2-Isoxazoline Derivatives. Part V.[1] Regio- and Stereo-selectivity in the Cycloaddition of Benzonitrile Oxide to Some Cycloalkene and 2-Isoxazoline Derivatives

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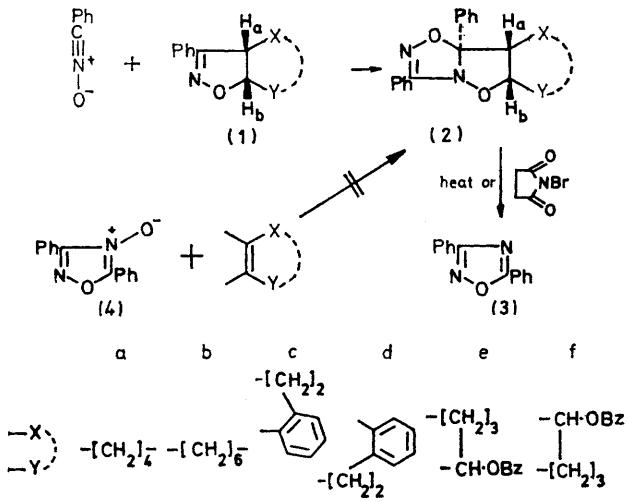
The oxime-like C=N bond of 2-isoxazolines undergoes 1,3-dipolar cycloaddition with benzonitrile oxide leading to new heterocyclic systems. The structures of the cycloadducts from benzonitrile oxide and cyclohexene systems have been established by spectral analysis and chemical evidence.

THE cycloaddition of nitrile oxides to aldimines and to oximes [2] (the latter with Lewis acid catalysis) is known to give 4,5-dihydro-1,2,4-oxadiazole derivatives; the reaction is influenced by electronic factors and takes place with maximum energy gain in the formation of the new σ-bonds.[3]

Pursuing our study of 2-isoxazolines (Δ^2-isoxazolines), we now report an investigation of their dipolarophilic activity towards benzonitrile oxide, together with some observations on the regioselectivity of some endocyclic C=C bonds. The endocyclic C=N bond of Δ^2-isoxazolines of type (1) can easily undergo cycloaddition with benzonitrile oxide, leading to the diadduct (2) (Scheme 1).



Compound (1a) has already been reported. However no mention is made of the diadduct (see ref. 5). Compounds (1e) and (1f) could not be separated

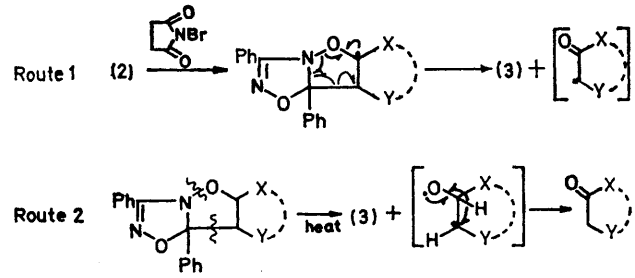
SCHEME 1

The monoadduct from benzonitrile oxide and cyclohexa-1,3-diene has already been reported to react further with benzonitrile oxide not only at the endocyclic C=C bond but also at the isoxazoline C=N bond.[4] We have obtained the diadducts (2a, e, and f) from the cycloaddition of benzonitrile oxide to the appropriate cycloalkenes, even when the reaction was carried out in a large excess of dipolarophile.

The oxadiazole (3) was also isolated from the reaction mixtures; this compound might be formed either by spontaneous decomposition of compounds (2) (see later) or by the action of triethylamine on benzohydroximic acid chloride.[6] Attempts to prepare the diadducts (2) by reactions of the oxadiazole oxide (4) with the alkenes were unsuccessful, ruling out the intermediate formation of compound (4) as an alternative route to the diadducts.

The structure of the diadducts (2) follows from their transformation into the oxadiazole (3) either on heating or on treatment with *N*-bromosuccinimide in carbon tetrachloride. In two cases [compounds (2b) and (2c)] we were able to detect and to characterise the other reaction products, cyclo-octanone and α-tetralone, by g.l.c. and as their phenylhydrazones. Fragmentation by the action of *N*-bromosuccinimide gave better yields of oxadiazole than thermolysis.

Suggested decomposition pathways are shown in Scheme 2. One route involves hydrogen abstraction by *N*-bromosuccinimide with formation of a radical which leads to compound (3) and the appropriate ketone, as already proposed by us for the radical fragmentation of some Δ^2-isoxazolines.[1] In the alternative a homolytic breakdown of two σ-bonds in the isoxazolidine ring leads to compound (3) and to a diradical intermediate which rearranges to the ketone.



SCHEME 2

All compounds (2) isolated were shown to be isomerically pure by n.m.r. spectroscopy. Their stereochemistry was assigned on the reasonable assumption

[1] Part IV, G. Bianchi, A. Gamba, and R. Gandolfi, *J. Chem. Soc.* (*C*), 1971, 2375.
[2] For a review see Ch. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, Berlin, 1971, p. 125.
[3] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633.
[4] G. F. Bettinetti and A. Gamba, *Gazzetta*, 1970, **100**, 1144; P. Caramella, P. Frattini, and P. Grünanger, *Tetrahedron Letters*, 1971, 3817.
[5] (*a*) G. Zinner and H. Günther, *Chem. Ber.*, 1965, **98**, 1353; (*b*) Ch. Grundmann, in 'Methoden der Organischen Chemie,' (Houten-Weyl), Springer-Verlag, Berlin, 1965, vol. X/3, p. 864.
[6] G. F. Bettinetti, personal communication.

that the cycloaddition to the C=N bond should occur on the face of the Δ^2-isoxazoline (1) *anti* to the cycloalkane ring, consistent with the high steric demand of the cycloalkane group.

The cycloadditions of benzonitrile oxide to 3-benzoyloxycyclohexene and 3,4-dihydronaphthalene yielded in each case a mixture of the two possible isomeric monoadducts. There are several other reported examples [7] of exceptions to the rule that only one isomer is obtained in the cycloaddition of nitrile oxides to asymmetrically substituted olefins.

Structures (1c) and (1d) follow from ^{1}H n.m.r. data (Table 1): signals from H_a and H_b ring appear as a multiplet-doublet and a doublet-multiplet, respectively.

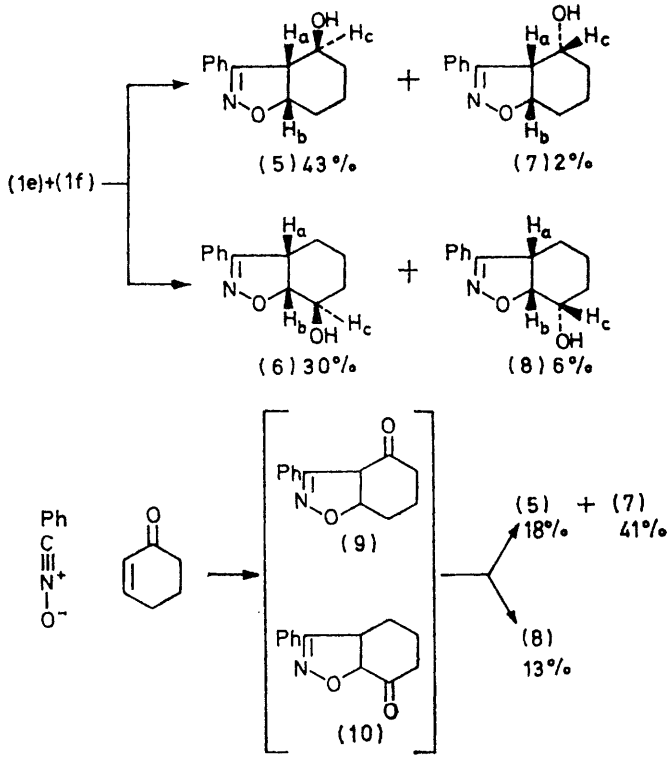
TABLE 1

^{1}H N.m.r. data for the Δ^2-isoxazolines(1a—d) and (2a—f) (δ in p.p.m.)

Compd.	H_a	H_b	J_{ab}/Hz
(1a)	3·25 (m)	4·46 (m)	
(1b)	3·00 (m)	4·25 (m)	
(1c)	3·83 (m)	5·51 (d)	9·2
(1d)	4·88 (d)	5·22 (m)	10·2
(2a)	2·75 (m)	4·32 (m)	
(2b)	3·45 (m)	4·45 (m)	
(2c)	3·00 (m)	5·18 (d)	4·0
(2d)	4·23 (d)	4·68 (m)	6·4
(2e) [a]	3·15 (m)	5·45 (m)	
(2f) [a]	3·07 (m)	5·07 (m)	

[a] Tentative assignments. The proton α to the benzoyloxy-group absorbs at 4·35 (2e) or 4·50 p.p.m. (2f).

The cycloaddition to 3-benzoyloxycyclohexene gave a mixture of mono- and di-adducts. Column chromatography of the products afforded pure diadducts (2e) and (2f), but did not separate the monoadducts (1e) and (1f); the latter mixture was therefore hydrolysed directly to the corresponding carbinols (Scheme 3). All the four possible regio- and stereo-isomeric carbinols (5)—(8) were isolated, two of them in relatively high yields and the other two as low-yield by-products. Their structures were demonstrated from chemical and spectroscopical evidence. Cyclohex-2-enone was shown to react with benzonitrile oxide to give an 85% yield of 3 : 1 mixture of the isomeric ketones (9) and (10).[8] Without further separation, the mixture was reduced with sodium borohydride. Three out of the four isomeric carbinols, *i.e.* (7), (8), and (5) in yields of 41·5, 13, and 18, respectively, were thus obtained. We can now reasonably assume that (i) the hydride has attacked preferentially from the least hindered side of the keto-group (opposite to the isoxazoline ring) and that (ii) the nitrile oxide has attacked preferentially from the least hindered side of the double bond (opposite the benzoyloxy-group). Since the major isomer from the reduction must have the hydroxy-group adjacent to the isoxazoline 4-position and is one of the low-yield products from the hydrolysis, the configuration with H_a and OH *trans* can be safely deduced for (7). The only isomer lacking in the reduction mixture must have the hydroxy-group adjacent to the isoxazoline 5-position and since it corresponds to a major isomer from the hydrolysis, the configuration with H_b and OH *cis* was assigned to (6). The other by-product from the hydrolysis must be regioisomeric with (7); therefore an H_b,OH *trans* structure was deduced for (8). Hence compound (5) has the configuration with H_a and OH *cis*. Our deductions have been confirmed by oxidation of compounds (5) and (7), which yielded the same ketone (9). Furthermore, if we assume a



SCHEME 3

concerted mechanism for the 1,3-dipolar cycloaddition, the lower yield of (7) than of (8) can be explained in terms of the higher steric demand of the phenyl-substituted carbon atom of the nitrile oxide in comparison with the oxygen atom in the transition states formed from the attack of the nitrile oxide at the side of the cycloalkene encumbered with the benzoyloxy-group.

The n.m.r. spectra of compounds (5)—(8) in the region δ 3·10—4·62 p.p.m. (see Table 2; H_a, H_b, and H_c) consisted of three groups of lines whose features allowed us to assign the position of the hydroxy-group. A specific distinction between the two pairs (5) and (7), and (6) and (8) was made possible by use of the known chemical shift correlation [9] which attributes to the Δ^2-isoxazoline 5-proton (H_b) a lower field resonance

[7] Ref. 2, p. 99.

[8] G. Bianchi, C. De Micheli, R. Gandolfi, P. Grunanger, P. Vita Finzi, and O. Vajna, submitted for publication to *J.C.S. Perkin I*.

[9] G. Bianchi, P. Grünanger, and A. Perotti, *Tetrahedron Letters*, 1964, 2157.

than that of the 4-proton (H_a). In the spectra of all of the four carbinols the signals due to H_c were found in a region between those of H_a and H_b. In carbinols (5) and (7) the H_a signal appeared as a quartet and those of H_b and H_c as two complex multiplets. The other pair of carbinols (6) and (8) showed similar splitting patterns, but with the H_b signal now a quartet. The quartets in all four spectra collapsed to doublets on irradiation at the frequency of the other bridgehead proton. This result permitted the attribution of the relative J values to the protons involved.

TABLE 2

^{1}H N.m.r. data for the Δ^2-isoxazolines (5)—(8) (δ in p.p.m.; J in Hz) [a]

	(8)	(6)	(7)	(5)
H_a	3·42 (m, J_{ab} 8)	3·62 (m, J_{ab} 8)	3·37 (q, J_{ab} 8)	3·10 (t, J_{ab} 7·7)
H_b	4·62 (q, J_{bc} 5)	4·37 (q, J_{bc} 4·5)	4·48 (m, J_{ac} 5)	4·50 (m, J_{ac} 7·7)
H_c	4·01 (m)	4·05 (m)	4·10 (m)	3·58 (m)
OH	2·27 (d)	2·21 (s)	2·28 (d)	2·24 (s)

[a] Methylenic protons absorb in the region 1·10—2·20 and aromatic protons in the region 7·18—7·96 p.p.m.

Furthermore the OH signals were of two types: compounds (7) and (8) showed widely spaced doublets owing to hydrogen bonding, whereas compounds (5) and (6) showed narrow singlets.

In conclusion, the cycloaddition of benzonitrile oxide to 3-benzoyloxycyclohexene is less regioselective than the cycloaddition to cyclohex-2-enone. This fact can be attributed to a better stabilization of partial charges in the four-centre transition state by the carbonyl group.

EXPERIMENTAL

U.v. and i.r. spectra were recorded on Perkin-Elmer 135 and 257 spectrophotometers, respectively. N.m.r. spectra were recorded with either a Varian HA100 (100 MHz) or a Perkin-Elmer R12 (60 MHz) instrument with sample spinning. Tetramethylsilane was used as internal standard.

T.l.c. was performed on silica gel G (Merck); plates were developed with a solution of chromium trioxide (3 g) in aqueous sulphuric acid (1 : 1; 100 ml).

To separate the mixtures of products, column chromatography was used with the following eluant systems: (A) cyclohexane–ethylene dichloride (1 : 1); (B) cyclohexane–ethyl acetate (95 : 5); and (C) cyclohexane–ethyl acetate (1 : 1).

TABLE 3

Compd.	Solvent for cryst.	M.p. (°C)	$\lambda_{max.}$(EtOH)/ nm (log ε) *	Found (%) C	H	N	Formula	Required (%) C	H	N
(1b)	MeOH [a]	77—78	266(4·06)	78·9	8·4	6·2	$C_{15}H_{19}NO$	78·6	8·35	6·1
(1c)	EtOH [b]	93—94	262(4·13)	81·5	6·2	5·6	$C_{17}H_{15}NO$	81·9	6·1	5·6
(1d)	EtOH [a]	101	259(3·95)	81·9	6·0	5·5				
(2a)	EtOH [a]	138 †	256(4·06), *284, 296*	74·7	6·4	8·9	$C_{20}H_{20}N_2O_2$	75·0	6·3	8·7
(2b)	MeOH [b]	129—131 †	257(4·06), *277, 287*	75·8	7·0	7·9	$C_{22}H_{24}N_2O_2$	75·8	6·9	8·0
(2c)	MeOH [c]	115—118 †	249(4·05), *276, 287*	78·3	5·35	7·6	$C_{24}H_{20}N_2O_2$	78·2	5·5	7·6
(2d)	MeOH [a]	115—117 †	255(4·04), *276, 286*	78·8	5·4	7·6				
(2e)	MeOH [a]	155—156 †	233(4·11), *259, 284*	73·7	5·7	6·3	$C_{27}H_{24}N_2O_4$	73·6	5·5	6·4
(2f)	MeOH [b]	178 †	237·5(4·18), *259, 278*	73·7	5·5	6·3				
(5)	Benzene [a]	121—123		71·7	6·8	6·55	$C_{13}H_{15}NO_2$	71·9	7·0	6·5
(6)	Cyclohexane [a]	86—88		72·3	7·0	6·7				
(7)	Cyclohexane [a]	141—143		71·5	7·1	6·6				
(8)	Cyclohexane [a]	122—123		72·0	6·9	6·6				

* Shoulders in italics. † Decomp.
[a] Needles. [c] Plates. [c] Prisms.

Physical and analytical data of products are given in Table 3.

Cycloaddition of Benzonitrile Oxide to Cycloalkenes.—A standard procedure was followed: benzonitrile oxide, liberated *in situ* from benzohydroximic acid chloride [10] was mixed with an excess of cycloalkene and set aside for 6 h. The mixture was then poured into water, and extracted with a suitable solvent; the extract was evaporated to give the crude product, which was further purified by column chromatography when necessary.

9-Phenyl-7-oxa-8-azabicyclo[4,3,0]*non-8-ene* (1a) *and* 4,7-*Diphenyl-2,6-dioxa-3,5-diazatricyclo*[6,4,0,$0^{3,7}$]*dodec-4-ene* (2a).—Benzohydroximic acid chloride (3·0 g) in cyclohexene (100 ml) was treated with the stoicheiometric amount of triethylamine, added dropwise with stirring during 2 h. Work-up and chromatographic separation [eluant (A)] gave compounds (1a) (2·25 g, 58·4%), m.p. 86—87°

[10] R. Huisgen and W. Mack, *Tetrahedron Letters*, 1961, 583.

(lit.,[5b] 84·5—86°; lit.,[5a] 78—80°), and (2a) (0·53 g, 16·6%).

11-*Phenyl*-9-*oxa*-10-*azabicyclo*[6,3,0]*undec*-10-*ene* (1b).—Similarly prepared from benzohydroximic acid chloride and cyclo-octene this compound was obtained in 92% yield.

5- *and* 2-*Benzoyloxy*-9-*phenyl*-7-*oxa*-8-*azabicyclo*[4,3,0]*non*-8-*ene* (1e) *and* (1f) *and* 4,7-*Diphenyl*-12- *and* -9-*benzoyloxy*-2,6-*dioxa*-3,5-*diazatricyclo*[6,4,0,$0^{3,7}$]*dodec*-4-*ene* (2e) *and* (2f).—Benzohydroximic acid chloride (3·21 g), 3-benzoyloxycyclohexene (25·4 g), and the theoretical amount of triethylamine in dichloromethane (15 ml) gave a mixture of compounds separated by column chromatography [eluant (A)] to give (2e) (0·09 g, 2%), (2f) (0·45 g, 10%), and a mixture of (1e) and (1f) (2·3 g, 35%).

3a,4,5,9b-*Tetrahydro*-3-*phenylnaphth*[2,1-d]*isoxazole* (1c) *and* 3a,4,5,9b-*Tetrahydro*-1-*phenylnaphth*[1,2-d]*isoxazole*(1d).—Benzohydroximic acid chloride (0·5 g) and 1,2-dihydronaphthalene (2·5 g) in methanol, on treatment as before followed by column chromatography [eluant (B)] gave compounds (1c) (0·64 g, 80%) and (1d) (0·13 g, 16%). The ratio of the two regioisomers (1c) and (1d) is not changed appreciably by carrying out the reaction in different solvents (diethyl ether, dioxan, and methylene chloride).

Cycloaddition of Benzonitrile Oxide and Δ^2-*Isoxazolines*.—Stoicheiometric amounts of the Δ^2-isoxazoline and benzohydroximic acid chloride were dissolved in a little methylene dichloride and triethylamine (1 equiv.) was added dropwise with stirring during 2 h. The mixture was set aside for 6 h, then washed with water, dried, and evaporated to give a mixture. Column chromatography [eluants (A) and (B)] as previously described gave compound (2a) (53%), (2b) (48%), (2c) (40%), or (2d) (35%). Some starting material (Δ^2-isoxazolines), 3,4-diphenylfurazan *N*-oxide, and a little of the oxadiazole (3) was also obtained. Compounds (2f) (25%) and (21) (11·5%) were obtained by the reaction of benzonitrile oxide directly with the crude mixture of (1e) and (1f).

Reactions of the 2,6-*Dioxa*-3,5-*diazatricyclo*[6,4,0,$0^{3,7}$]-*dodeca*-4-*enes* (2a) *and* (2f) *and of* 4,7-*Diphenyl*-2,6-*dioxa*-3,5-*diazatricyclo*[6,6,0,$0^{3,7}$]*tetradec*-4-*ene* (2b) *with* N-*Bromosuccinimide*.—The reactions were carried out in refluxing dry carbon tetrachloride. *N*-Bromosuccinimide was mixed with compound (2b) in the ratio 2 : 1 [or with compounds (2a) and (2f) in the ratio 3 : 1], with a little αα′-azoisobutyronitrile as catalyst. The reaction times were 1 h for (2b), 44 h for (2a), and 70 h for (2f). The solution was cooled to room temperature and, after the succinimide had been filtered off, evaporated to dryness under reduced pressure. 3,5-Diphenyl-1,2,4-oxadiazole (3) was separated by column chromatography in 68, 69, and 72% yields from (2b), (2a), and (2f), respectively.

Thermolysis of 4,7-*Diphenyl*-2,6-*dioxa*-3,5-*diazatricyclo*-[6,6,0,$0^{3,7}$]*tetradec*-4-*ene* (2b) *and* 4,7-*Diphenyl*-2,6-*dioxa*-3,5-*diazatricyclo*[6,4,0,$0^{3,7}$]*dodec*-4-*ene* (2a).—Compound (2b) (0·4 g), heated for a few minutes in benzene, developed a blue colour, which disappeared only after 96 h under reflux. The solvent was evaporated off to leave an oily residue, which solidified on treatment with a little ethanol and was shown to be the oxadiazole (3) (0·09 g, 35%). The mother liquor, refluxed with an ethanolic solution of 2,4-dinitrophenylhydrazine, gave the hydrazone of cyclo-octanone (0·09 g, 26%), identical with an authentic sample (i.r. spectroscopy and mixed m.p.). A similar result was achieved by carrying out the thermolysis in carbon tetrachloride. The reaction mixture was also analysed by g.l.c. (Apiezon; 180°) and cyclo-octanone was easily detected. Similar results were obtained from compound (2a), which gave oxadiazole in low yield after 120 h refluxing in carbon tetrachloride.

9-*Phenyl*-7-*oxa*-8-*azabicyclo*[4,3,0]*non*-8-*enols* (5)—(8).—(*a*) The mixture of (1e) and (1f) (2·3 g) was refluxed with an excess of potassium hydroxide in methanol for 5 min, then poured into water and extracted with ether. The extract was dried and evaporated and the residue was separated by column chromatography to give compounds (5) (0·58 g, 43%), (6) (0·4 g 30%), (7) (0·03 g, 2%), and (8) (0·08 g, 6%).

(*b*) The mixture of the two regioisomeric adducts from the cycloaddition of benzonitrile oxide to cyclohex-2-enone was treated with a slight excess of sodium borohydride in methanol and set aside at room temperature for 2 h. The whole was poured into water (pH acid) and extracted with ether; the extract was evaporated to dryness and the residue was separated by column chromatography [eluant (C)] to give compounds (7) (41·5%), (8) (13%), and (5) (18%).

9-*Phenyl*-7-*oxa*-8-*azabicyclo*[4,3,0]*non*-8-*en*-2- *and* -5-*ones* (9) *and* (10).—The carbinols (5) and (7) were separately oxidised by treating solutions in acetone with chromium trioxide in 25% sulphuric acid. The yields of ketone (9) (m.p. 81—84°) were 80% [from (5)] and 56% [from (7)].

Similar treatment of the carbinol (6) gave the ketone (10), m.p. 96—101° (76%).

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