Neighbouring Group Participation in Isoxazole Ring Bromination. Part I. Spirobi-isoxazolines from 5-Phenacyl-3-phenylisoxazole Oxime

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Bromination with *N*-bromosuccinimide or bromine of the (*E*)-oxime of 5-phenacyl-3-phenylisoxazole (2) gives (4*RS*,5*SR*)-4-bromo-3,8-diphenyl-1,6-dioxa-2,7-diazaspiro[4.4]nona-2,7-diene (3), which results from *cis*-addition of the neighbouring oxime group to the highly stabilized isoxazolium ion derived from the electrophilic attack of bromine upon the isoxazole ring. (4*RS*,5*SR*,9*RS*)-4,9-Dibromo-3,8-diphenyl-1,6-dioxa-2,7-diazaspiro-[4.4]nona-2,7-diene (4) is also formed by $-CH_2-$ group radical bromination of oxime (2) before the electrophilic attack on the isoxazole ring.

NEIGHBOURING group participation in electrophilic addition of bromine to olefins has been investigated.[1,2] It has been demonstrated that this participation occurs through a *trans* attack of the neighbouring group on a bromonium ion leading to compounds of definite stereochemistry.[3]

We have investigated neighbouring group participation by an oxime in electrophilic bromination of the isoxazole ring of the (*E*)-oxime of 5-phenacyl-3-phenylisoxazole (2), which can be obtained from the hydrolytic cleavage[4] of spiro-compound (1). Bromination was carried out with *N*-bromosuccinimide (NBS)[5] or bromine[6] and the bromospirobi-isoxazolines (3)—(5) were obtained.

[1] L. Goodman and S. Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 4788; L. Goodman, S. Winstein, and R. Boschan, *ibid.*, 1958, **80**, 4312.

[2] D. V. Nightingale, J. E. Johnson, and D. H. Heints, *J. Org. Chem.*, 1968, **33**, 360.

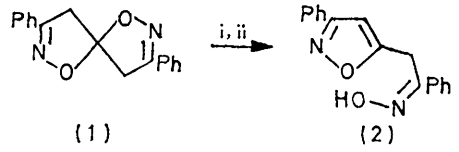
[3] S. Winstein, L. Goodman, and R. Boschan, *J. Amer. Chem. Soc.*, 1950, **72**, 2311.

[4] G. Stagno d'Alcontres and G. Lo Vecchio, *Gazzetta*, 1960, **90**, 1239.

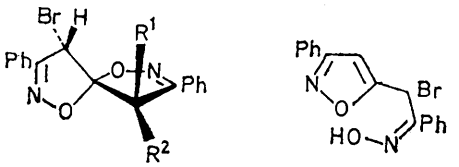
[5] N. K. Kochetkov, S. D. Sokolov and N. M. Vagurtova, *Zhur. obshchei Khim.*, 1962, **32**, 325 (*Chem. Abs.*, 1963, **57**, 12,455c).

[6] A. Quilico in ' The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Interscience, New York, 1956, vol. XVII, p. 49.

The reaction of oxime (2) with NBS, in the presence of oxygen, affords the *trans*-bromo- * (3) (59%) and



(1) (2)



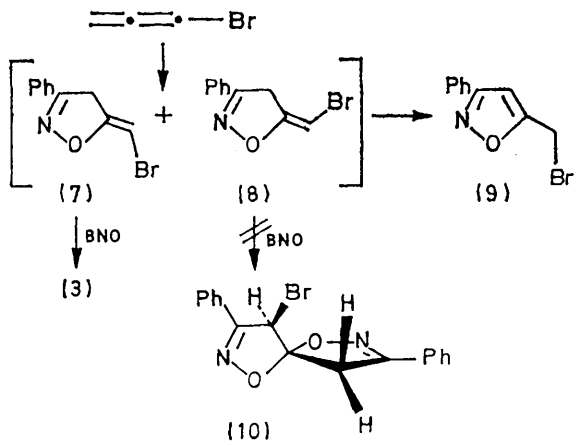
(3) $R^1 = R^2 = H$
(4) $R^1 = H$; $R^2 = Br$
(5) $R^1 = R^2 = Br$

(6)

Reagents: i, EtO^-; ii, H^+

trans,trans-dibromo- (4) (1%) spiro-compounds, while bromination with bromine in chloroform gives (4) (59%), (3) (1%), and traces of the 4-*trans*-bromo-9,9-dibromospiro-compound (5).

The structure of the bromo-derivatives (3)—(5) can be inferred from analytical, spectral, and synthetic data: either direct radical bromination [7] of spiro-compound (1) with NBS or 1,3-dipolar cycloaddition of benzonitrile oxide (BNO) to bromoallene affords the monobromospiro-compound (3), as the unique configurational isomer. Stereoselective *trans*-bromination can be expected in the former reaction leading to the *trans*-bromo-derivative (3). In the cycloaddition of BNO to bromoallene, two stereoisomeric 5-(bromomethylene)isoxazolines (7) and (8),



(7) (8) (9) (3) (10)

BNO = Benzonitrile oxide

which have not been isolated, can be postulated as intermediates formed during the initial addition of the dipole to the more reactive $>C=CH_2$ bond.[8] According to the high activation energy [9] expected for a further stereospecific cycloadditon to the *cis*-isomer (8), only the *trans*-intermediate (7) reacts to give (3). Isomerization of isoxazolines (7) and (8) to 5-bromomethyl-3-phenylisoxazole (9) occurs.

The n.m.r. spectrum of compound (3) agrees with a *trans*-configuration of bromine: the changes observed in the ^1H resonance of the 9-H_2 system on going from (1) to (3) are only reasonable in the absence of a strong steric compression [10] by a *cis*-bromine would occur in (10).

The *trans*-configuration of dibromide (4) is deduced from the resonance of the two $-CHBr-$ protons which appear as a singlet showing almost the same chemical shift as the corresponding $-CHBr-$ in (3).

The structure of tribromo-derivative (5) was deduced from the strong deshielding of the $-CHBr-$ resonance caused by steric compression [10] of the *cis*-bromine on C-9 (see Table).

^1H N.m.r. spectra ($CDCl_3$) (δ values)

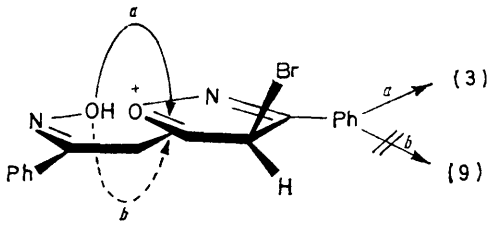
Compound	CH_2	CHBr	ArH
(1)	3·75 (2H, s)		7·1—7·8 (10H, m)
(3)	4·13 (1H, d) 3·80 (1H, d) J_{gem} 18·5 Hz	5·41 (1H, s)	7·4—7·9 (10H, m)
(4)		5·50 (2H, s)	7·4—7·8 (10H, m)
(5)		6·20 (1H, s)	7·4—8·1 (10H, m)

The configuration of bromo-spiran (3) gives some indication of the mechanism of neighbouring oxime group participation in the electrophilic bromination of the isoxazole ring. It is widely recognized that the stereochemistry of the addition of bromine to olefins depends on the relative stability of intermediate bromonium and carbonium ions; [11] vinyl ethers and related compounds which can form highly stabilized cations are less prone to form bridged cations, and they may give mixtures of stereoisomeric adducts.[12,13] Owing to the calculated low aromaticity of 3-phenylisoxazole,[14] we conclude that bromination on the isoxazole ring of the oxime (2) occurs *via* a stabilized oxonium ion, as in vinyl ethers, rather than through a cyclic bromonium ion: the neighbouring oxime group adds *cis* to bromine, yielding only the less sterically hindered *trans*-bromospiro-compound (3). The *trans,trans*-dibromospiro-compound (4) originates from the radical bromination of the $-CH_2-$ group prior to the electrophilic bromination on the isoxazole nucleus. In fact (3) cannot be further brominated to (4), neither with NBS nor with free bromine. The yield of (4) increases if the bromination of oxime (2) with NBS is carried out in the presence of benzoyl peroxide; from this reaction mixture the (*Z*)-oxime of 5-(α-bromophenacyl)-3-phenylisoxazole (6) can also be

* In this paper the term '*trans*' applied to a substituent at C-4 (or C-9) indicates that the substituent lies on the opposite side of the ring to C-9 (or C-4, respectively). Systematic names, using *RS*-nomenclature, are given in the Experimental section.

[7] G. Bianchi and P. Grünanger, *Tetrahedron*, 1965, **21**, 817.
[8] Ch. Grundmann and P. Grünanger, in ' The Nitrile Oxides,' Springer-Verlag, Berlin, 1971, p. 93.
[9] H. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633.
[10] S. Winstein, P. Carter, F. A. L. Anet, and J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5247.
[11] G. A. Olah and J. M. Bollinger, *J. Amer. Chem. Soc.*, 1967, **89**, 4744.
[12] R. U. Lemieux and B. Fraser-Reid, *Canad. J. Chem.*, 1965, **43**, 1460; 1964, **42**, 532.
[13] G. Dana and C. Roos, *Bull. Soc. chim. France*, 1973, 371.
[14] G. Del Re, *J. Chem. Soc.*, 1962, **30**, 3324.

recovered, which on further bromination with NBS gives the dibromospiro-compound (4).



The radical bromination of the methylene group is predominant when the oxime (2) is made to react with bromine in chloroform.

A steric approach control [13,15] on the electrophilic addition of bromine to the intermediate bromo-oxime (6) could explain the high yield of *trans,trans*-dibromo-derivative (4).

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian A-60 instrument (tetramethylsilane as internal standard). I.r. spectra were recorded for Nujol mulls on a Perkin-Elmer 225 spectrometer. The mass spectra were determined with a Varian MAT CH-5DF instrument using a direct insertion probe.

Bromination of the Oxime of 5-Phenacyl-3-phenylisoxazole.—(a) *With NBS.* (i) Oxygen was bubbled through a mixture of compound (2) (1 g), NBS (0·7 g), and CCl_4 (250 ml), which was heated for a few minutes at 60°, and then left for 3 h at room temperature with stirring. The succinimide was filtered off and the solvent was evaporated under reduced pressure to dryness. The residual oil treated with ether afforded (4RS,5SR)-4-*bromo*-3,8-*diphenyl*-1,6-*dioxa*-2,7-*diazaspiro*[4,4]*nona*-2,7-*diene* (3) (0·75 g, 59%) m.p. 167° (from chloroform) (Found: C, 57·5; H, 3·75; Br, 22·3; N, 7·8. $C_{17}H_{13}BrN_2O_2$ requires C, 57·15; H, 3·65; Br, 22·35; N, 7·85%); $\nu_{max.}$ 1368, 897, 820, 785, 770, 752, 683, and 667 cm^{-1}; *m/e* 358 and 356 (7%, M^+), 277 (12), 239 and 237 (6), 195 and 197 (7), 174 (13), 158 (16), 144 (23), 132 (37), 117 (52), 105 (42), 103 (61), and 77 (100). From the ethereal mother liquors (4RS,5SR,9RS)-4,9-*dibromo*-3,8-*diphenyl*-1,6-*dioxa*-2,7-*diazaspiro*[4,4]*nona*-2,7-*diene* (4) (1%) m.p. 195° (decomp.) was recovered (Found: C, 46·85; H, 2·7; Br, 36·8; N, 6·2. $C_{17}H_{12}Br_2N_2O_2$ requires C, 46·8; H, 2·75; Br, 36·65; N, 6·4%); $\nu_{max.}$ 1368, 897, 841, 762, 682, and 668 cm^{-1}; *m/e* 434, 436, and 438 (8, 25, 8%, M^+) 357 and 355 (6), 317 (12), 276 (34), 246 (23), 238 and 236 (12), 197 and 195 (40), 144 (32), 115 (46), 103 (71), and 77 (100).

(ii) A mixture of compound (2) (3 g), NBS (2·1 g), benzoyl peroxide (0·02 g), and CCl_4 (450 ml) was heated for a few min under reflux, and then stirred at room temperature for 3 h. The succinimide was filtered off, and the solvent evaporated under reduced pressure. The residual oil treated with ether afforded (3) (1·5 g, 39%). The residue obtained from the evaporation of the ethereal mother liquors was treated with methanol and yielded (4) (0·2 g, 4%) and the (*Z*)-*oxime* of 5-(α-*bromophenacyl*)-3-*phenylisoxazole* (6) (0·3 g, 8%), m.p. 148° (from chloroform) (Found: C, 57·4; H, 3·5; Br, 22·55; N, 7·9. $C_{17}H_{13}BrN_2O_2$ requires C, 57·15; H, 3·65; Br, 22·35; N, 7·85%); $\nu_{max.}$ 3240, 1445, 942, 912, and 685 cm^{-1}; δ [$(CD_3)_2CO$] 7·00 (1H, d, *J* 1·0 Hz, CHBr), 7·26 (1H, d, *J* 1·0 Hz, 4-H), and 7·3—8·0 (10H, m, ArH).

Compound (6) reacted with NBS under the same experimental conditions as described under (i) to give (4), (70%).

(b) *With molecular bromine.* Compound (2) (10 g) in chloroform (600 ml) was heated with bromine (12·48 g) at 40° for 3 h under a nitrogen stream. Hydrogen bromide was evolved. The mixture was treated in turn with dilute aqueous sodium thiosulphate solution, sodium hydrogen carbonate solution, and finally with water, dried, and evaporated to dryness. The residual oil worked up with methanol gave (4) (9·25 g, 59%); from the residual mother liquors (3) (1%) and traces of 4-*trans*-(4RS,5SR)-4,9,9-*tribromo*-3,8-*diphenyl*-1,6-*dioxa*-2,7-*diazaspiro*[4,4]*nona*-2,7-*diene* (5) m.p. 164° (from chloroform) (Found: C, 39·75; H, 2·2; Br, 46·4; N, 5·5. $C_{17}H_{11}Br_3N_2O_2$ requires C, 39·65; H, 2·15; Br, 46·55; N, 5·45%); $\nu_{max.}$ 1352, 925, 875, 853, 807, 778, 683, and 675 cm^{-1}; *m/e* 512, 514, 516, and 518 (2, 6, 6, 2%, M^+), 354 and 356 (6), 334, 336, and 338 (7, 12, 6), 314, 316, and 318 (5, 9, 5), 273, 275, and 277 (18, 35, 16), 195 (24), 129 (30), and 103 (100), which crystallized on standing.

Bromination of 3,8-Diphenyl-1,6-dioxa-2,7-diazaspiro[4,4]*nona-2,7-diene* (1) with *NBS.*—A mixture of compound (1) (2 g), NBS (1·4 g), benzoyl peroxide (0·015 g), and CCl_4 (800 ml) was heated at 60° for 3 h, under stirring. The mixture was allowed to cool, and starting materials and succinimide were filtered off; the filtrate was evaporated to dryness and the residue repeatedly crystallized from methanol, to give (3) (0·62 g, 24%) together with some unchanged starting compound (1).

1,3-Dipolar Cycloaddition of Benzonitrile Oxide to Bromoallene.—From this reaction diphenylfuroxan, 5-bromomethyl-3-phenylisoxazole, and the *trans*-bromospiro-compound (3) were recovered. An overall yield variation was observed by changing the experimental conditions.

In a typical run, bromoallene [16] (3 g) in dry benzene (20 ml) was slowly added under stirring to a mixture of benzohydroxamoyl chloride (10 g), triethylamine (6·4 g), and dry benzene (80 ml), at room temperature. Stirring was continued for an additional hour, and the mixture filtered. The solvent was evaporated under reduced pressure, and methanol was added to the oily residue. The precipitate, fractionally crystallized from methanol, gave (3) (0·9 g, 10%), 5-bromomethyl-3-phenylisoxazole, m.p. 88° (2·5 g, 41%), identical with an authentic sample, and diphenylfuroxan.

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[16] T. L. Jacobs and W. F. Brill, *J. Amer. Chem. Soc.*, 1953, **75**, 1314.