*Aust. J. Chem.*, 1984, **37**, 1791–4

# Pyrazine Chemistry. II*
# Reduction of 3,6-Dibenzylidenepiperazine-2,5-diones

*Sebastian M. Marcuccio and John A. Elix*

Department of Chemistry, The Faculties, Australian National University, P.O. Box 4, Canberra, A.C.T. 2601.

*Abstract*

A reinvestigation of the reduction of 3,6-dibenzylidenepiperazine-2,5-dione (1) with zinc and acetic acid established that this reaction gave (*Z*)-6-benzyl-3-benzylidenepiperazine-2,5-dione (10). When a mixture of acetic acid and hydrochloric acid was used in the reduction, a mixture of *trans*- (12) and *cis*-3,6-dibenzylpiperazine-2,5-dione (5) was obtained. Direct catalytic reduction of 3,6-di(2-chlorobenzylidene)piperazine-2,5-dione (2) to (±)-*cis*-3,6-di(2-chlorobenzyl)piperazine-2,5-dione (6) was also accomplished.

## Introduction

In the course of our study of the lichen piperazine-2,5-diones picroroccellin[1] and the scabrosin derivatives[2] we needed to accomplish the stereospecific reduction of a number of 3,6-dibenzylidenepiperazine-2,5-diones.

The reduction of the parent compound, 3,6-dibenzylidenepiperazine-2,5-dione (1), was first investigated by Sasaki[3] in 1921 using zinc in acetic acid and was reported to give the fully reduced product, 3,6-dibenzylpiperazine-2,5-dione (4). Later Elkaschef *et al.*[4] reported that reduction of (1) with zinc in hydrochloric acid and acetic acid gave an isomer of (4), identical with that obtained by catalytic hydrogenation of (1). This indicated that (±)-*cis*-3,6-dibenzylpiperazine-2,5-dione (5)[5–8] was formed in both these reactions. More recently, Coffen and coworkers[9] reported that the reduction of 3,6-di(2-chlorobenzylidene)piperazine-2,5-dione (2) under identical conditions to those used by Sasaki[3] gave a 1 : 1 mixture of (*E*)- and (*Z*)-6-(2-chlorobenzyl)-3-(2-chlorobenzylidene)piperazine-2,5-dione (8) and (9) respectively. However, unlike the parent 3,6-dibenzylidenepiperazine-2,5-dione (1),[4,5]

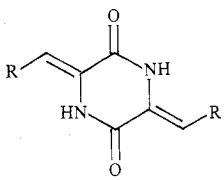
* Part I, *Tetrahedron Lett.*, 1983, **24**, 1445.

[1] Marcuccio, S. M., and Elix, J. A., *Tetrahedron Lett.*, 1983, **24**, 1445.
[2] Begg, W. R., Elix, J. A., and Jones, A. J., *Tetrahedron Lett.*, 1978, **19**, 1047.
[3] Sasaki, T., *Ber. Dtsch. Chem. Ges.*, 1921, **54**, 163.
[4] Elkaschef, M. A. F., Mokhtar, K. E., Abdel-Megeid, F. M. E., and Khallaf, S. A. A., *J. Chem. Soc. C*, 1969, 622.
[5] Brown, R., Kelley, C., and Wiberley, S. E., *J. Org. Chem.*, 1965, **30**, 277.
[6] Izumiya, N., Lee, S., Kanmera, T., and Aoyagi, H., *J. Am. Chem. Soc.*, 1977, **99**, 8346.
[7] Bycroft, B. W., and Lee, G. R., *J. Chem. Soc., Chem. Commun.*, 1975, 988.
[8] Kanmera, T., Lee, S., Aoyagi, H., and Izumiya, N., *Tetrahedron Lett.*, 1979, 4483.
[9] Coffen, D. L., Katonak, D. A., Nelson, N. R., and Sancilio, F. D., *J. Org. Chem.*, 1977, **42**, 948.

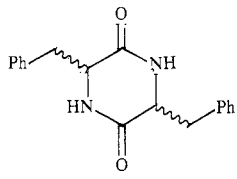
0004-9425/84/081791$02.00

direct catalytic reduction of (2) was unsuccessful[9] and the authors attributed this to the low solubility of the latter compound. In an effort to resolve these contradictions, we have reinvestigated the above reduction reactions and have now clarified the nature and stereochemistry of the products.

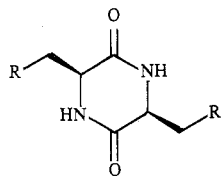
The 3,6-dibenzylidenepiperazine-2,5-diones (1)–(3) used in this study were prepared in excellent yield by a modification of the procedure of Gallina and Liberatori.[10] Thus 1,4-diacetylpiperazine-2,5-dione (11) was condensed with the appropriate aromatic aldehyde in the presence of dimethylformamide and triethylamine.



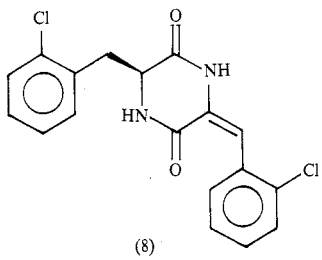
(1) R = Ph
(2) R = 2-$ClC_6H_4$
(3) R = 4-$OAcC_6H_4$



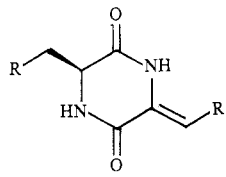
(4)



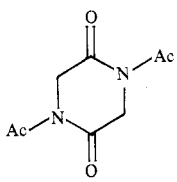
(5) R = Ph
(6) R = 2-$ClC_6H_4$
(7) R = 4-$OHC_6H_4$



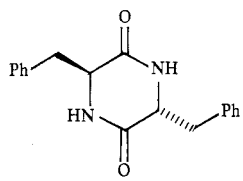
(8)



(9) R = 2-$ClC_6H_4$
(10) R = Ph



(11)



(12)

**Reduction of 3,6-Dibenzylidenepiperazine-2,5-diones**

In contrast to Sasaki's report[3] we found that the reduction of 3,6-dibenzylidenepiperazine-2,5-dione (1) with zinc dust and acetic acid gave (±)-(*Z*)-6-benzyl-3-benzylidenepiperazine-2,5-dione (10). Similarly reduction of (2) gave only the *Z*-isomer (9) rather than a 1 : 1 mixture of (8) and (9) as had previously been reported.[9]

The reduction of (1) with zinc and a mixture of acetic acid and hydrochloric acid gave a mixture of (±)-*cis*-3,6-dibenzylpiperazine-2,5-dione (5) and the *trans*-isomer (12) (*c.* 3 : 2) and not the pure (±)-*cis*-isomer (5) as implied by Elkaschef

[10] Gallina, C., and Liberatori, A., *Tetrahedron*, 1974, **30**, 667.

*et al.*[4] The pure (±)-*cis*-3,6-dibenzylpiperazine-2,5-diones (5)–(7) were readily produced by catalytic hydrogenation of (1)–(3). Although the 2-chlorophenyl derivative (2) was resistant to hydrogenation at room temperature, it was readily hydrogenated at 50–55° and 4 atm to give the (±)-*cis*-isomer (6). Similarly, the catalytic reduction of (3) in aqueous methanolic sodium hydroxide readily gave (±)-*cis*-di(4-hydroxybenzyl)piperazine-2,5-dione (7). The (±)-*cis*-geometry of (7) was assigned by comparison of the observed $^1$H n.m.r. spectrum with that of *cyclo*-(L-Tyr-L-Tyr).[11]

## Experimental

All melting points were determined on a Gallenkamp melting point apparatus, and are uncorrected. Microanalyses were performed by the Australian National University Microanalytical Service. $^1$H n.m.r. spectra were recorded on a Varian CFT-20 (80 MHz, Fourier mode), a JEOL JNM-MH-100 (100 MHz, continuous wave), or an EMI 360 (60 MHz, continuous wave) n.m.r. spectrometer. Fourier transform $^{13}$C n.m.r. spectra were recorded on a Varian CFT-20 (20·00 MHz) or a Bruker HFX-270 (67·89 MHz) n.m.r. spectrometer. $^1$H and $^{13}$C n.m.r. spectra were obtained for solutions in 5 mm and 10 mm tubes respectively, with tetramethylsilane as internal standard. Low-resolution mass spectra were recorded on either a Varian MAT CH7 or an A.E.I. MS902 mass spectrometer. The latter instrument was used for high-resolution mass measurements. Merck silica gel (70–230 mesh ASTM) was employed in column chromatography. Unless otherwise stated, all organic extracts were dried over magnesium sulfate and solvents removed (*c.* 17 mmHg) on a rotary evaporator.

*1,4-Diacetylpiperazine-2,5-dione* (*11*)

A suspension of glycine anhydride (11·4 g) in acetic anhydride (50 ml) was boiled under reflux for 6 h. The solvent was evaporated under reduced pressure and the residue crystallized from ethyl acetate/light petroleum to give the product (11) (18·1 g, 91%) as colourless needles, m.p. 99·5–100·5° (lit.[12] 102°).

(Z)-*3,6-Dibenzylidenepiperazine-2,5-dione* (*1*)

A mixture of 1,4-diacetylpiperazine-2,5-dione (11) (19·8 g), benzaldehyde (25 g), triethylamine (40 ml) and dimethylformamide (10 ml) was boiled under reflux for 5 h. The reaction mixture was cooled and the deposited solid broken up, and then the mixture was reheated to reflux for a further 16 h. The reaction mixture was then cooled, ethyl acetate (100 ml) added and the crystalline product filtered and washed with more ethyl acetate. This yielded the piperazinedione (1) (27·0 g, 93%) as pale yellow crystals, m.p. 297–299° (lit.[5] 298–300°).

(Z)-*3,6-Di*(*2-chlorobenzylidene*)*piperazine-2,5-dione* (*2*)

A mixture of 1,4-diacetylpiperazine-2,5-dione (11) (1·98 g), 2-chlorobenzaldehyde (3·5 g) and triethylamine (10 ml) was heated under reflux for 16 h. The reaction mixture was cooled, ethyl acetate (10 ml) added, and the pale yellow crystalline solid (3·47 g, 97%) was filtered and washed with ethyl acetate. A sample was recrystallized from acetic acid to afford the *piperazinedione* (2) as pale yellow needles, m.p. >300° (Found: C, 60·2; H, 3·5; Cl, 19·6; N, 8·1. $C_{18}H_{12}Cl_2N_2O_2$ requires C, 60·2; H, 3·4; Cl, 19·7; N, 7·8%). $^1$H n.m.r. ($CF_3CO_2D$/$CDCl_3$) $\delta$ 7·32–7·54, m, ArH and =CH. Mass spectrum *m*/*z* 358 ($M^+$, <1%), 325 (30), 323 (100).

(Z)-*3,6-Di*(*4-acetoxybenzylidene*)*piperazine-2,5-dione* (*3*)

This compound was prepared from 4-acetoxybenzaldehyde (4·0 g) by the method described above. The *piperazinedione* (3) (3·25 g, 80%) crystallized from acetic acid in pale yellow prisms, m.p. >300° (Found: C, 65·4; H, 4·5; N, 6·8. $C_{22}H_{18}N_2O_6$ requires C, 65·0; H, 4·5; N, 6·9%). Mass spectrum *m*/*z* 406 ($M^+$, 27%), 364 (35), 43 (100).

[11] Kopple, K. D., and Marr, D. H., *J. Am. Chem. Soc.*, 1967, **89**, 6193.
[12] Franchimont, A. P. N., and Friedmann, H., *Recl Trav. Chim. Pays-Bas*, 1908, **27**, 192.

(±)-(Z)-*6-Benzyl-3-benzylidenepiperazine-2,5-dione* (*10*)

A suspension of 3,6-dibenzylidenepiperazine-2,5-dione (1) (2·0 g) and zinc dust (5·0 g) in glacial acetic acid (100 ml) was stirred at reflux for 18 h. Water (10 ml) was carefully added to the hot reaction mixture to dissolve the precipitated zinc salts. The excess zinc was filtered and the filtrate concentrated (*c.* 40 ml). Water (150 ml) was added and the precipitate filtered. After recrystallization from acetone, *piperazinedione* (10) was obtained as colourless crystals, m.p. 282–283° (lit.[5] 283–284°). $^1$H n.m.r. ($CDCl_3/CF_3CO_2D$) $\delta$ 3·34, m, $ArCH_2$; 4·80, m, $CH_2CH$; 7·00, s, =CH; 7·32, m, $C_6H_5$. Mass spectrum *m/z* 292 ($M^+$, 100%).

(±)-(Z)-*6-(2-Chlorobenzyl)-3-(2-chlorobenzylidene)piperazine-2,5-dione* (*9*)

3,6-Di(2-chlorobenzylidene)piperazine-2,5-dione (2) (2·0 g) was reduced with zinc dust and acetic acid as described above. The *piperazinedione* (9) (1·95 g, 97%) crystallized from glacial acetic acid in colourless crystals, m.p. 241–243° (Found: C, 59·7; H, 4·0; N, 7·4. $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59·9; H, 3·9; N, 7·8%). $^1$H n.m.r. ($CDCl_3/CD_3SOCD_3/D_2O$) $\delta$ 2·56, m, $ArCH_2$; 4·30, m, $CH_2CH$; 6·60, s, =CH; 7·34, m, ArH. Mass spectrum *m/z* 360 ($M^+$, 3%), 325 (100).

*Reduction of* (*1*) *with Zinc, Acetic Acid and Hydrochloric Acid*

A mixture of 3,6-dibenzylidenepiperazine-2,5-dione (0·5 g), zinc dust (3·5 g), glacial acetic acid (40 ml) and concentrated hydrochloric acid (2·5 ml) was boiled under reflux for 9 h. The reaction mixture was filtered hot, cooled and diluted with water. The precipitate was filtered and dried to give the product (0·2 g, 40%) as colourless crystals, m.p. 274–282° (lit.[4] 280°). The proportion of the (±)-*cis*-isomer (5)/*trans*-isomer (12) was determined to be *c.* 3 : 2 by integration of the respective $CH_2CH$ protons in the $^1$H n.m.r. spectrum of the mixture ($\delta$ *cis* 4·60, $\delta$ *trans* 4·00[13]). Mass spectrum *m/z* 295 (14%), 294 ($M^+$, 66), 203 (39), 175 (54), 120 (24), 103 (13), 92 (26), 91 (100) and 65 (10).

(±)-cis-*3,6-Di(2-chlorobenzyl)piperazine-2,5-dione* (*6*)

A suspension of 3,6-di(2-chlorobenzylidene)piperazine-2,5-dione (2) (0·2 g) and 10% palladium on charcoal (0·2 g) in dioxan (50 ml) was warmed to 50° and shaken under a pressure of 4 atm of hydrogen for 60 h. The catalyst was filtered and the filtrate reduced in volume to *c.* 10 ml, diluted with water and the crude product collected by filtration. The piperazinedione (6) (174 mg, 86%) crystallized from acetic acid/diethyl ether as colourless needles, m.p. 223–224° (lit.[9] 220–222°). $^1$H n.m.r. ($CDCl_3/CD_3SOCD_3$) $\delta$ 2·62, 3·21, 2m, $ArCH_2$; 4·10, m, $CH_2CH$; 7·30, m, $C_6H_5$ and 7·90, s, NH.

(±)-cis-*3,6-Di(4-hydroxybenzyl)piperazine-2,5-dione* (*7*)

A mixture of 3,6-di(4-acetoxybenzylidene)piperazine-2,5-dione (3) (2·0 g), sodium hydroxide (0·4 g), water (25 ml) and methanol (25 ml) was boiled under reflux for 1 h. The clear solution was cooled to room temperature, 10% palladium on charcoal (0·2 g) added and the resulting suspension was shaken under 3 atm of hydrogen for 16 h. The catalyst was then filtered and the filtrate acidified with dilute hydrochloric acid. The precipitate was filtered, washed with water and air-dried. The piperazinedione (7) (1·32 g, 82%) crystallized from ethanol in colourless needles, m.p. 280–280·5° (dec.) [lit.[14] 285–287° (dec.)]. $^1$H n.m.r. ($CF_3CO_2D$) $\delta$ 2·34, dd, *J* 16, 7 Hz, $ArCH_2$; 3·04, dd, *J* 16, 2 Hz, $ArCH_2$; 4·50, m, $CH_2CH$; 7·10, m, ArH. Mass spectrum *m/z* 326 ($M^+$, 20%), 107 (100).

## Acknowledgment

The award of an Australian National University Ph.D. Scholarship to S.M.M. is gratefully acknowledged.

Manuscript received 30 March 1984

[13] Eguchi, C., and Kakuta, A., *J. Am. Chem. Soc.*, 1974, **96**, 3985.
[14] Anderson, G. W., Blodinger, J., Young, R. W., and Welcher, A. D., *J. Am. Chem. Soc.*, 1952, **74**, 5304.