Aust. J. Chem., 1984, **37**, 2397–402

Pyrazine Chemistry. III*
Synthesis and Stereochemistry of 1,4-Dimethyl and 1,4-Diacetyl Derivatives of 3,6-Dibenzylpiperazine-2,5-dione

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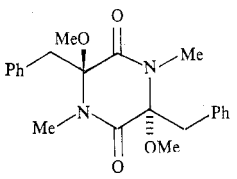
Abstract

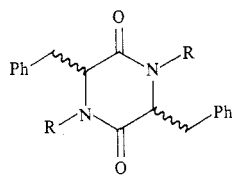
The *trans*- and (±) *cis*-isomers of 1,4-dimethyl- and 1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione were synthesized. The hydriodic acid reduction of 3,6-dibenzylidene-1,4-dimethylpiperazine-2,5-dione gave (±)-*cis*-3,6-dibenzyl-1,4-dimethylpiperazine-2,5-dione although this product has previously been assigned the *trans*-geometry. The unknown isolated from the permanganate oxidation of (+)-*cis*-1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione has been identified as the corresponding *trans*-isomer.

Introduction

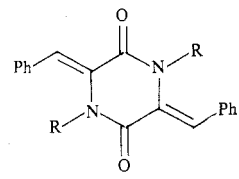
In their investigation of the structure of the lichen piperazine-2,5-dione, picroroccellin, Forster and Saville[1] found that dimethylpicroroccellin (1)[2] was reduced to (2) on using the Zeisel method[3,4] to estimate the methoxy content. Subsequently they were able to synthesize (2) by reduction of 3,6-dibenzylidene-1,4-dimethylpiperazine-2,5-dione (4) with hydriodic acid.



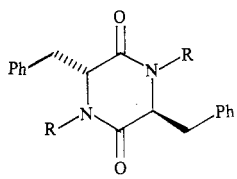
(1)



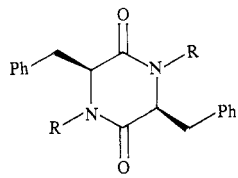
(2) R = Me
(3) R = H



(4) R = Me
(5) R = H



(6) R = Me
(7) R = Ac



(8) R = H
(9) R = Me
(10) R = Ac

* Part II, *Aust. J. Chem.*, 1984, **37**, 1791.

[1] Forster, M. O., and Saville, W. B., *J. Chem. Soc.*, 1922, 816.
[2] Marcuccio, S. M., and Elix, J. A., *Tetrahedron Lett.*, 1983, **24**, 1445.
[3] Ziesel, S., *Monatsh. Chem.*, 1885, **6**, 989.
[4] Ziesel, S., *Monatsh. Chem.*, 1886, **7**, 406.

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Machin and Sammes[5] assigned the *trans*-geometry (6) to this product. However, neither the melting point nor the ^{1}H n.m.r. spectrum of this compound are consistent with that subsequently reported by Radding and coworkers[6] for the *trans*-isomer (6). Stereochemical anomalies were also encountered in the chemistry of the corresponding 1,4-diacetyl derivatives (7) and (10). Treatment of (8) with acetic anhydride in acetic acid has been reported[7] to give the corresponding optically active *cis*-diacetate (10) while treatment with acetic anhydride and sodium acetate gave an optically inactive product, of unspecified stereochemistry. Subsequent oxidation of (10) with potassium permanganate gave benzoic acid, benzaldehyde and an 'unknown' compound, isomeric with (7) and (10)!

In this paper we describe the clarification of the stereochemistry of (2) and the structure of the 'unknown' derived by permanganate oxidation of (10).

Stereochemistry of 3,6-Dibenzyl-1,4-dimethylpiperazine-2,5-dione

A mixture of the (±) *cis*-isomer (9) and the *trans*-isomer (6) of (2) was prepared by methylation of (3) with methyl iodide in the presence of sodium hydride in dimethylformamide solution,[5] and the isomers were separated by column chromatography. The faster moving band was found to have a melting point and ^{1}H n.m.r. spectrum identical with that reported for the *trans*-isomer (6)[6] while the slower band [i.e. the (±) *cis*-isomer (9)] was found to have a ^{1}H n.m.r. spectrum identical to that reported for *cis* L-L (9)[6] (Table 1).

Table 1. Physical data for isomers of 3,6-dibenzyl-1,4-dimethylpiperazine-2,5-dione

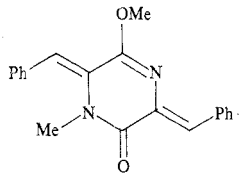
Isomer	M.p. (°C)	^{1}H n.m.r. (δ) α-CH	β-CH_A	β-CH_B	NMe	Reference
trans D-L (6)	187–189	3·46	3·32	2·96	2·84	6
trans D-L (6)	188–189	3·40	3·14	3·03	2·84	this work
cis L-L (9)	150–151	4·06	2·84	2·20	2·75	6
(±)-*cis* (9)	165	4·04	2·90	2·20	2·76	this work
Isomer of (2)	161	4·07	2·93	2·24	2·75	5
Isomer of (2)	165	—	—	—	—	1

The higher R_F value of the *trans*-isomer (6) provided further support for these assignments.[8,9]

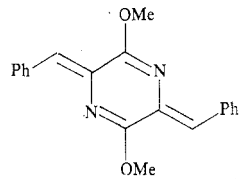
To further clarify these stereochemical assignments, we have repeated the synthesis of (2) as described by Forster and Saville.[1] Methylation of the parent 3,6-dibenzylidenepiperazine-2,5-dione (5) with dimethyl sulfate and sodium hydroxide gave the desired 1,4-dimethyl derivative (4) together with the *O*-methyl and di-*O*-methyl derivatives (11) and (12) respectively. Although this procedure has been used repeatedly,[10,11] the byproducts (11) and (12) have not previously been reported. An

[5] Machin, P. J., and Sammes, P. G., *J. Chem. Soc., Perkin Trans. 1*, 1976, 624.
[6] Radding, W., Donzel, B., Ueyama, N., and Goodman, M., *J. Am. Chem. Soc.*, 1980, **102**, 5999.
[7] Birkinshaw, J. H., and Mohammed, Y. S., *Biochem. J.*, 1962, **85**, 523.
[8] Mauger, A. B., *J. Chromatogr.*, 1968, **37**, 315.
[9] Westley, J. W., Close, V. A., Nitecki, D. N., and Halpern, B., *Anal. Chem.*, 1968, **40**, 1888.
[10] Yoshimura, J., Sugiyama, Y., and Nakamura, H., *Bull. Chem. Soc. Jpn*, 1973, **46**, 2850.
[11] Herscheid, J. D. M., Scholten, H. P. H., Tijhuis, M. W., and Ottenheijm, H. C. J., *Recl Trav. Chim. Pays-Bas*, 1981, **100**, 73.

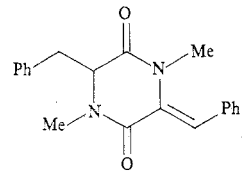
alternative procedure[12] for methylation of (5) by treatment with sodium hydride and methyl iodide in dimethylformamide, also resulted in the formation of the byproducts (11) and (12).[13]



(11)



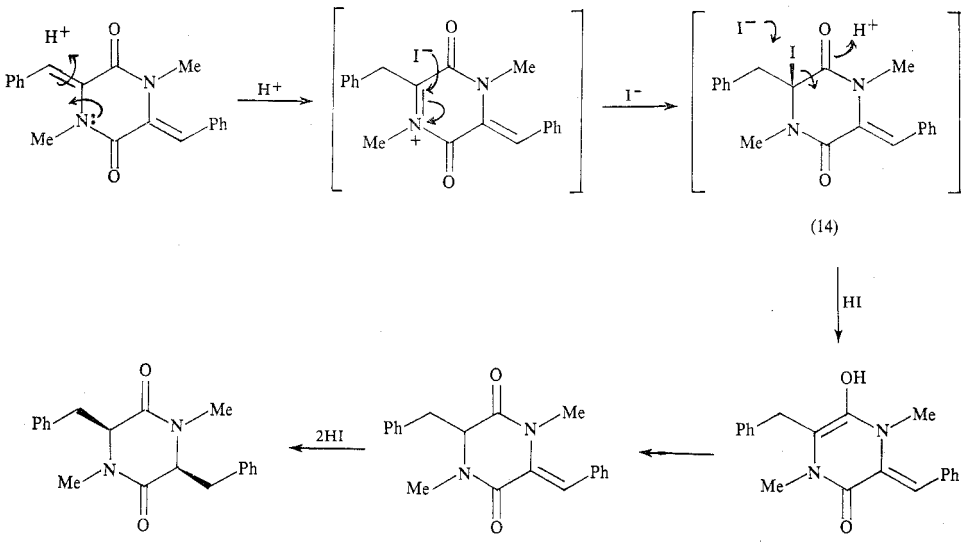
(12)



(13)

The reduction of (4) by using hydriodic acid gave (±)-*cis* (9) in reasonable yield. Subsequently it was found that the yield could be improved by using diethyl ketone as a cosolvent. If the reaction temperature was lowered further by using acetone as cosolvent, 3-benzyl-6-benzylidene-1,4-dimethylpiperazine-2,5-dione (13) could be isolated as the major product. As expected, catalytic hydrogenation of (4) also gave (±)-*cis* (9). Hence the product obtained by Forster and Saville[1] by reduction of (4) or (1) with hydriodic acid was the racemic *cis*-isomer (9) and not the *trans*-isomer (6) as had previously been reported.[5]

The difference in melting points (Table 1) between the *cis* L-L isomer and the racemic *cis*-isomer (9) was not unexpected since racemic compounds often have melting points higher than the pure enantiomers.[14]



Scheme 1

[12] Shin, C., Sato, Y., Hayakawa, M., and Kondo, M., *Heterocycles*, 1981, **16**, 1573.
[13] Marcuccio, S. M., and Elix, J. A., unpublished data.
[14] Finar, I. L., 'Organic Chemistry' Vol. 2, p. 57 (Longmans: London 1959).

It is interesting to speculate why reduction of (4) with hydriodic acid should give the (±) *cis*-isomer (9). Such reduction could be expected to involve intermediate iodides such as (14) formed by the Markownikoff addition[15] of hydriodic acid to the double bond, followed by reduction with hydriodic acid (Scheme 1). The benzyl group of the intermediate (13) may hinder the approach of the bulky iodide anion to the same side of the molecule, so that the (±) *cis*-isomer (9) is formed in high yield.

Stereochemistry of 1,4-Diacetyl-3,6-dibenzylpiperazine-2,5-dione

The *trans*- and (±)-*cis*-1,4-diacetyl-3,6-dibenzylpiperazine-2,5-diones (7) and (10) were synthesized by heating (3) with acetic anhydride, and were separated by column chromatography.

The *trans*-isomer (7) was distinguished by the upfield shift of the C_α protons in comparison with those of the (±) *cis*-isomer (10) (the benzylic protons are deshielded in the latter by the proximity of the non-bonded aromatic ring) and further supported by the higher R_F of the *trans*-isomer.[8,9] The melting point of the *trans*-isomer (7) corresponded to that of the 'unknown'[7] isolated after treatment of the (+)-*cis*-1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione (10) with potassium permanganate (Table 2), and indicated that some epimerization occurred during this oxidation procedure. It would appear from the reported physical data (melting point, optical rotation) that the product obtained by treating (3) with acetic anhydride and sodium acetate[7] was a mixture of the *trans*-isomer (7) and the (±) *cis*-isomer (10).

Table 2. Physical data for isomers of 1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione

Product and geometry	M.p. (°C)	$[\alpha]^{20}_{5461}$ (deg)	Reference
trans D-L (7)	193	0	this work
Product from $KMnO_4$ oxidation	193	0	[7]
cis L-L (10)	178	+201	[7]
(±)-*cis* (10)	151·5–152·5	0	this work
(±)-*cis*/*trans* mixture	145–151	0	[5]
Product from (3)+NaOAc/Ac_2O	149	0	[7]

Experimental

The general experimental details have been reported previously.[16]

3,6-Dibenzylpiperazine-2,5-dione (3)

L-Phenylalanine (10 g) was heated in refluxing ethylene glycol (20 ml) for 24 h. The mixture was cooled to room temperature, the product filtered, washed with methanol and ether and dried. The product (3) (7·1 g, 80%) was obtained as a colourless solid, m.p. 301–303° (lit.[17] m.p. of LL *cis*-isomer, 311–312°). ^{1}H n.m.r. analysis showed that both *cis*- and *trans*-isomers of (3) were present in a ratio of *c.* 3 : 1 [by integration of methine resonances at δ 4·46 (*cis*) and 3·86 (*trans*) in CF_3CO_2H solvent].

Methylation of 3,6-Dibenzylpiperazine-2,5-dione (3)

A mixture of 3,6-dibenzylpiperazine-2,5-dione (3) (3·6 g), sodium hydride (1·1 g of 50% w/w dispersion in oil) and dimethylformamide (20 ml) was stirred at room temperature for 15 min. The

[15] Machin, P. J., and Sammes, P. G., *J. Chem. Soc., Perkin Trans. 1*, 1974, 698.
[16] Marcuccio, S. M., and Elix, J. A., *Aust. J. Chem.*, 1984, **37**, 1791.
[17] Brown, R., Kelly, C., and Wiberley, S. E., *J. Org. Chem.*, 1965, **30**, 277.

reaction mixture was cooled to 0° and methyl iodide (8 ml) was added dropwise. The solution was warmed to room temperature, diluted with water and extracted with dichloromethane. The organic layer was separated, washed with water and dried ($MgSO_4$). Column chromatography of the crude reaction product (silica gel, with 40% ethyl acetate/light petroleum as eluent) gave two products. The more mobile component was crystallized from ethyl acetate/light petroleum to yield *trans*-3,6-dibenzyl-1,4-dimethylpiperazine-2,5-dione (6) (1·05 g, 27%) as colourless prisms, m.p. 188–189° (lit.[6] m.p. 187–189°). ^{1}H n.m.r. ($CDCl_3$) δ 2·84, s, NMe; 3·03, d, J 4·1 Hz, CH_2; 3·14, d, J 3·0 Hz, CH_2; 3·40, dd, J 4·1, 3·0 Hz, CH; 6·97–7·22, m, ArH. ^{13}C n.m.r. ($CDCl_3$) δ 32·2, NMe; 36·9, CH_2; 61·7, CH; 127·3, 128·3, 129·6, 130·5, 134·8, Ar; and 165·2, C=O. Mass spectrum m/z 322 (M^+, 17%), 231 (100).

The residue obtained from the slower moving band was crystallized from ethyl acetate/light petroleum to yield (±)-*cis*-3,6-dibenzyl-1,4-dimethylpiperazine-2,5-dione (9) (2·4 g, 61%) as colourless needles, m.p. 165° (Found: C, 74·4; H, 6·8; N, 8·4. Calc. for $C_{20}H_{22}N_2O_2$: C, 74·5; H, 6·9; N, 8·7%). ^{1}H n.m.r. ($CDCl_3$) δ 2·20, dd, J 14·2, 6·6 Hz, CH_2; 2·76, s, NMe; 2·90, dd, J 14·2, 4·3 Hz, CH_2; 4·04, dd, J 6·6, 4·3 Hz, CH; 7·05–7·30, m, ArH. ^{13}C n.m.r. ($CDCl_3$) 33·5 NMe; 39·0 CH_2; 64·3, CH; 127·3, 128·9, 129·2, 129·6, 137·0, Ar; 165·5, C=O. Mass spectrum m/z 322 (M^+, 25%), 231 (100).

Methylation of 3,6-Dibenzylidenepiperazine-2,5-dione (5)

Dimethyl sulfate (49 ml) and 10% aqueous sodium hydroxide (400 ml) were simultaneously added dropwise to a stirred solution of 3,6-dibenzylidenepiperazine-2,5-dione (5)[1] (14·5 g) in ethanol (100 ml) and 10% aqueous sodium hydroxide (100 ml). After the addition was completed, the reaction mixture was stirred at room temperature for a further 3 h. The yellow solid obtained was filtered, washed with water and air-dried. The crude product was purified by column chromatography on silica gel by using 20% ethyl acetate/light petroleum as eluent.

The residue obtained from the faster moving band was recrystallized from ethyl acetate/light petroleum to give (Z)-*3,6-dibenzylidene-2,5-dimethoxy-3,6-dihydropyrazine* (12) (0·13 g, 1%) as yellow needles, m.p. >300° (Found: C, 75·2; H, 5·8; N, 8·9. $C_{20}H_{18}N_2O_2$ requires C, 75·5; H, 5·7; N, 8·8%). ^{1}H n.m.r. ($CDCl_3$) δ 4·05, s, OMe; 7·00, s, CH; 7·42, m, ArH; 8·25, m, ArH. ^{13}C n.m.r. ($CDCl_3$) 54·1, OMe; 122·8, CH; 128·0, 128·2, 128·3, 130·2, 131·4, 136·0, Ar and C6, C3; 158·7, C–O. Mass spectrum m/z 318 (M^+, 100%).

The second band yielded (Z)-*3,6-dibenzylidene-5-methoxy-1-methyl-3,6-dihydropyrazin-2(1H)-one* (11) (1·64 g, 10%) which crystallized from ethyl acetate/light petroleum in pale yellow needles, m.p. 118–119° (Found: C, 75·5; H, 5·8; N, 8·9. $C_{20}H_{18}N_2O_2$ requires C, 75·5; H, 5·7; N, 8·8%). ^{1}H n.m.r. ($CDCl_3$) δ 3·05, s, NMe; 4·11, s, OMe; 7·00, s, CH; 7·40, m, ArH, CH; 8·22, m, ArH. ^{13}C n.m.r. ($CDCl_3$) 36·1, NMe; 54·4, OMe; 115·0, CH; 120·7, 127·4, 127·7, 127·9, 128·1, 128·2, 128·6, 129·3, 131·5, 134·6, 135·3, CH, Ar, C6, C3; 156·2, C–O; 162·3, C=O. Mass spectrum m/z 318 (M^+, 100%).

The slowest moving band yielded 3,6-dibenzylidene-1,4-dimethylpiperazine-2,5-dione (4) (12·7 g, 80%) which crystallized from ethyl acetate/light petroleum in colourless needles, m.p. 142–143° (lit.[1] m.p. 143°). ^{1}H n.m.r. ($CDCl_3$) 3·00, s, NMe; 7·32, s, CH; 7·42, s, ArH. ^{13}C n.m.r. ($CDCl_3$) 35·2, NMe; 121·7, CH; 128·3, 128·5, 129·4, 131·3, 133·5, Ar and C3, C6; 162·2, C=O. Mass spectrum m/z 318 (M^+, 100%).

Reduction of 3,6-Dibenzylidene-1,4-dimethylpiperazine-2,5-dione (4)

(i) *By catalytic hydrogenation.*—A mixture of the piperazinedione (4) (0·5 g) and 10% palladium on carbon (0·3 g) in glacial acetic acid (10 ml) were stirred under an atmosphere of hydrogen for 16 h. The mixture was then filtered through Celite and the solvent evaporated. The residue was recrystallized from water to give (±)-*cis*-3,6-dibenzyl-1,4-dimethylpiperazine-2,5-dione (9) (0·49 g, 96%), m.p. 165° alone, or admixed with an authentic sample.

(ii) *With hydriodic acid.*—A suspension of the piperazinedione (4) (0·5 g) in hydriodic acid (10 ml, d 1·70) was heated under reflux for 3 h. The reaction mixture was then cooled to room temperature, poured into water (50 ml) and extracted with ethyl acetate. The organic phase was washed with 5% aqueous sodium bicarbonate solution, 5% aqueous sodium thiosulfate solution, water and then dried ($MgSO_4$) and evaporated. The residue was recrystallized from water to give the (±) *cis*-isomer (9) (0·33 g, 65%) as colourless needles, m.p. and m.m.p. 165°.

(iii) *With hydriodic acid in diethyl ketone.*—A solution of the piperazinedione (4) (0·5 g) in diethyl ketone (20 ml) and hydriodic acid (10 ml, *d* 1·70) was heated under reflux for 5 h. The volume of solvent was reduced (*c.* 10 ml) and the reaction mixture worked up in the usual manner. The crude product was crystallized from water to give the (±) *cis*-isomer (9) (0·41 g, 81%) as colourless needles, m.p. 165°.

(iv) *With hydriodic acid in acetone.*—A solution of the piperazinedione (4) (0·5 g) in acetone (20 ml) and hydriodic acid (10 ml, *d* 1·70) was heated under reflux until no starting material remained (t.l.c.). The volume of solvent was reduced (*c.* 10 ml) and the reaction mixture worked up in the usual manner. The residue was crystallized from ethyl acetate/light petroleum to afford (Z)-*3-benzyl-6-benzylidene-1,4-dimethylpiperazine-2,5-dione* (13) (0·23 g, 46%) as colourless plates, m.p. 161·5–162° (Found: C, 74·9; H, 6·2; N, 8·8. $C_{20}H_{20}N_2O_2$ requires C, 75·0; H, 6·3; N, 8·7%). ^{1}H n.m.r. ($CDCl_3$) δ 2·85, 3·03, 2s, NMe; 3·28, d, *J* 6·0 Hz, CH_2; 4·37, t, *J* 6·0 Hz, $CHCH_2$; 7·12, s, =CH; 7·36, m, ArH. ^{13}C n.m.r. ($CDCl_3$) δ 33·6, 35·1, NMe; 38·2, CH_2; 65·1 $CHCH_2$; 120·5, CH=; 127·7, 128·0, 128·2, 129·0, 129·5, 129·6, 131·0, 133·8, 135·0, Ar and C6; 162·0, C5; 166·9, C2. Mass spectrum *m/z* 320 (M^+, 59%), 229 (100).

Acetylation of 3,6-Dibenzylpiperazine-2,5-dione (3)

A suspension of the piperazinedione (3) (1·0 g) in acetic anhydride (20 ml) was heated under reflux for 5 h. The reaction mixture was cooled, poured into ice and the crude product filtered. This material was applied to a silica gel column and eluted with 20% ethyl acetate/light petroleum.

The faster moving band yielded trans-*1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione* (7) (0·08 g, 6%) which crystallized from ethyl acetate/light petroleum as colourless prisms, m.p. 190–191° (Found: C, 69·9; H, 6·0; N, 7·5. $C_{22}H_{22}N_2O_4$ requires C, 69·8; H, 5·9; N, 7·4%). ^{1}H n.m.r. ($CDCl_3$) δ 2·58, s, COMe; 3·18, d, *J* 4 Hz, CH_2; 4·48, t, *J* 4 Hz, CH; 7·00–7·32, m, ArH. Mass spectrum *m/z* 378 (M^+, 30%), 91 (100). The slower moving band yielded (±)-cis-*1,4-diacetyl-3,6-dibenzylpiperazine-2,5-dione* (10) (0·59 g, 46%) which crystallized from ethyl acetate/light petroleum in colourless crystals, m.p. 151·5–152·5° (Found: C, 69·9; H, 5·8; N, 7·3. $C_{22}H_{22}N_2O_4$ requires C, 69·8; H, 5·9; N, 7·4%). ^{1}H n.m.r. ($CDCl_3$) δ 2·50, s, COMe; 2·68, m, *J* 16, 8, 6 Hz, CH_2; 5·36, dd, *J* 8, 6 Hz, CH; 7·28, m, ArH. Mass spectrum *m/z* 378 (M^+, 25%), 91 (100).

Acknowledgment

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

Manuscript received 19 April 1984