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Monosubstitution of Symmetric Piperazine-2,5-dione Derivatives

Terry W. Badran[A] *and Christopher J. Easton*[A,B]

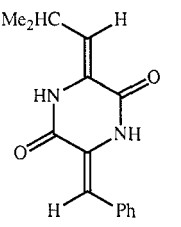
[A] Organic Chemistry Department, University of Adelaide, G.P.O. Box 498, Adelaide, S.A. 5001.
[B] Author to whom correspondence should be addressed.

Abstract

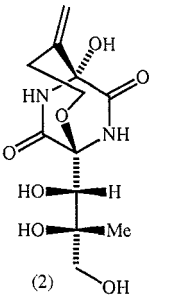
Bromination and methanolysis of derivatives of glycine anhydride affords the corresponding 3-bromo- and 3-methoxy-substituted piperazine-2,5-dione derivatives in a simple one-pot procedure.

Introduction

Piperazine-2,5-dione derivatives constitute a large and important class of naturally occurring compounds, many of which are biologically active. For example, albonoursin (1) has been isolated from *Streptomyces albus* var. *fungatus*, *Streptomyces noursei* and *Actinomyces tume-macerance*, and has been found to exhibit antibacterial and antitumour activity,[1] while bicyclomycin (2) has been obtained from *Streptomyces sapporonensis* and *Streptomyces aizunensis*, and has been shown to be a broad-spectrum antibiotic.[2] In the course of developing procedures for the synthesis of these compounds, Williams and Kwast[3] observed that the bromination of symmetric derivatives of glycine anhydride shows a strong tendency to give exclusively 3,6-dibrominated products in preference to the corresponding monobromides. As an example they reported that



(1)



(2)

[1] Brown, R., and Kelley, C., *Annu. Rep. N. Y. State Dep. Health, Albany*, 1957, 10; 1958, 47; 1960, 50; 1960, 52; 1961, 40; Rao, K. U., and Cullen, W. P., *J. Am. Chem. Soc.*, 1960, **82**, 1127; Rosenfeeld, G. S., Rostovtseva, L. I., Baikiam, V. M., Trakhtenbery, D. M., and Khokhlov, A. S., *Antibiotiki*, 1963, **8**, 201; 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., Ochiai, H., *J. Antibiot.*, 1973, **26**, 479.
[3] Williams, R. M., and Kwast, A., *J. Org. Chem.*, 1988, **53**, 5785.

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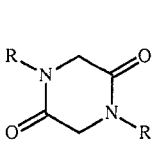
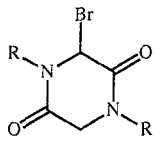
treatment of (3a) with 0·9 equiv. of *N*-bromosuccinimide gave approximately 50% of the dibromide (5a) and 50% unreacted (3a). In stark contrast to that work, we have found that bromination of derivatives of glycine anhydride affords the corresponding monobromides. Methanolysis of the monobromides *in situ* affords ethers that are of interest in the synthesis of asymmetric piperazinediones.[3–5]


(3)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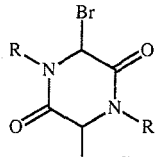
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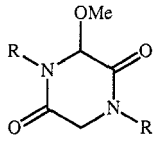
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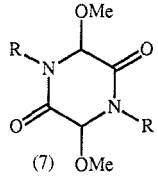
(7)

(a) R = $CH_2C_6H_4$-*p*-OMe (b) R = CH_2Ph (c) R = Me

Results and Discussion

In a typical experiment, (3a) was treated with *N*-bromosuccinimide (0·9 equiv.) in carbon tetrachloride at reflux under nitrogen for 0·5 h, with azobisisobutyronitrile to initiate the reaction. Analysis of the crude reaction mixture by ^{1}H n.m.r. spectroscopy showed the presence of (3a), the monobromide (4a) and the dibromide (5a), in the ratio *c.* 2:6:1. Similar treatment of (3b) gave a mixture of (3b), (4b) and (5b), in the ratio *c.* 1:6:1. The reaction of (3c) with *N*-bromosuccinimide was carried out in dichloromethane instead of carbon tetrachloride, in order to dissolve (3c), and gave a mixture of (3c), (4c) and (5c), in the ratio *c.* 5:15:1.

Since the monobromides (4a–c) were not sufficiently stable for isolation and purification, they were characterized by conversion into the corresponding ethers (6a–c), through the addition of methanol and triethylamine directly to crude reaction mixtures after cooling to 0°. Subsequent chromatography on silica gave (6a), (6b) and (6c), in yields of 41, 61 and 54%, based on (3a–c), respectively.

The dibromides (5a–c) were identified by comparison with authentic samples, prepared by treatment of (3a–c) with 2·1 equiv. of *N*-bromosuccinimide, and characterized as the corresponding ethers (7a–c). Only one diastereomer of each of the dibromides (5a–c) was detected, even by 300-MHz ^{1}H n.m.r. spectroscopy. The ethers (7a) and (7c) were isolated as mixtures of diastereomers, in the ratios 2·3:1 and 3:1, respectively. Only one diastereomer of the diether (7b) was detected, either in the crude reaction mixture or in the purified product.

These results show that in our hands the monobromides (4a–c) are produced through reaction of the corresponding substituted diketopiperazines (3a–c) with *N*-bromosuccinimide. While the earlier report[3] implied that the monobromides

[4] Williams, R. M., *Tetrahedron Lett.*, 1981, **22**, 2341.
[5] Williams, R. M., Anderson, O. P., Armstrong, R. W., Josey, J., Meyers, H., and Ericksson, C., *J. Am. Chem. Soc.*, 1982, **104**, 6092.

(4a–c) are much more reactive than (3a–c), our results show the converse. For the consecutive reactions

$$(3a) \xrightarrow{k_1} (4a) \xrightarrow{k_2} (5a) \qquad (i)$$

the concentration of the monobromide (4a) reaches a maximum when

$$d[(4a)]/dt = k_1[(3a)][Br^\bullet] - k_2[(4a)][Br^\bullet] = 0 \qquad (ii)$$

At this point

$$k_1/k_2 = [(4a)]/[(3a)] \qquad (iii)$$

When the relative percentage concentrations of (3a), (4a) and (5a) were monitored as a function of the mole ratio of (3a) to *N*-bromosuccinimide, the monobromide (4a) reached a maximum concentration of over 70%, at which stage less than 10% of the starting material (3a) remained. On this basis the rate constant for the reaction of (3a) is at least seven times greater than that of (4a). Similar results were obtained for the reactions of (3b) and (3c).

Each of the reactions of (3a–c) was repeated at least five times, and the results were always consistent. There was no interconversion between the monobromides (4a–c) and the dibromides (5a–c) in carbon tetrachloride or dichloromethane, at room temperature or at reflux, unless both *N*-bromosuccinimide and azobisisobutyronitrile were present. Homogenous reactions of (3a) and (3b) carried out under dilute conditions gave similar results to those carried out in more concentrated solution, where all of the *N*-bromosuccinimide and the by-product succinimide did not dissolve. All of the reactions of (3c) with *N*-bromosuccinimide in dichloromethane were homogeneous.

In summary, we can offer no explanation for the disparity between our results and those reported previously;[3] however, the syntheses of (4a–c) and (6a–c) described above illustrate an alternative,[3–5] direct and simple one-pot procedure for the preparation of monosubstituted piperazine-2,5-dione derivatives. Ready access to these compounds should facilitate the synthesis of other substituted diketopiperazines.

Experimental

General experimental details have been reported previously.[6] 1,4-Di(*p*-methoxybenzyl)piperazine-2,5-dione (3a) and 1,4-dibenzylpiperazine-2,5-dione (3b) were prepared by alkylation of piperazine-2,5-dione.[7] 1,4-Dimethylpiperazine-2,5-dione (3c) was purchased from Sigma Chemical Company.

*Bromination and Methanolysis of 1,4-Di(*p*-methoxybenzyl)piperazine-2,5-dione (3a)*

A mixture of (3a) (1·03 g, 2·9 mmol), *N*-bromosuccinimide (1·08 g, 6·1 mmol) and azobisisobutyronitrile (*c.* 5 mg) in carbon tetrachloride (50 ml) was heated at reflux under nitrogen for 0·5 h; then it was cooled and filtered. The filtrate was concentrated in vacuum to give crude *3,6-dibromo-1,4-di(*p*-methoxybenzyl)piperazine-2,5-dione* (5a). ^{1}H n.m.r. δ 3·81, s, 6H; 3·96, d, *J* 14·5 Hz, 2H; 5·26, d, *J* 14·5 Hz, 2H; 5·87, s, 2H; 6·85–6·95, m, 4H; 7·20–7·25,

[6] Easton, C. J., and Peters, S. C., *Aust. J. Chem.*, 1990, **43**, 87.
[7] Sera, A., Itoh, K., Yamada, H., and Aoki, R., *Heterocycles*, 1984, **22**, 713.

m, 4H. Alternatively the filtrate was cooled to 0°, and methanol (20 ml) and triethylamine (1·0 ml, 7·2 mmol) were added. After stirring for 2 h at 0° the mixture was concentrated in vacuum. The residue was dissolved in chloroform, washed with water, dried (Na_2SO_4) and concentrated, to give an oil which was chromatographed on silica. Elution with a gradient of ethyl acetate/light petroleum gave *3,6-dimethoxy-1,4-di(*p*-methoxybenzyl)piperazine-2,5-dione* (7a) which crystallized from ethyl acetate/light petroleum as colourless needles of a 2·3:1 mixture of diastereomers (0·66 g, 55%), m.p. 108–115° (Found: C, 63·3; H, 6·4; N, 6·9. $C_{22}H_{26}N_2O_6$ requires C, 63·8; H, 6·3; N, 6·8%). ^{1}H n.m.r. δ 3·44, s, 0·7×6H; 3·49, s, 0·3×6H; 3·80, s, 0·7×6H; 3·81, s, 0·3×6H; 4·02, d, *J* 14 Hz, 0·7×2H; 4·06, d, *J* 14·5 Hz, 0·3×2H; 4·64, s, 0·3×2H; 4·78, s, 0·7×2H; 5·11, d, *J* 14·5 Hz, 0·3×2H; 5·24, d, *J* 14 Hz, 0·7×2H; 6·8–7·3, m, 8H. Mass spectrum: *m/z* 383 (7%), 382 (31), 121 (100).

When the reaction of (3a) was repeated with 0·9 equiv. of *N*-bromosuccinimide, concentration of the cooled and filtered reaction mixture afforded a crude mixture of (3a), *3-bromo-1,4-di(*p*-methoxybenzyl)piperazine-2,5-dione* (4a) [^{1}H n.m.r. δ 3·80, s, 3H; 3·81, s, 3H; 3.82, d, *J* 18 Hz, 1H; 3·91, d, *J* 14 Hz, 1H; 3·94, d, *J* 18 Hz, 1H; 4·26, d, *J* 14·5 Hz, 1H; 4·84, d, *J* 14·5 Hz, 1H; 5·18, d, *J* 14 Hz, 1H; 5·79, s, 1H; 6·6–6·9, m, 4H; 7·1–7·3, m, 4H] and (5a) in the ratio *c.* 2:6:1, as determined by analysis with ^{1}H n.m.r. spectroscopy. Alternatively treatment of the cooled and filtered reaction mixture with methanol and triethylamine, followed by chromatography, gave *3-methoxy-1,4-di(*p*-methoxybenzyl)piperazine-2,5-dione* (6a) as colourless needles from ethyl acetate/light petroleum (yield 41%), m.p. 96·5–97° (Found: C, 65·4; H, 6·2; N, 7·2. $C_{21}H_{24}N_2O_5$ requires C, 65·6; H, 6·3; N, 7·3%). ^{1}H n.m.r. δ 3·39, s, 3H; 3·78, d, *J* 18 Hz, 1H; 3·79, s, 6H; 4·02, d, *J* 18 Hz, 1H; 4·11, d, *J* 14·5 Hz, 1H; 4·33, d, *J* 14·5 Hz, 1H; 4·67, s, 1H; 4·68, d, *J* 14·5 Hz, 1H; 5·05, d, *J* 14·5 Hz, 1H; 6·8–6·9, m, 4H; 7·1–7·3, m, 4H. Mass spectrum: *m/z* 384 (2%), 121 (100).

Bromination and Methanolysis of 1,4-Dibenzylpiperazine-2,5-dione (3b)

The reactions of (3b) were carried out as described above for (3a).

Treatment of (3b) with 2·1 equiv. of *N*-bromosuccinimide afforded crude *1,4-dibenzyl-3,6-dibromopiperazine-2,5-dione* (5b) [^{1}H n.m.r. δ 4·03, d, *J* 14·6 Hz, 2H; 5·34, d, *J* 14·6 Hz, 2H; 5·90, s, 2H; 7·3–7·4, m, 10H], which reacted with methanol in the presence of triethylamine to give *1,4-dibenzyl-3,6-dimethoxypiperazine-2,5-dione* (7b) as colourless needles from ethyl acetate/light petroleum (yield 66%), m.p. 169–171·5° (Found: C, 67·6; H, 6·2; N, 8·0. $C_{20}H_{22}N_2O_4$ requires C, 67·8; H, 6·3; N, 7·9%). ^{1}H n.m.r. δ 3·46, s, 6H; 4·17, d, *J* 15 Hz, 2H; 4·69, s, 2H; 5·11, d, *J* 15 Hz, 2H; 7·25–7·35, m, 10H. Mass spectrum: *m/z* 322 (43%), 263 (60), 91 (100).

The reaction of (3b) with 0·9 equiv. of *N*-bromosuccinimide afforded a crude mixture of (3b), *1,4-dibenzyl-3-bromopiperazine-2,5-dione* (4b) [^{1}H n.m.r. δ 3·87, d, *J* 18 Hz, 1H; 3·94, d, *J* 14·5 Hz, 1H; 3·99, d, *J* 18 Hz, 1H; 4·32, d, *J* 14·5 Hz, 1H; 4·93, d, *J* 14·5 Hz, 1H; 5·24, d, *J* 14·5 Hz, 1H; 5·84, s, 1H; 7·2–7·4, m, 10H] and (5b), in the ratio *c.* 1:6:1. Treatment of the mixture with methanol and triethylamine, followed by chromatography, gave *1,4-dibenzyl-3-methoxypiperazine-2,5-dione* (6b) as colourless needles from ethyl acetate/light petroleum (yield 61%), m.p. 87·5–88° (Found: C, 70·1; H, 6·0; N, 8·4. $C_{19}H_{20}N_2O_3$ requires C, 70·4; H, 6·2; N, 8·6%). ^{1}H n.m.r. δ 3·41, s, 3H; 3·80, d, *J* 18 Hz, 1H; 4·06, d, *J* 18 Hz, 1H; 4·18, d, *J* 15 Hz, 1H; 4·38, d, *J* 14·5 Hz, 1H; 4·70, s, 1H; 4·76, d, *J* 14·5 Hz, 1H; 5·15, d, *J* 15 Hz, 1H; 7·2–7·4, m, 10H. Mass spectrum: *m/z* 293 (94%), 91 (100).

Bromination and Methanolysis of 1,4-Dimethylpiperazine-2,5-dione (3c)

The reactions of (3c) were carried out as described above for (3a), except that dichloromethane was used instead of carbon tetrachloride.

Treatment of (3c) with 2·1 equiv. of *N*-bromosuccinimide afforded crude *3,6-dibromo-1,4-dimethylpiperazine-2,5-dione* (5c) [^{1}H n.m.r. δ 3·10, s, 6H; 6·13, s, 2H], which reacted with methanol in the presence of triethylamine to give a 3:1 mixture of diastereomers of 3,6-dimethoxy-1,4-dimethylpiperazine-2,5-dione (7c) (68%), as a colourless oil with spectral properties consistent with those reported previously.[8]

[8] Nakatsuka, S., Sasaki, K., Yamaguchi, K., and Goto, T., *Chem. Lett.*, 1981, 695.

The reaction of (3c) with 0·9 equiv. of *N*-bromosuccinimide afforded a crude mixture of (3c), *3-bromo-1,4-dimethylpiperazine-2,5-dione* (4c) [^{1}H n.m.r. δ 3·01, s, 3H; 3·06, s, 3H; 3·92, d, J 18 Hz, 1H; 4·16, d, J 18 Hz, 1H; 6·02, s, 1H] and (5c), in the ratio *c.* 5:15:1. Treatment of the mixture with methanol and triethylamine, followed by chromatography, gave 3-methoxy-1,4-dimethylpiperazine-2,5-dione (6c) (54%) as a colourless oil with spectral properties consistent with those reported previously.[5]

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