (OH), 1775 cm^{-1} (C=O,lactam), 1625 (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. Nitrone 1 slowly polymerizes in solution, even at room temperature.
4. Satisfactory elemental analyses were obtained for all new compounds (C,H,N ± 0.3%).
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9. See for instance: E. Schaumann and F. Grabley, Chem. Ber., 113, 3024 (1980).
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