FIRST EXAMPLES OF ISOXAZOLIDIN-4-ONES

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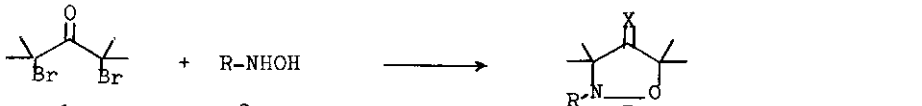
Abstract: First examples of isoxazoldin-4-ones were prepared from 2,4-dibromo-2,4-dimethylpentan-3-one and hydroxylamine and N-acylhydroxylamines.

Although isoxazolidines and their derivatives are well known[2], so far, to our knowledge, no isoxazolidin-4-one has been reported. Herein we report the first examples of the isoxazolidin-4-one system.

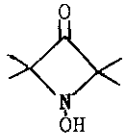
An aqueous methanolic solution of 2,4-dibromo-2,4-dimethylpentan-3-one (1)[3] and hydroxylamine upon refluxing and usual work-up afforded besides the starting ketone two other compounds. The minor compound (6.3%, mp 93-95°) was assigned the structure, 3,3,5,5-tetramethylisoxazolidin-4-one (3a) on the basis of elemental and spectral analyses[4]. The ir absorption at 1770 cm^{-1} for the carbonyl group could



1 + R-NHOH (2) ⟶ (3)

2
a; R = H
b; R = COPh
c; R = $COOC_2H_5$

3
a; R = H, X = O
b; R = COPh, X = O
c; R = $COOC_2H_5$, X = O
d; R = H, X = N-OH
e; R = NO, X = O



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also fit an alternative structure 4 with an azetidin-3-one skeleton. However, benzoylation of the compound gave an amide but not an ester as revealed by the ir absorption at 1730 cm^{-1} (>C=O) and 1640 cm^{-1} (Ph-C=O) of the benzoyl derivative 3b.

The major compound (31.6%, mp 144-151°) was found to be 3,3,5,5-tetramethylisoxazolidin-4-one oxime (3d) (as a mixture of syn and anti isomers)[4]. The ketone 3a was

found to be the precursor for the oxime 3d as revealed by an nmr analysis of different aliquots of the above reaction mixture. The signals due to the methyl groups of 3a decreased in intensity while those of 3d increased during the reaction. The oxime could be converted to the parent ketone 3a in good yield by treatment with titanium trichloride[5].

The aforementioned cyclization could also be effected with N-acylhydroxylamines. Thus the dibromoketone 1 on reaction with the potassium salt of benzohydroxamic acid (2b) afforded N-benzoyl-3,3,5,5-tetramethylisoxazolidin-4-one (3b) (40%, mp 50-52°) which was identical with the product obtained by benzoylation of 3a. Similarly, N-carbethoxy-3,3,5,5-tetramethylisoxazolidin-4-one (3c) (18%, mp 61-62°) was obtained by reaction of 1 with N-hydroxyurethane (2c). The yields of the above reactions were not optimised[6].

A preliminary study of the photochemical behavior of the above isoxazolidin-4-ones revealed that all of them underwent slow photochemical decomposition leading to acetone as the only detectable product. However, N-nitroso-3,3,5,5-tetramethylisoxazolidin-4-one (3e) (84%, mp 68-70°), obtained by nitrosation of 3a with sodium nitrite and acetic acid, was found to be highly sensitive to light. A solution of 3e in benzene on being kept overnight in a lighted room underwent decomposition giving rise to acetone as the only detectable product. Photolysis of 3e in benzene under Vycor filtered light was complete in 30 minutes and the only detectable product was acetone, as identified by nmr, ir and vpc analysis, and comparison with an authentic sample of acetone. The detailed study of the photochemical behavior of these first examples of isoxazolidin-4-ones are in progress.

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References:

1. Present address : Medicinal Chemistry Division, Indian Institute of Chemical Biology, 4-Raja S.C. Mullick Road, Calcutta-700032, INDIA.

2. a) Y. Takeuchi and F. Furusaki, 'Advances in Heterocyclic Chemistry', Academic Press, 1977, 21, p 207.

b) A. Quilico, 'Heterocyclic Compounds', Interscience Publisners, 1962, 17, p 229.

3. G. Claeson and A. Thalen, Acta. Chem. Scand., 1963, 17, 1173.

4. Infrared and nmr spectral data for the different isoxazolidin-4-ones.
   3,3,5,5-Tetramethylisoxazolidin-4-one (3a): ir ($CHCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$) δ 1.23 (s,6H), 1.26 (s,6H) and 5.20 (br s,1H).
   N-Benzoyl-3,3,5,5-tetramethylisoxazolidin-4-one (3b): ir ($CHCl_3$) 1780 and 1640 (br) cm^{-1}; nmr (CCl_4) δ 1.38 (s,6H), 1.58 (s,6H) and 7.20-7.80 (m,5H).
   N-Carbethoxy-3,3,5,5-tetramethylisoxazolidin-4-one (3c): ir ($CHCl_3$) 1785 and 1730 (br) cm^{-1}; nmr (CCl_4) δ 1.30 (s,3H,J=7.5 Hz), 1.32 (s,6H), 1.38 (s,6H) and 4.12 (q,2H,J=7.5 Hz).
   3,3,5,5-Tetramethylisoxazolidin-4-one oxime (3d): ir ($CHCl_3$) 3590 and 3300 (br) cm^{-1}; nmr ($CDCl_3$) one isomer exhibits peaks at δ 1.35 (s,6H), 1.55 (s,6H); the other isomer has signals at δ 1.38 (s,6H), 1.50 (s,6H); the signal due to NH and OH comes as a broad peak at δ 6.95.
   N-Nitroso-3,3,5,5-tetramethylisoxazolidin-4-one (3e): ir ($CHCl_3$) 1790 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (s,6H) and 1.75 (s,6H).

5. G.H. Timms and E. Wildsmith, Tetrahedron Letters, 1971, 195.

6. Preliminary attempts to effect cyclization of other dibromoketones viz 1,3-dibromo acetone, dibromodicyclohexyl ketone and 2,6-dibromo-2,6-dimethylcyclohexanone with hydroxylamine or N-acylhydroxylamines under usual conditions have, so far, been unsuccessful. However, modifications of the conditions involving aprotic solvents e.g. diglyme, HMPT and higher temperatures are currently being attempted.

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