Aust. J. Chem., 1995, **48**, 1379–1384

Directing Bromination of Piperazine-2,5-diones

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Abstract

From intermolecular and intramolecular competition experiments, it has been established that, by comparison with an *N*-methyl substituent, an *N*-acetyl group deactivates glycine residues in piperazine-2,5-diones towards free-radical bromination. Combined with the ease of introduction and removal of *N*-acetyl substituents, the deactivating effect provides a method for regiocontrolled functionalization of these compounds.

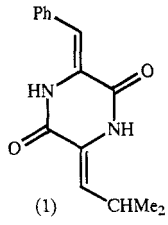
Introduction

Interest in the synthesis of piperazine-2,5-diones stems from the wide ranging natural occurrence and biological activity of this class of compounds. For example, albonoursin (1) has been isolated from *Streptomyces albus* var. *fungatus*, *Streptomyces noursei* and *Actinomyces tumemacerance*, and has been found to exhibit antibacterial and antitumour activity,[1] bicyclomycin (2) has been obtained from *Streptomyces sapporonensis* and *Streptomyces aizunensis*, and has been shown to be a broad spectrum antibiotic,[2] while gliotoxin (3) has been isolated from a variety of sources including *Aspergillus fumigatus*, *Gliocladium fimbriatum* and *Penicillium obsurum*, and is known to have antibacterial, antifungal, antiviral and immunosuppressive properties.[3]

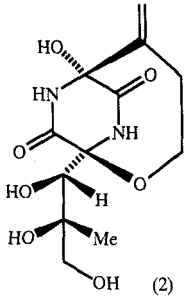
[1] Brown, R., and Kelley, C., *Annu. Rep. N.Y. State Dep. Health*, 1957, 10; 1958, 47; 1960, 50; 1960, 52; 1961, 40; Rao, K. V., and Cullen, W. P., *J. Am. Chem. Soc.*, 1960, **82**, 1127; Fukushima, K., Yazawa, K., and Arai, T., *J. Antibiot.*, 1973, **26**, 175.
[2] Miyoshi, T., Miyairi, N., Aoki, H., Kohsaka, M., Sakai, H., and Imanaka, H., *J. Antibiot.*, 1972, **25**, 569; Kamiya, T., Maeno, S., Hashimoto, M., and Mine, Y., *J. Antibiot.*, 1972, **25**, 576; Nishida, M., Mine, Y., and Matsubara, T., *J. Antibiot.*, 1972, **25**, 582; Nishida, M., Mine, Y., Matsubara, T., Goto, S., and Kuwahara, S., *J. Antibiot.*, 1972, **25**, 594; Miyamura, S., Ogasawara, N., Otsuka, H., Niwayama, S., Tanaka, H., Take, T., Uchiyama, T., Ochiai, H., Abe, K., Koizumi, K., Asao, K., Matsuki, K., and Hoshino, T., *J. Antibiot.*, 1972, **25**, 610; Miyamura, S., Ogasawara, N., Otsuka, H., Niwayama, S., Tanaka, H., Take, T., Uchiyama, T., and Ochiai, H., *J. Antibiot.*, 1973, **26**, 479.
[3] Waring, R., and Mullbacher, A., *Med. Res. Rev.*, 1988, **8**, 76; Taylor, A., in 'Microbial Toxins' (Eds S. Kadis, A. Ciegler and S. J. Ajl) Vol. 7, p. 337 (Academic: New York 1971).

Manuscript received 22 February 1995 0004-9425/95/071379$05.00

A common approach to the synthesis of the more complex piperazine-2,5-diones is through elaboration of simple precursors derived from proteinogenic amino acids.[4] In this regard, procedures for the regiocontrolled functionalization of piperazine-2,5-diones have considerable potential as many of the target molecules are asymmetrically substituted. The radical bromination of certain symmetric glycine anhydride derivatives with *N*-bromosuccinimide is known,[5–7] but no attempts to direct bromination using different *N*-substituents have been reported. Accordingly, we have now examined the effect of *N*-methyl and *N*-acetyl substituents on the halogenation.



(1)



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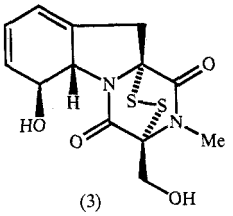


(3)

Results and Discussion

Initially, to gauge the effect of the substituents on reactivity, we examined reactions of sarcosine anhydride (4) and 1,4-diacetylpiperazine-2,5-dione (7). Bromination of the sarcosine derivative (4) to give the corresponding bromides (5a) and (6) has been reported.[5] In a similar fashion, the reaction of 1,4-diacetylpiperazine-2,5-dione (7) with *N*-bromosuccinimide in carbon tetrachloride, initiated with azobisisobutyronitrile, gave the bromides (8a) and (9a). Due to their instability, the bromides (8a) and (9a) were characterized by conversion into the corresponding thioethers (8b) and (9b), through treatment with 4-chlorothiophenol and pyridine. The di(thioether) (9b) was only obtained in 15% yield, presumably as a result of the particular instability of the dibromide (9a). The ^{1}H n.m.r. spectrum of the dibromide (9a) showed only one signal for the methyl group hydrogens, at δ 2·65, and one for the hydrogens attached to C3 and C6, at δ 6·93. Likewise, the spectrum of the di(thioether) (9b) showed only one resonance for each type of hydrogen. On this basis, it appears that the dibromide (9a) and the di(thioether) (9b) were each formed as a single diastereomer. Presumably this

[4] Ganem, B., *Tetrahedron*, 1978, **34**, 3353; Trown, P. W., *Biochem. Biophys. Res. Commun.*, 1968, **33**, 402; Fukuyama, T., Nakatsuka, S., and Kishi, Y., *Tetrahedron*, 1981, **37**, 2045; Williams, R. M., *Tetrahedron Lett.*, 1981, **22**, 2341; Williams, R. M., and Rastetter, W. H., *J. Org. Chem.*, 1980, **45**, 2625.

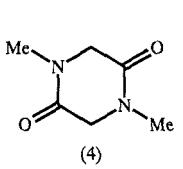
[5] Badran, T. W., and Easton, C. J., *Aust. J. Chem.*, 1990, **43**, 1455.

[6] Chai, C. L. L., and Page, D. M., *Tetrahedron Lett.*, 1993, **34**, 4373.

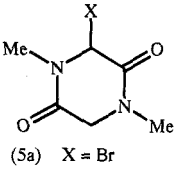
[7] Williams, R. M., Armstrong, R. W., Maruyama, L. K., Dung, J., and Anderson, O. P., *J. Am. Chem. Soc.*, 1985, **107**, 3246; Williams, R. M., and Kwast, A., *J. Org. Chem.*, 1988, **53**, 5785.

reflects the greater thermodynamic stability of the *cis* isomers of 3,6-disubstituted piperazine-2,5-diones.[8]

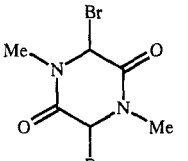
The relative reactivity of the piperazinediones (4) and (7) was determined by reaction of an equimolar mixture of each substrate and *N*-bromosuccinimide, in the presence of *N*-t-butylbenzamide (0·1 mole equiv.) as an internal standard. The crude reaction mixture was cooled and concentrated, and the residue was analysed by means of ^{1}H n.m.r. spectroscopy. Integration of signals for the internal standard (δ 1·44, s, 9H, Me_3, 100%), the piperazinediones (4) (δ 3·96, s, 2×CH_2, 4H, 20%) and (7) (δ 4·66, s, 2×CH_2, 4H, 420%), and the bromides (5a) (δ 6·02, s, H3, 1H, 85%) and (6) (δ 6·13, s, H3,6, 2H, 22%) showed that 5% of the sarcosine anhydride (4) remained and the bromides (5a) and (6) were produced in yields of approximately 75 and 10%, respectively, while 95% of the diacetylpiperazinedione (7) remained unreacted. There was no indication of formation of either of the bromides (8a) or (9a), as indicated by the absence of resonances at δ 6·87 and 6·93, respectively.



(4)



(5a) X = Br
(5b) X = 4-ClC_6H_4S



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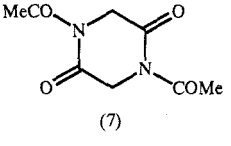
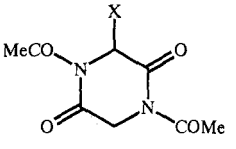
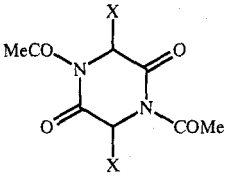


(7)



(8a) X = Br
(8b) X = 4-ClC_6H_4S



(9a) X = Br
(9b) X = 4-ClC_6H_4S

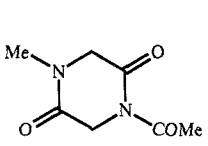
The deactivating effect of the *N*-acetyl substituent was further examined by studying reactions of 1-acetyl-4-methylpiperazine-2,5-dione (10), obtained by acetylation of glycylsarcosine anhydride[9] with acetic anhydride. Reaction of the piperazinedione (10) with *N*-bromosuccinimide under conditions analogous to those described above gave only the unstable bromide (11a), which was characterized by conversion into the thioether (11b) on treatment with 4-chlorothiophenol, and the ether (12) on treatment with methanol. Presumably the reaction of the bromide (11a) with methanol afforded the ether (11c) but the *N*-acetyl substituent of that compound hydrolysed during workup of the reaction mixture and chromatography of the crude product.

The regioselectivity of the halogenation of the piperazinedione (10) was assigned by comparison of the ^{1}H n.m.r. spectrum of the bromide (11a) with those of

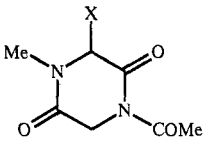
[8] Williams, R. M., Anderson, O. P., Armstrong, R. W., Josey, J., Meyers, H., and Eriksson, C., *J. Am. Chem. Soc.*, 1982, **104**, 6092; Williams, R. M., Armstrong, R. W., Maruyama, L. K., Dung, J., and Anderson, O. P., *J. Am. Chem. Soc.*, 1985, **107**, 3246; Benedetti, E., Marsh, R. E., and Goodman, M., *J. Am. Chem. Soc.*, 1976, **98**, 6676.

[9] Levene, P. A., Bass, L. W., Rothen, A., and Steiger, R. E., *J. Biol. Chem.*, 1954, **81**, 697.

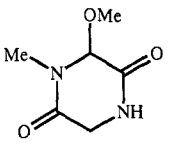
the bromides (5a) and (8a). The C3 proton of the bromide (11a) gave rise to a singlet resonance at δ 5·98. This chemical shift is similar to that of the signal for the C3 proton of the dimethylpiperazinedione (5a), at δ 5·79,[5] but different from that of the corresponding diacetyl derivative (8a), at δ 6·87. The ^{1}H n.m.r. spectra of the thioethers (11b), (5b) and (8b) support the assignment of regioselectivity of functionalization of the piperazinedione (10). The resonance for the C3 proton of the thioether (11b) appeared as a singlet at δ 4·99, with a similar chemical shift to that for the dimethyl derivative (5b) at δ 4·94, but 1·23 ppm upfield from that of the corresponding diacetyl derivative (8b). The thioether (5b) was obtained by treatment of the piperazinedione (4) with *N*-bromosuccinimide, followed by reaction of the crude product bromide (5a) with 4-chlorothiophenol.



(10)



(11a) X = Br
(11b) X = 4-ClC$_6$H$_4$S
(11c) X = OMe



(12)

Confirmation of the regioselectivity of bromination of the piperazinedione (10) was obtained by heating the ether (12) in refluxing 6 N hydrochloric acid, in the presence of alanine as an internal standard. Analysis of the concentrated product mixture by means of ^{1}H n.m.r. spectroscopy showed that glycine was produced in 60% yield, but there was no evidence of the presence of sarcosine.

From the reactions of the piperazinediones (4), (7) and (10), it is clear that, by comparison with an *N*-methyl substituent, an *N*-acetyl group deactivates glycine residues in piperazine-2,5-diones towards free-radical bromination. This effect is analogous to that observed with amino acid derivatives where the amino group is protected as a benzamide or a phthalimide.[10] Relative to the amido substituent, the greater steric bulk and reduced electron-donating capability of the imido group disfavour radical formation at the adjacent position.

An *N*-acetyl substituent is easily introduced on to a piperazinedione and readily removed,[11] as indicated in the synthesis of the piperazinediones (7) and (10) and the interconversion of the bromide (11a) into the ether (12), outlined above. On this basis, there is considerable scope to exploit the effect of the *N*-acetyl substituent, on reactions of piperazinediones with *N*-bromosuccinimide, in the regiocontrolled halogenation and elaboration of these compounds.

Experimental

Melting points are uncorrected. Light petroleum refers to the fraction with b.p. 66–68°. Radial chromatography was carried out on a Chromatotron 7924T (Harrison Research, Palo

[10] Easton, C. J., Tan, E. W., and Hay, M. P., *J. Chem. Soc., Chem. Commun.*, 1989, 385; Easton, C. J., Hutton, C. A., Rositano, G., and Tan, E. W., *J. Org. Chem.*, 1991, **56**, 5614.
[11] Gallina, C., and Liberatori, A., *Tetrahedron*, 1974, **30**, 667; Badran, T. W., Easton, C. J., Horn, E., Kociuba, K., May, B. L., Schliebs, D. M., and Tiekink, E. R. T., *Tetrahedron: Asymmetry*, 1993, **4**, 197.

Alto/TC Research, Norwich) by using Merck silica gel 60 PF_{254}, eluting with a gradient of light petroleum/ethyl acetate. N.m.r. spectra were recorded on either a Bruker CXP-300 or a Varian FT80A spectrometer, as dilute solutions in (D)chloroform, with tetramethylsilane as the internal standard. Electron impact mass spectra were recorded on either an AEI MS-902 or a Hewlett Packard HP-5995C spectrometer. Microanalyses were performed by the Microanalytical Facility, Otago University, New Zealand.

Glycine anhydride and sarcosine anhydride (4) were purchased from Sigma Chemical Co. 1,4-Diacetylpiperazine-2,5-dione (7) was prepared by treatment of glycine anhydride with acetic anhydride.[9]

1,4-Diacetyl-3-(4-chlorophenylthio)piperazine-2,5-dione (8b)

A mixture of the piperazinedione (7) (0·2 g, 1 mmol), *N*-bromosuccinimide (0·18 g, 1 mmol) and azobisisobutyronitrile (17 mg, 0·1 mmol) in dry carbon tetrachloride (10 ml) was heated at reflux under nitrogen for 2 h, then it was cooled and filtered. The filtrate was concentrated under reduced pressure to give a pale yellow oil, the ^1H n.m.r. spectrum of which showed the presence of the bromides (8a) and (9a) in the ratio 13:1. Signals for 1,4-diacetyl-3-bromopiperazine-2,5-dione (8a) were observed at δ 2·61, s, 3H; 2·62, s, 3H; 4·30, d, *J* 19 Hz, 1H; 5·24, d, *J* 19 Hz, 1H; 6·87, s, 1H.

The crude product of bromination of the piperazinedione (7) was dissolved in dry dichloromethane at 0°, then 4-chlorothiophenol (0·22 g, 1·5 mmol) and pyridine (0·15 g, 1·5 mmol) were added. The mixture was stirred at room temperature for 16 h, before it was washed with dilute hydrochloric acid and brine, then dried and concentrated under reduced pressure. Chromatography of the residual oil afforded a colourless solid which was recrystallized from light petroleum/ethyl acetate to give *1,4-diacetyl-3-(4-chlorophenylthio)piperazine-2,5-dione* (8b) (235 mg, 69%), m.p. 85–87° (Found: C, 49·3; H, 3·8; N, 8·1; S, 9·5. $C_{14}H_{13}ClN_2O_4S$ requires C, 49·3; H, 3·9; N, 8·2; S, 9·4%). ^1H n.m.r. δ 2·55, s, 3H; 2·56, s, 3H; 4·09, d, *J* 18 Hz, 1H; 5·13, d, *J* 18 Hz, 1H; 6·22, s, 1H; 7·4–7·6, m, 4H.

3-(4-Chlorophenylthio)-1,4-dimethylpiperazine-2,5-dione (5b)

The piperazinedione (4) (0·4 g, 2·81 mmol) was treated with *N*-bromosuccinimide (0·5 g, 2·81 mmol), and that crude product mixture was treated with 4-chlorothiophenol (0·61 g, 4·21 mmol), as described above for the synthesis of the thioether (8b). Chromatography of the crude product afforded a colourless solid which was recrystallized from ethyl acetate/methanol to give *3-(4-chlorophenylthio)-1,4-dimethylpiperazine-2,5-dione* (5b) (54%), m.p. 160–161° [Found: *m/z* 283·0309. $C_{12}H_{12}{}^{35}ClN_2O_2S$ ($M^{+\bullet} - H$) requires *m/z* 283·0308]. ^1H n.m.r. δ 2·52, d, *J* 18 Hz, 1H; 2·78, s, 3H; 3·15, s, 3H; 3·46, d, *J* 18 Hz, 1H; 4·94, s, 1H; 7·3–7·5, m, 4H.

1,4-Diacetyl-3,6-di(4-chlorophenylthio)piperazine-2,5-dione (9b)

The piperazinedione (7) was treated with *N*-bromosuccinimide (2 mole equiv.), and that crude product mixture was treated with 4-chlorothiophenol, as described above for the synthesis of the thioether (8b). The ^1H n.m.r. spectrum of the product of bromination showed signals for one diastereomer of 1,4-diacetyl-3,6-dibromopiperazine-2,5-dione (9a) at δ 2·65, s, 6H; 6·93, s, 2H.

Chromatography of the product of the reaction with 4-chlorothiophenol gave one diastereomer of *1,4-diacetyl-3,6-di(4-chlorophenylthio)piperazine-2,5-dione* (9b) (15%) as a white solid after recrystallization from light petroleum/ethyl acetate, m.p. 167–169° (Found: C, 50·0; H, 3·4; N, 5·8; S, 13·3. $C_{20}H_{16}Cl_2N_2O_4S_2$ requires C, 49·7; H, 3·3; N, 5·8; S, 13·3%). ^1H n.m.r. δ 2·60, s, 6H; 6·11, s, 2H; 7·3–7·6, m, 8H.

Competitive Reaction of 1,4-Dimethylpiperazine-2,5-dione (4) and 1,4-Diacetylpiperazine-2,5-dione (7) with N-Bromosuccinimide

Treatment of a mixture of the piperazinediones (4) (0·38 g, 2·65 mmol) and (7) (0·52 g, 2·64 mmol) and *N*-t-butylbenzamide (0·047 g, 0·265 mmol) with *N*-bromosuccinimide (0·47 g,

2·64 mmol), as described above for the reactions of the diacetylpiperazinedione (7), afforded a crude product mixture. The ^{1}H n.m.r. spectrum of the mixture indicated the presence of the starting materials (4), (7) and *N*-t-butylbenzamide, and the bromides (5a) and (6), in the ratio 0·05 : 0·95 : 1·0 : 0·75 : 0·10.

1-Acetyl-4-methylpiperazine-2,5-dione (10)

Glycylsarcosine anhydride[9] (200 mg, 1·56 mmol) was dissolved in acetic anhydride (2 ml), and the mixture was heated at reflux for 4 h, then it was cooled and concentrated under reduced pressure. Chromatography of the residual oil afforded a colourless solid which was recrystallized from light petroleum/ethyl acetate to give *1-acetyl-4-methylpiperazine-2,5-dione* (10) (212 mg, 81%), m.p. 60–61° (Found: C, 49·3; H, 5·6; N, 16·4. $C_7H_{10}N_2O_3$ requires C, 49·4; H, 5·9; N, 16·5%). ^{1}H n.m.r. δ 2·56, s, 3H; 3·01, s, 3H; 4·14, s, 2H; 4·37, s, 2H.

1-Acetyl-3-(4-chlorophenylthio)-4-methylpiperazine-2,5-dione (11b)

The piperazinedione (10) was treated with *N*-bromosuccinimide (1 mole equiv.), and that crude product mixture was treated with 4-chlorothiophenol, as described above for the synthesis of the thioether (8b). The ^{1}H n.m.r. spectrum of the product of bromination showed signals for 1-acetyl-3-bromo-4-methylpiperazine-2,5-dione (11a) at δ 2·62, s, 3H; 3·01, s, 3H; 3·82, d, *J* 18 Hz, 1H; 4·99, d, *J* 18 Hz, 1H; 5·98, s, 1H.

Chromatography of the product of the reaction with 4-chlorothiophenol gave *1-acetyl-3-(4-chlorophenylthio)-4-methylpiperazine-2,5-dione* (11b) (74%) as a colourless solid after recrystallization from light petroleum/ethyl acetate, m.p. 115–117° (Found: C, 49·8; H, 4·2; N, 9·1; S, 10·5. $C_{13}H_{13}ClN_2O_3S$ requires C, 49·9; H, 4·2; N, 9·0; S, 10·3%). ^{1}H n.m.r. δ 2·57, s, 3H; 3·13, s, 3H; 3·08, d, *J* 18 Hz, 1H; 4·49, d, *J* 18 Hz, 1H; 4·99, s, 1H; 7·3–7·5, m, 4H.

6-Methoxy-1-methylpiperazine-2,5-dione (12)

A mixture of the piperazinedione (10) (0·57 g, 3·3 mmol), *N*-bromosuccinimide (0·59 g, 3·3 mmol) and azobisisobutyronitrile (5 mg) in carbon tetrachloride (30 ml) was heated at reflux under nitrogen for 0·5 h, then it was cooled. Methanol (1·0 ml) was added and the resultant mixture was stirred at room temperature for 16 h, before it was concentrated under reduced pressure. Chromatography of the residual oil gave *6-methoxy-1-methylpiperazine-2,5-dione* (12) (36%) as an oil, which crystallized from ethyl acetate/light petroleum, in 21% yield, as a colourless solid, m.p. 116–117° (Found: C, 45·7; H, 6·2; N, 17·6. $C_6H_{10}N_2O_3$ requires C, 45·6; H, 6·4; N, 17·7%). ^{1}H n.m.r. δ 3·10, s, 3H; 3·52, s, 3H; 3·96, dd, *J* 4, 17 Hz, 1H; 4·16, d, *J* 17 Hz, 1H; 4·70, s, 1H; 6·3, br, 1H. ^{13}C n.m.r. δ 34·9, 46·8, 58·4, 90·1, 166·5, 167·7.

Hydrolysis of 6-Methoxy-1-methylpiperazine-2,5-dione (12)

A mixture of the piperazinedione (12) (21 mg, 0·13 mmol), alanine (12 mg, 0·13 mmol) and hydrochloric acid (6 N, 10 ml) was heated at reflux for 12 h, then it was cooled and concentrated under reduced pressure. The residue was dissolved in deuterium oxide (3 ml), and the solution was concentrated under reduced pressure. The ^{1}H n.m.r. spectrum (CD_3OD) of that residue showed the presence of alanine (δ 1·56, d, *J* 7 Hz, 3H) and glycine (δ 3·77, s, 2H) in the mole ratio 3 : 2. The presence of glycine and the absence of sarcosine were confirmed by the addition of authentic samples.

Acknowledgments

This work was supported by grants from the Australian Research Council and the Research Fund of Victoria University of Wellington.