Neighbouring Group Participation in Isoxazole Ring Bromination.† Part II.[1]

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Electrophilic bromination of the isoxazole ring proceeds *via* a stabilized isoxazolium ion, which can undergo an intramolecular *cis*-addition of a neighbouring benzamido- or carboxylate group to afford bromospirobi-heterocyclic compounds containing the isoxazoline ring, or rearrangement products.

INTRAMOLECULAR cyclization in carbocation reactions has attracted widespread attention. Oxazolines, thiazolines, cyclic ethers, and lactones have been obtained by intramolecular attack of a neighbouring benzamido-,[2,3] ureido-,[3] thioureido-,[3,4] hydroxy-,[5] or carboxylato-[6] group on an intermediate ion formed by electrophilic attack upon an olefinic double bond. However, no reports of such neighbouring group participation in additions to heteroaromatic 'double bonds' have appeared.

We recently reported [1] that bromination of 5-phenacyl-3-phenylisoxazole (*E*)-oxime gives the bromospirobi-isoxazoline (1). This prompted us to determine whether the pronounced tendency of the oxime group to participate in the bromination of the isoxazole ring was also exhibited by other neighbouring groups. We now report the results of electrophilic bromination of the 5-substituted 3-phenylisoxazoles (2), (4), (5), (8), (10), and (12).

Bromination of the benzamidomethylisoxazole (2)

† Presented at the XII Congresso della S.C.I., Cagliari, Italy, 1975.

[1] Part I, C. Caristi and M. Gattuso, *J.C.S. Perkin I*, 1974, 679.

[2] L. Goodman, S. Winstein, and R. Boschan, *J. Amer. Chem. Soc.*, 1958, **80**, 4312.

[3] S. P. McManus, J. T. Carroll, and C. U. Pittman, *J. Org. Chem.*, 1970, **35**, 3768.

[4] A. S. Deutsch and P. E. Fanta, *J. Org. Chem.*, 1956, **21**, 892.

[5] D. L. H. Williams, E. Bienvenüe-Goetz, and J. E. Dubois, *J. Chem. Soc.* (*C*), 1969, 517.

[6] W. E. Barnett and J. C. McKenna, *Tetrahedron Letters*, 1971, 2595.

with *N*-bromosuccinimide (NBS) in acetic acid gave the spiro-5′-oxazoline (3) in high yield. The isoxazolylpropionate (4) readily cyclized to the spiro-γ-lactone (6) if stirred at room temperature with bromine in aqueous solution. Under the same conditions the carboxylate salt (8) gave 4,4-dibromo-3-phenylisoxazolin-5-one (9) in 10% yield, together with most of the 3-phenylisoxazole-5-carboxylic acid unchanged. Attempts to obtain bromo-spiro-derivatives or rearrangement products from phenylureido- (10) and phenylthioureido- (12) isoxazoles by bromination with an equimolecular amount of NBS in acetic acid failed; *p*-bromophenylureido- (11) and benzothiazole (13) derivatives were obtained instead. The structures of the bromination products were established from elemental analyses and spectral data (see Table).

^{1}H N.m.r. spectra ($CDCl_3$) (δ values) [a]

Compd.	CH_2	4-H	ArH	Others
(1)	4.13 (1 H, d), 3.80 (1 H, d) (J_{gem} 18.5)	5.41 (1 H, s)	7.4—7.9 (10 H, m)	
(3)	4.72 (1 H, d), 4.43 (1 H, d) (J_{gem} 18.0)	5.41 (1 H, s)	7.2—8.1 (10 H, m)	
(6)	2.5—3.3 (4 H, m)	5.37 (1 H, s)	7.4—8.0 (5 H, m)	
(7)	2.86 (1 H, d), 2.56 (1 H, d) (J_{gem} 18.0)	5.37 (1 H, s)	7.4—8.0 (5 H, m)	
(10) [b]	4.49 (2 H, d) [c] ($J_{HC,NH}$ 5.8)	6.76 (1 H, s)	6.8—8.0 (11 H, m, ArH and CH_2·N*H*)	8.6 (0.8 H, br, s, ArN*H*)
(11) [b]	4.49 (2 H, s and d) [c] ($J_{HC,NH}$ 5.5)	6.83 (1 H, s)	7.3—8.0 (9 H, m) [e]	6.83 (0.7 H, br, t, CH_2·N*H*) [d] ($J_{HC,NH}$ 5.5), 8.8 (0.6 H, br, s, ArN*H*) [d]
(12) [b]	4.92 (2 H, br, s and d) [c] ($J_{HC,NH}$ 5.0)	6.83 (1 H, s)	6.9—8.0 (10 H, m)	8.22 (0.5 H, br, t, CH_2·N*H*) [d] ($J_{HC,NH}$ 5.0), 9.73 (0.5 H, br, s, ArN*H*) [d]
(13) [f]	4.90 (2 H, d) ($J_{long\ range}$ 0.7)	6.81 (1 H, t) ($J_{long\ range}$ 0.7)	6.7—7.9 (9 H, m) [g]	

[a] Coupling constants (*J*) in Hz. [b] In $(CD_3)_2SO$. [c] On addition of D_2O the doublet collapses to a singlet. [d] The signal disappears on adding D_2O. [e] In CF_3CO_2D the aromatic protons (7.0—7.9) show an A_2B_2 pattern typical of a *para*-substituted benzene ring. [f] In $(CD_3)_2CO$. [g] A pattern typical of an *ortho*-condensed benzene ring can be identified.

The configuration of the bromine atom in compounds (3) and (6) comes from (i) the CHBr proton chemical shift, identical with that observed for compound (1), and (ii) the small difference in chemical shift (Δδ 0.3 p.p.m.) observed for the 9-proton resonances, which should be larger if one of them suffers from steric compression by a *cis*-4-bromo-substituent.[7] The chemical shift of the 9-protons of the spiro-lactone (6) cannot be measured directly because the signals overlap those of the 8-protons; however the ^{1}H n.m.r. spectrum of the [8-$^2H_2$]spirolactone (7) shows the 9-proton resonances at δ 2.86 (1 H, d) and 2.56 (1 H, d) (Δδ 0.3 p.p.m.).

The above stereochemical assignment agrees with *cis*-addition of the benzamido- or carboxylate groups to the intermediate stabilized isoxazolium ion formed during electrophilic bromination, leading to the less hindered bromo-spiro-derivative, as pointed out previously.[1]

It is likely that the spiro-α-lactone is an intermediate in the bromination of the salt (8). Its decarbonylation [8] would be expected to give 4-bromo-3-phenylisoxazolin-5-one, which could then be further brominated to afford the dibromoisoxazolone (9). *para*-Bromination of the phenylureido-group and bromination of the thioureido-group followed by Hugershoff rearrangement [9] to the benzothiazole (13) in the cases of (10) and (12) appear to be preferred to bromination at C-4 of the isoxazole.

In the light of (i) the low aromaticity [10] and high degree of ' bond fixation ' [11] of isoxazole derivatives; (ii) the fact that unstable addition products have been obtained in the halogenation of some substituted isoxazoles; [12] and (iii) the involvement of neighbouring oxime,[1] benzamido-, and carboxylate groups in the bromination of the isoxazole ring, one might predict other ' additions ' of this nature. The method could provide an alternative route to spirobi-heterocyclic compounds containing the isoxazoline ring, previously obtained by cycloadditions of nitrile oxides to exocyclic double bonds of heterocyclic compounds.[13] 5-Substituted isoxazoles having the 4-position free are readily available.[14]

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian A-60 instrument (tetramethylsilane as internal standard). I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 225 spectrometer.

(4RS,5SR)-4-*Bromo*-3,7-*diphenyl*-1,6-*dioxa*-2,8-*diazaspiro*-[4.4]*nona*-2,7-*diene* (3).—*N*-(3-Phenylisoxazol-5-ylmethyl)-benzamide (2) (1 g) was treated with stirring at room temperature with NBS (0.65 g) in acetic acid (30 ml) for 3 h. Benzene (50 ml) was then added and the resulting solution was washed with water, dried, and evaporated. The residue (0.96 g) was treated with boiling petroleum from which the *product* (3) (0.4 g) crystallized; m.p. 173° (after repeated recrystallization) (Found: C, 58.15; H, 4.1; Br, 22.25; N, 7.6. $C_{17}H_{13}BrN_2O_2$ requires C, 57.15; H, 3.65; Br, 22.35; N, 7.9%); $\nu_{max.}$ 1 667 and 1 348 cm^{-1}.

[7] S. Winstein, P. Carter, F. A. L. Anet, and J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5247.
[8] W. Adam and R. Rucktäschel, *J. Amer. Chem. Soc.*, 1971, **93**, 557; L. O. Chapman, P. W. Wojtkowski, W. Adam, O. Rodriguez, and R. Rucktäschel, *ibid.*, 1972, **94**, 1365.
[9] G. Barnikow and J. Bödeker, *Chem. Ber.*, 1967, 1394.
[10] G. Del Re, *J. Chem. Soc.*, 1962, **30**, 3324.
[11] S. Clementi, P. P. Forsyte, C. D. Johnson, A. R. Katritzky, and B. Terem, *J.C.S. Perkin II*, 1974, 399.
[12] A. Quilico, in ' The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Interscience, New York, 1956, vol. 17, p. 49.
[13] G. Lo Vecchio, G. Cum, and G. Stagno d'Alcontres, *Tetrahedron Letters*, 1964, 3495; G. Stagno d Alcontres, G. Cum, and M. Gattuso, *Ricerca Sci.*, 1967, **37**, 750; G. Lo Vecchio, M. Gattuso, and G. Stagno d Alcontres, *Gazzetta*, 1969, **99**, 121.
[14] Ch. Grundmann and P. Grünanger, in ' The Nitrile Oxides,' Springer-Verlag, Berlin, 1971, pp. 112—119.

(4RS, 5SR)-4-*Bromo*-3-*phenyl*-1,6-*dioxa*-2-*azaspiro*[4.4]-*non*-2-*en*-7-*one* (6).—3-(3-Phenylisoxazol-5-yl)propionic acid was synthesized by cycloaddition of benzonitrile oxide to diethyl prop-2-ynylmalonate.

(i) The adduct was heated for 30 h with aqueous 10% sulphuric acid. On cooling, the isoxazolylpropionic acid separated; m.p. 153° (from $CHCl_3$). To the acid (500 mg) dissolved in aqueous sodium hydrogen carbonate (166 mg) was added bromine (415 mg) in aqueous solution with stirring at room temperature. The *spiro-derivative* (6) which separated was collected, washed, dried, and crystallized from chloroform; m.p. 142° (yield 370 mg) (Found: C, 49.1; H, 3.45; N, 4.8. $C_{12}H_{10}BrNO_3$ requires C, 48.65; H, 3.4; N, 4.75%); $\nu_{max.}$ 1 792, 1 631, 1 133, and 1 007 cm^{-1}.

(ii) The adduct was heated for 12 h in methan[^{2}H]ol (10 g) containing [$^2H_2$]sulphuric acid (1 g). Deuterium oxide was then added and the mixture was heated for an additional 20 h. The organic solution was evaporated and the isoxazolyl[$^2H_2$]propionic acid was separated and brominated as above to give the dideuterio-compound (7).

4,4-*Dibromo*-3-*phenyl*-Δ^2-*isoxazolin*-5-*one* (9).—Potassium 3-phenylisoxazole-5-carboxylate (8) was brominated under the above conditions with an equimolar amount of bromine. The solution became acidic and a precipitate which separated was filtered off, washed, and stirred in aqueous sodium hydrogen carbonate–chloroform. The organic layer was dried and evaporated to give the product (9) (0.5 g), m.p. 77° (from ethanol), identical with an authentic sample. From the aqueous layer, 3-phenylisoxazole-5-carboxylic acid was recovered by acidification.

1-*Phenyl*-3-(3-*phenylisoxazol*-5-*ylmethyl*)*urea* (10) *and* 1-*Phenyl*-3-(3-*phenylisoxazol*-5-*ylmethyl*)*thiourea* (12).—These were prepared in the usual manner from 5-aminomethyl-3-phenylisoxazole;[15] the urea derivative (10) had m.p. 176°, $\nu_{max.}$ 3 311, 1 639, 1 572, 1 447, 1 244, 817, 771, and 690 cm^{-1}; the thiourea (12) had m.p. 168°, $\nu_{max.}$ 3 226, 3 175, 3 021, 1 603, 1 548, and 1 318 cm^{-1}.

1-p-*Bromophenyl*-3-(3-*phenylisoxazol*-5-*ylmethyl*)*urea* (11).—The urea (10) (1 g) was treated with an equimolecular amount of NBS in acetic acid (30 ml) for 3 h with stirring at room temperature. After a few minutes the product (11) began to separate; it was filtered off and crystallized from ethanol (m.p. 226°) and was identical with an authentic sample (Found: C, 55.0; H, 3.85; N, 11.5. Calc. for $C_{17}H_{14}BrN_3O_2$: C, 54.85; H, 3.8; N, 11.5%); $\nu_{max.}$ 3 289, 1 645, 1 595, 1 570, 1 471, and 1 245 cm^{-1}.

2-(3-*Phenylisoxazol*-5-*ylmethylamino*)*benzothiazole* (13).—The thiourea (12) (1 g) was brominated with an equimolecular amount of NBS in acetic acid (40 ml) for 3 h with stirring at room temperature. The white *benzothiazole hydrobromide* which separated was collected and crystallized from anhydrous ethanol; m.p. 204—208° (Found: C, 53.1; H, 3.75; N, 11.1. $C_{17}H_{14}BrN_3OS$ requires C, 52.6; H, 3.65; N, 10.8%); $\nu_{max.}$ (Nujol) 1 645, 1 471, and 1 412 cm^{-1}; $\nu_{max.}$ (hexachlorobuta-1,3-diene) 2 890, 2 841, 2 786, and 2 747 cm^{-1}. From a stirred aqueous suspension of the hydrobromide the benzothiazole (13) was recovered by adding cold sodium hydrogen carbonate solution; it was filtered off, washed, and crystallized from benzene; m.p. 173° (Found: C, 66.4; H, 4.55; N, 13.5. $C_{17}H_{13}N_3OS$ requires C, 66.45; H, 4.25; N, 13.65%); $\nu_{max.}$ 1 631, 1 582, 1 479, and 1 208 cm^{-1}.

This research was supported by the C.N.R. (Rome).

[6/068 *Received*, 12*th January*, 1976]

[15] P. Caramella and P. Vita Finzi, *Chimica e Industria*, 1966, **48**, 963.