2-Isoxazoline Derivatives. Part I. A Base-promoted Fragmentation of 2-Isoxazolines. (1)

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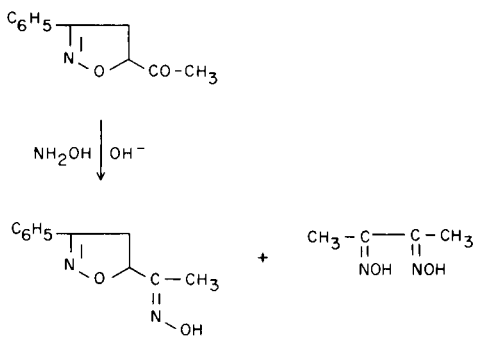
The action of bases on 3-aryl (or alkyl)-5-acyl-2-isoxazolines has been shown to give rise to the corresponding aromatic (or aliphatic) nitriles and α-diketones by cleavage of the O-N and C_3-C_4 bonds of the heterocyclic ring. This fragmentation reaction has been extended to other 2-isoxazolines substituted in the 5-position with electron-attracting groups.

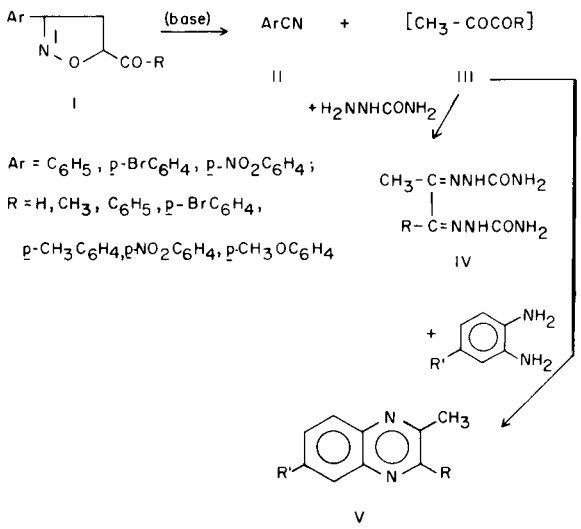
The behaviour of the isoxazole ring toward alkaline reagents has been widely studied (2). Different modes of ring cleavage are observed which are dependent upon the nature of the substituents, in particular the C_3-C_4 linkage is cleaved when a 3-aryl or 3-alkyl monosubstituted isoxazole is heated with sodium hydroxide (3) or sodium ethoxide (4).

The dihydro derivative, 2-isoxazoline, is known to undergo N-O cleavage by reducing agents, such as lithium aluminium hydride (5), sodium amalgam or catalytic hydrogenation (6,7). Acidic agents such as boron trifluoride etherate and acetic anhydride also promote the rupture of the O-N bond as well as the O-C_5 bond (8), while hydroiodic acid initially cleaves only the O-C_5 bond (5). Apart from the well-known cleavage and subsequent rearrangement of 2-isoxazoline-4-carboxylic esters to aryl-idenisoxazolones (9, 10), and the very recent report (11) on the alkaline cleavage of some 2-isoxazolines, which repeats the pattern already known for the corresponding isoxazoles, nothing was known about the behaviour of 2-isoxazoline derivatives in alkaline mediums.

We have recently found (12) that alkaline oximation of 3-phenyl-5-acetyl-2-isoxazoline gives, along with the expected oxime, an almost equivalent yield of dimethylglyoxime, thus involving rupture of the O-N and C_3-C_4 linkages.

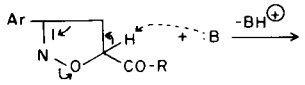


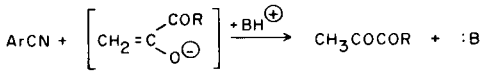
We therefore investigated the action of bases on 5-acyl-2-isoxazolines, which are easily prepared from nitrile oxides and vinyl ketones or directly from hydroxamyl chlorides and Mannich bases (13). Treatment of 3-aryl-5-acyl-2-isoxazolines (I) with aqueous sodium hydroxide gave fairly good yields of the corresponding aromatic nitrile (II) and the α-diketone (III), isolated usually as the bis-semicarbazone (IV) or the quinoxaline derivative (V), in the latter case after having added *in situ* the *o*-phenylenediamine.



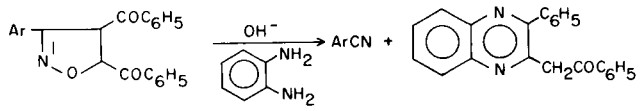
This base-promoted fragmentation is quite general and relatively independent of the nature of the base (triethylamine, alkaline hydroxide or alkoxide, sodium or sodium hydride) and the nature of R (alkyl, aryl or even hydrogen). 3-Methyl-5-acetyl-2-isoxazoline, the only 3-alkylsubstituted 2-isoxazoline so far tested, cleaved analogously by alkaline treatment to acetonitrile and diacetyl. The fact that a ketone with a second substituent in the 5-position, 3-phenyl-5-methyl-5-benzoyl-2-isoxazoline, is fairly stable

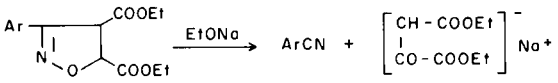
to alkali, supports the mechanism in which ring cleavage depends upon the acidity of the 5-hydrogen, α to the carbonyl group.





Even 4,5-disubstituted isoxazolines undergo the same fragmentation pattern: *e.g.*, 3-phenyl-4,5-dibenzoyl-2-isoxazoline, obtainable by cycloaddition of benzonitrile oxide and *trans*-dibenzoylethene, was easily cleaved by methanolic potassium hydroxide to benzonitrile and 1,4-diphenyl-1,2,4-butanetrione. The latter was trapped as the quinoxaline derivative, and diethyl *trans*-3-aryl-2-isoxazoline-4,5-dicarboxylate gave the aromatic nitrile and the sodium salt of oxalacetic ester.





In some other cases, the aromatic nitrile could be obtained in higher yields by simply heating a 2-isoxazoline substituted in the 5-position with an electron-withdrawing group in the absence of base. This was observed in the case of 3-phenylisoxazoline-5-boronic acid, potassium 3-(*p*-bromophenyl)-2-isoxazoline-5-carboxylate and sodium 3-(*p*-bromophenyl)-5-methyl-2-isoxazoline-5-carboxylate; in the latter case the behaviour is quite different from that of the corresponding ester (14).

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed by Dr. Lucia Maggi Dacrema. The ultraviolet spectra were recorded on a Perkin-Elmer 137 UV spectrometer in 95% ethanol solution.

Preparation of 2-Isoxazoline Derivatives.

Ia (15), Ie-Ih (13) (see Table 1), 3-phenyl-2-isoxazoline-5-aldehyde (16), 3-(*p*-bromophenyl)-2-isoxazoline-5-carboxylic acid (17), 3-(*p*-bromophenyl)-5-methyl-2-isoxazoline-5-carboxylic acid (12) and 3-phenyl-2-isoxazoline-5-boronic acid (18) have been prepared by literature methods. The compounds described below have been synthesized for the first time.

3-*p*-(Nitrophenyl)-5-acetyl-2-isoxazoline (Ib).

To a solution of 4.0 g. of *p*-nitrobenzohydroxamyl chloride and 1.36 g. of methylvinylketone in 100 ml. of ether was added dropwise with stirring a solution of 2.3 g. of triethylamine in 20 ml. of ether. The precipitate was filtered and washed with water to dissolve the triethylamine hydrochloride. The insoluble material (2.5 g.) was combined with the crystalline residue (0.26 g.) obtained after evaporation of the ether and was recrystallized from ethanol to give colourless needles, m.p. 121-122°; the UV spectrum showed maxima at 225 mμ (log ε 3.95) and 310 mμ (log ε 4.13).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.74; H, 4.22; N, 12.12.

3-(*p*-Bromophenyl)-5-acetyl-2-isoxazoline (Ic).

Compound Ic was obtained by the same procedure described above from *p*-bromobenzonitrile oxide, prepared *in situ* from *p*-bromobenzohydroxamyl chloride and triethylamine, and methylvinylketone; yield 75%, colourless needles, m.p. 88.5-89.5°; the UV spectrum showed a maximum at 269.5 mμ (log ε 4.25).

Anal. Calcd. for $C_{11}H_{10}BrNO_2$: C, 49.27; H, 3.76; Br, 29.81; N, 5.22. Found: C, 49.70; H, 3.87; Br, 29.98; N, 5.35.

3-(*p*-Bromophenyl)-5-benzoyl-2-isoxazoline (Id).

An ethanol solution of 11.3 g. of *p*-bromobenzohydroxamyl chloride was added dropwise to a boiling ethanol solution of 10.6 g. of 3-morpholinyl-1-phenylpropan-1-one and 12.3 g. of the corresponding hydrochloride. The resulting reaction mixture was refluxed for 3 hours, then concentrated under reduced pressure in a rotary evaporator to a small volume. The residue was treated with water and the insoluble solid was filtered to give 9.72 g. (60.4%) of colourless leaves, m.p. 185-186°. The analytical sample was recrystallized from benzene.

Anal. Calcd. for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; Br, 24.20; N, 4.24. Found: C, 58.36; H, 3.23; Br, 24.51; N, 4.39.

3-Phenyl-5-*p*-anisoyl-2-isoxazoline (Ii).

This compound was obtained by the same procedure described above from benzohydroxamyl chloride, 3-morpholinyl-1-*p*-anisyl-propan-1-one and the corresponding hydrochloride; yield 48%, colourless leaflets, m.p. 128.5-129.5°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.33; H, 5.51; N, 4.90.

3-Methyl-5-acetyl-2-isoxazoline.

3-Methyl-5-acetyl-2-isoxazoline was prepared from acetonitrile oxide obtained *in situ* (19) and methylvinylketone; yield 49%, colourless oil, b.p. 56-57°/0.8 mm.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.59; H, 7.01; N, 11.16.

The semicarbazone melted at 176°, colourless needles from ethanol.

Anal. Calcd. for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.75; H, 6.60; N, 30.27.

trans-3-Phenyl-4,5-dibenzoyl-2-isoxazoline.

To a well stirred solution of 5.0 g. of *trans*-dibenzoylethene and 3.8 g. of benzohydroxamyl chloride in 100 ml. of toluene the theoretical amount of triethylamine was added dropwise. After 2 hours the precipitated hydrochloride was filtered off and the solution was concentrated in a rotary evaporator. The residual

solid was recrystallized from ethanol to give 6.7 g. (89%) of white needles, m.p. 129-130°; the UV spectrum showed a maximum at 254.5 mμ (log ε 4.55).

Anal. Calcd. for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.85; H, 4.65; N, 3.93.

Diethyl *trans*-3-(*p*-Bromophenyl)-2-isoxazoline-4,5-dicarboxylate.

The product was obtained by the same method from *p*-bromobenzonitrile oxide prepared *in situ* and diethyl fumarate; yield 70% of colourless needles (from petroleum ether) m.p. 51-52°.

Anal. Calcd. for $C_{15}H_{16}BrNO_5$: C, 48.66; H, 4.35; N, 3.78; Br, 21.59. Found: C, 48.87; H, 4.12; N, 3.95; Br, 21.14.

Reaction of 2-Isoxazoline Derivatives with Bases.

Method A.

Example 1.

Two tenths ml. of 14% aqueous sodium hydroxide were added to a suspension of 2.10 g. of 3-phenyl-5-acetyl-2-isoxazoline in 30 ml. of water and the mixture was steam distilled at once, collecting the distillate in a concentrated solution of semicarbazide hydrochloride and sodium acetate. After standing overnight, the distillate was filtered to give 0.65 g. (36.5%) of diacetyl bis-semicarbazone, m.p. 278°, identified by its IR-spectrum and mixed melting point with an authentic sample. The mother liquor was extracted several times with ether. The combined extracts were dried and the solvent evaporated cautiously. The oily residue (0.75 g., 66%) was practically pure benzonitrile. From the nonvolatile fraction 0.55 g. of a product was obtained, which was recrystallized from ethanol to give light green leaflets, m.p. 197.5-198.5° dec. The structure of this byproduct is under investigation.

Example 2.

A few drops of methanolic potassium hydroxide were added to a solution of 1.0 g. of *trans*-3-phenyl-4,5-dibenzoyl-2-isoxazoline and 0.31 g. of *o*-phenylenediamine in 30 ml. of ethanol. After refluxing for 0.5 hours, the reaction mixture was cooled to room temperature. The precipitate was filtered and crystallized from ethanol, yielding 0.42 g. (46%) of orange-coloured 2-phenacyl-3-phenylquinoxaline, m.p. 168.5-169.5° (literature (20), m.p. 169-170°). To the mother liquor 10 ml. of 14% aqueous sodium hydroxide was added. After refluxing for 24 hours, the excess of ethanol was evaporated and the aqueous solution was acidified. Repeated extractions with ether, drying and evaporation of the ether extracts afforded 0.17 g. (49.5%) of benzoic acid.

Analogously treated, 3-phenyl-2-isoxazoline-5-aldehyde yielded 49% of 2-methylquinoxaline and 39% of benzoic acid.

Method B.

Example 3.

A solution of sodium ethoxide, prepared from 0.12 g. of sodium, was added to a solution of 2.0 g. of diethyl *trans*-3-(*p*-bromophenyl)-4,5-dicarboxylate in 25 ml. of anhydrous ethanol. After standing at room temperature for 4 hours, the solvent was removed under reduced pressure, and the residue was treated with dry ether. The insoluble sodium salt of diethyl oxalacetate (0.45 g.) was filtered and treated with a concentrated solution of semicarbazide hydrochloride, giving 0.45 g. (34%) of diethyl oxalacetate semicarbazone, m.p. 159-161°, identical with an authentic sample. From the ethereal extracts 0.56 g. (57%) of *p*-bromobenzonitrile, m.p. 110-112°, was recovered.

Method C.

The following general procedure has been used for the sake of comparison. A mixture of 1.0 g. of the 2-isoxazoline derivative and an equimolecular amount of *o*-phenylenediamine resp., 4-nitro-*o*-phenylenediamine was dissolved in 25 ml. of a 10% solution of triethylamine in dry benzene. The solution was heated under reflux until a thin-layer chromatographic assay revealed the disappearance of the starting 2-isoxazoline. The solvent then was removed and the residue was eluted through a column of silica gel H with benzene-ethyl acetate (95:5). The solid aromatic nitriles were isolated directly and identified by comparison with authentic samples; benzonitrile was hydrolyzed with aqueous-ethanolic sodium hydroxide to benzoic acid. The quinoxaline derivatives were identified by comparison with authentic samples prepared according to literature methods. The following compounds were unknown: 2-methyl-3-(*p*-bromophenyl)quinoxaline, m.p. 105-106°, yellow needles from *n*-hexane; UV spectrum showed maxima at 242.5 mμ (log ε 4.49) and 329 mμ (log ε 4.10).

Anal. Calcd. for $C_{15}H_{11}BrN_2$: C, 60.22; H, 3.70; Br, 26.71; N, 9.36. Found: C, 60.31; H, 3.94; Br, 26.71; N, 9.53.

2-Methyl-3-(*p*-anisyl)quinoxaline, m.p. 91°, yellow needles from *n*-hexane.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.55; H, 5.72; N, 11.09.

TABLE I

No.	5-Acyl-2-isoxazolines (I) Ar	R	Phenylene-diamine R′	ArCN (II) Yield %	Quinoxaline derivative (IV) Yield %	M.p.	Lit.	Reaction time (hours)
Ia	C_6H_5	CH_3	NO_2	40	52	137-138°	21	55
Ib	*p*-$NO_2C_6H_4$	CH_3	NO_2	55	48	"	"	25
Ic	*p*-BrC_6H_4	CH_3	NO_2	24	19	"	"	25-30
Id	*p*-BrC_6H_4	C_6H_5	H	47	45	52-53°	22	7-8
Ie	C_6H_5	C_6H_5	H	46	51	"	"	8
If	C_6H_5	*p*-$CH_3C_6H_4$	H	32	48	63-65°	23	12-13
Ig	C_6H_5	*p*-BrC_6H_4	H	22	45	105-106°	---	2
Ih	C_6H_5	*p*-$NO_2C_6H_4$	H	10	18	141-142°	24	1
Ii	C_6H_5	*p*-$CH_3OC_6H_4$	H	48	59	91°	---	36

The results are reported in Table 1. Yields are calculated on the pure products, without any claim for optimal conditions.

In two cases (Ia, Ih) the corresponding 5-acyl-isoxazole has been isolated as a byproduct: 3-phenyl-5-acetylisoxazole, m.p. and mixed m.p. 104-105° (25), in 2-3% yield; 3-phenyl-5-*p*(nitrobenzoyl)isoxazole, m.p. and mixed m.p.172-173°(26), in 16% yield.

A mixture of 3-methyl-5-acetyl-2-isoxazoline and *o*-phenylenediamine was refluxed for 0.5 hour with triethylamine in methanol. The solvent and acetonitrile were distilled off and the residue after elution on a silica gel column gave a 93% yield of 2,3-dimethylquinoxaline. The distillate was heated with an excess of methanolic potassium hydroxide. Evaporation, neutralization and treatment with *S*-benzylisothiuronium chloride allowed the isolation of a 47% yield of the *S*-benzylisothiuronium salt of acetic acid.

Thermal Fragmentation of 2-Isoxazoline Derivatives.

Two tenths g. of dry sodium 3-(*p*-bromophenyl)-5-methyl-2-isoxazoline-5-carboxylate was heated for 0.5 hours at 280°/1.5 mm. The sublimate (0.05 g., 42%) was collected and identified as *p*-bromobenzonitrile, m.p. and mixed m.p. 112-113°.

A slightly smaller yield of *p*-bromobenzonitrile has been obtained by heating sodium 3-(*p*-bromophenyl-2-isoxazoline-5-carboxylate at 250°/1.5 mm.

3-Phenyl-2-isoxazoline-5-boronic acid, heated at 80°/25-30 mm., decomposed with extensive darkening of the fused mass. The colourless distillate was practically pure benzonitrile (IR spectrum and hydrolysis to benzoic acid); yield 14% of benzoic acid.

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