

## CATALYTIC HYDROGENATION OF 2,5-DIALKYLPIRAZINES AND 3,6-DIALKYL-2-HYDROXYPIRAZINES

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Abstract — Hydrogenation of several 2,5-dialkylpyrazines and 3,6-dialkyl-2-hydroxypyrazines was achieved in the presence of platinum oxide. In the former cases, the corresponding trans piperazines were mainly obtained. In the latter cases, the products were further treated with lithium aluminum hydride to give mainly the cis isomers.

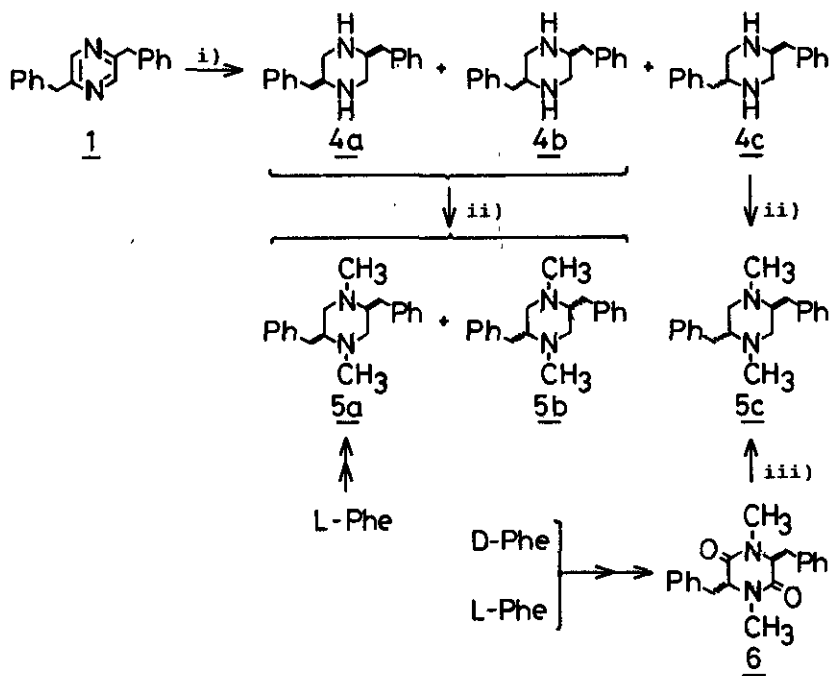
Catalytic hydrogenation of aromatics, such as benzenes and naphthalenes, has been well established<sup>1</sup>. However, there have been only a few precedent cases of catalytic hydrogenation of pyrazines. For instance, hydrogenation of 2,5-diphenylpyrazine in the presence of 10% palladium on carbon was reported to give the corresponding trans piperazine<sup>2</sup>. In our investigation of pyrazines, this paper reports the catalytic hydrogenation of 2,5-dialkylpyrazines and 3,6-dialkyl-2-hydroxypyrazines.

First, 2,5-dibenzylpyrazine (1)<sup>3</sup> was hydrogenated in an autoclave using the catalyst, platinum oxide, and the products were purified by preparative HPLC. Because the hydrogenation was not successful at low pressure, the reaction was carried out at 130 kg/cm<sup>2</sup> at room temperature for 18 h. Contrary to our expectations, trans-2,5-dibenzylpiperazine (4c)<sup>4</sup> was produced in 51% yield as a crystalline mass, and a mixture of the cis products (4a,b)<sup>4</sup> was produced in 26% yield as an oil. Both products were optically inactive.

In an attempt to produce the cis piperazine as a main product, some other

catalysts, such as 10% rhodium on carbon and 5% ruthenium on carbon, were used on probation. The hydrogenated products could not be obtained at room temperature.

Chart 1



i)  $\text{H}_2/\text{PtO}_2$  ii)  $\text{HCHO}$ ,  $\text{HCOOH}$  iii)  $\text{LiAlH}_4$

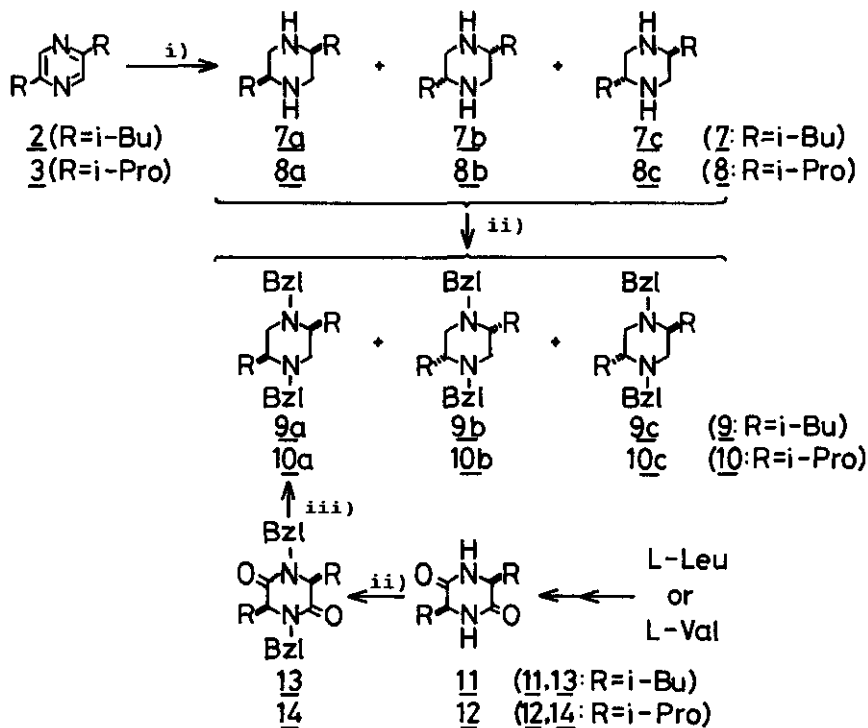
Hydrogenation of 2,5-diisobutylpyrazine (**2**)<sup>5</sup> and 2,5-diisopropylpyrazine (**3**)<sup>6</sup> was next studied. Both compounds were submitted to hydrogenation under the same manner as above. Although in both cases two spots were recognized on a TLC plate, these products could not be separated from each other by column chromatography or HPLC equipped with a UV detector. These products were, therefore, converted to the N,N-dibenzyl derivatives, which were separated from each other by preparative HPLC, and each one was optically inactive. As shown in experimental section, the trans isomer was the main product in each case.

In order to determine the structure of the products, the derivatives of the products were synthesized from the corresponding L- or D- amino acids. According to the reported method<sup>7</sup>, (2S,5S)-2,5-dibenzyl-1,4-dimethylpiperazine (**5a**) was prepared from L-phenylalanine and identified with the mixed products (**5a,b**), which were derived from **4a,b** by the Eschweiler-Clarke reaction. (3R,6S)-3,6-Dibenzyl-1,4-dimethylpiperazine-2,5-dione (**6**) was also prepared from L- and

D-phenylalanine by the reported method<sup>8</sup> and treated with lithium aluminum hydride. The product was identified with the compound 5c, derived from the trans piperazine (4c).

As described above, hydrogenation products from 2,5-diisobutylpyrazine (2)<sup>5</sup> and 2,5-diisopropylpyrazine (3)<sup>6</sup> were converted to the dibenzyl derivatives. On the other hand, (3S,6S)-3,6-diisobutylpiperazine-2,5-dione (11)<sup>9</sup> and (3S,6S)-3,6-diisopropylpiperazine-2,5-dione (12)<sup>10</sup>, prepared respectively from L-leucine and L-valine, were benzylated and then reduced with lithium aluminum hydride. The products were identified respectively with the compounds (9a,b and 10a,b), which were considered respectively a mixture of the cis compounds. The trans isomers (9c and 10c) were therefore deductively determined.

Chart 2



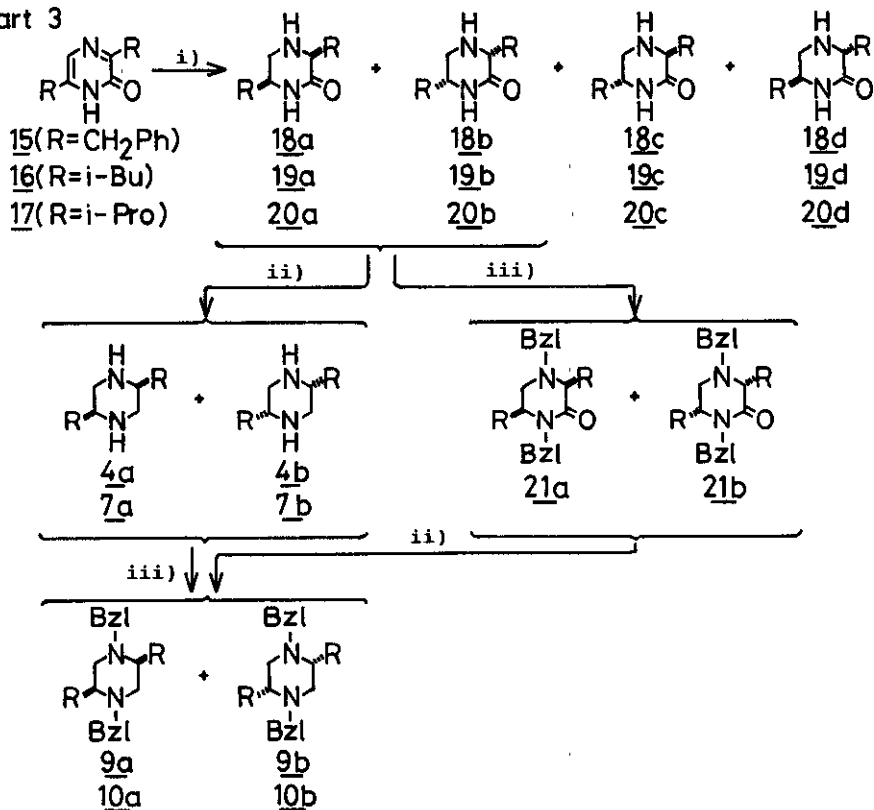
i) H<sub>2</sub>/PtO<sub>2</sub>    ii) NaH, PhCH<sub>2</sub>Br    iii) LiAlH<sub>4</sub>    \*Bzl = CH<sub>2</sub>Ph

Thus, the hydrogenation of 2,5-dialkylpyrazines gave mainly the trans isomers. We already reported the catalytic hydrogenation of 2,5-dialkyl-3,6-dihydroxypyrazine 1,4-dioxides and obtained the cis compounds as a sole product<sup>11</sup>.

Anticipating the formation of the cis compounds from 3,6-dialkyl-2-hydroxy-

pyrazines, 3,6-dibenzyl- (15)<sup>3</sup>, 3,6-diisobutyl- (16)<sup>12</sup> and 3,6-diisopropyl-2-hydroxypyrazines (17)<sup>13</sup>, were submitted to catalytic hydrogenation, and as described below, the cis compounds were mainly obtained in all cases.

Chart 3



i) H<sub>2</sub>/PtO<sub>2</sub> ii) LiAlH<sub>4</sub> iii) NaH, PhCH<sub>2</sub>Br \* Bzl = CH<sub>2</sub>Ph

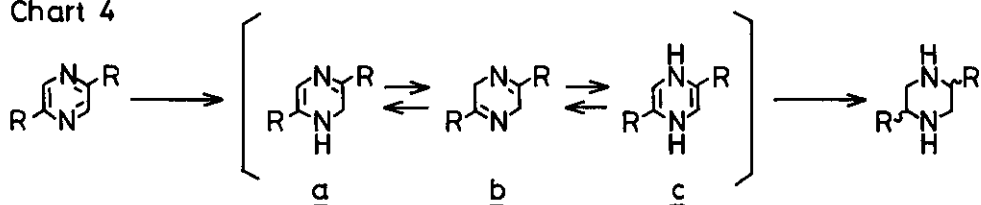
\* 4, 18 : R = CH<sub>2</sub>Ph ; 7, 9, 19 : R = i-Bu ; 10, 20, 21 : R = i-Pro

These three 2-hydroxypyrazines (15, 16, and 17) were hydrogenated under the same conditions as above. In all cases, the formation of two compounds was recognized on a TLC plate, and the optically inactive products were separated from each other by column chromatography. The products derived in higher yields from 15 and 16 were reduced with lithium aluminum hydride to give the corresponding piperazines. The products derived from 15 were identified with the mixture of the cis products (4a,b) derived from 1. On the other hand, the products, obtained in higher yields from 16, were converted to the benzyl derivatives, and the spectral data of the products were identified with 9a,b. The products obtained in higher yields from 17 were benzylated and then reduced with lithium aluminum hydride.

The spectral data of the products were identified with 10a,b. Namely, in all cases, the cis isomers<sup>14</sup> were the main products.

In summary, 2,5-dialkylpyrazines and 3,6-dialkyl-2-hydroxypyrazines were submitted to catalytic hydrogenations. The trans isomers were obtained mainly with the former substances and the cis isomers with the latter substances. We presume the reason as follows: 2-Hydroxypyrazines, which exist rather as 1,2-dihydro-2-ketopyrazines and carry, therefore, a conjugated double bond, should be adsorbed on the surface of the catalyst and hydrogenated to give mainly cis compounds. On the other hand, alkylpyrazines are first hydrogenated to dihydropyrazines, as shown in Chart 4. Among these dihydropyrazines, two double bonds of compounds b,c are probably hydrogenated respectively from the front or back side, to afford a mixture of cis and trans isomers and preferably a trans isomer.

Chart 4



## EXPERIMENTAL

All melting and boiling points are uncorrected. The following instruments were used for obtaining the spectral data: ms: Hitachi M-80 spectrometer; IR: Shimadzu IR-400; <sup>1</sup>H-nmr (CDCl<sub>3</sub>): Bruker AM-400; Optical Rotation: DIP-360 (Japan Spectroscopic Co., Ltd., Tokyo). For column chromatography, Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Tokyo) was used. The HPLC was carried out with UVILOG ALPC-100 (Oyo-Bunko Kiki Co., Ltd., Tokyo) as a pump, UVILOG 5 IIIA as a detector, and Kiesel Gel 60 (Merck AG., Darmstadt) as a packing material.

General Procedure for Hydrogenation of 2,5-Dialkylpyrazines (1, 2, and 3) -- An EtOH solution (40 ml) of a 2,5-dialkylpyrazine (5 mmol) was stirred under H<sub>2</sub> stream at 130 kg/cm<sup>2</sup> and room temperature in the presence of PtO<sub>2</sub> (25 mg) in an autoclave for 18 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness in vacuo. The residue was submitted to column chromatography (27 g) and eluted with CH<sub>2</sub>Cl<sub>2</sub> and MeOH. In the case of 1, the products were purified with HPLC using MeOH as an eluant to give successively a mixture of cis-isomers (4a,b) (340 mg, 26%) as an oil and a trans isomer (4c) (682 mg, 51%) as a crystalline mass.

4a,b: colorless viscous oil; bp 150°C/0.1 torr; ms: m/z 267 ( $M^+ + 1$ ), 175 ( $M^+ - CH_2C_6H_5$ );  $^1H$ -nmr:  $\delta$  1.71 (br s, 2H, 2 x NH), 2.75-3.05 (m, 10H, piperazine H and 2 x  $CH_2C_6H_5$ ), 7.17-7.37 (m, 10H, benzene H) ppm; Anal. Calcd. for  $C_{18}H_{22}N_2$ : C, 81.16; H, 8.33; N, 10.52. Found: C, 80.90; H, 8.45; N, 10.38.

4c: colorless prisms (from  $Me_2CO$ ); mp 170-172°C; ms: m/z 267 ( $M^+ + 1$ ), 175 ( $M^+ - CH_2C_6H_5$ );  $^1H$ -nmr:  $\delta$  1.58 (br s, 2H, 2 x NH), 2.46 (dd,  $J = 10.2$  and  $11.1$  Hz, 2H,  $C_3-$  and  $C_6-ax.$  H), 2.52 (dd,  $J = 8.6$  and  $13.4$  Hz, 2H, 2 x  $CH_aC_6H_5$ ), 2.68 (dd,  $J = 5.1$  and  $13.4$  Hz, 2H, 2 x  $CH_bC_6H_5$ ), 2.88 (m, 2H,  $C_2-$  and  $C_5-H$ ), 2.95 (dd,  $J = 2.7$  and  $11.3$  Hz, 2H,  $C_3-$  and  $C_6-eq.$  H), 7.16-7.30 (m, 10H, benzene H) ppm; Anal. Calcd. for  $C_{18}H_{22}N_2$ : C, 81.16; H, 8.33; N, 10.52. Found: C, 80.90; H, 8.45; N, 10.38.

Methylation of cis- (4a,b) and trans-2,5-Dibenzylpiperazine (4c) --- A mixture of 4a,b (228 mg, 0.857 mmol), 35% HCHO (160 mg, 1.89 mmol), and 90% HCOOH (350 mg, 6.86 mmol) was refluxed for 14 h. Conc. HCl (0.15 ml) was added to the reaction mixture, which was refluxed further for 4 h, made alkaline with 10% NaOH, and extracted with  $CH_2Cl_2$ . After the usual work-up, the crude product was purified by recrystallization to give 5a,b (227 mg, 90%). The trans isomer (4c) (617 mg, 2.3 mmol) was submitted to the reaction in the same manner, and the crude product was purified by recrystallization to give 5c (650 mg, 95%).

5a,b: colorless prisms (from MeOH); mp 105-107°C; ms: m/z 295 ( $M^+ + 1$ ), 203 ( $M^+ - CH_2C_6H_5$ );  $^1H$ -nmr:  $\delta$  2.23 (dd,  $J = 3.2$  and  $11.5$  Hz, 2H,  $C_3-$  and  $C_6-eq.$  H), 2.35 (s, 6H, 2 x  $CH_3$ ), 2.49 (dd,  $J = 6.2$  and  $11.5$  Hz, 2H,  $C_3-$  and  $C_6-ax.$  H), 2.52-2.63 (br m, 2H,  $C_2-$  and  $C_5-H$ ), 2.75 (dd,  $J = 9.9$  and  $13.0$  Hz, 2H, 2 x  $CH_aC_6H_5$ ), 2.98 (dd,  $J = 3.4$  and  $13.0$  Hz, 2H, 2 x  $CH_bC_6H_5$ ), 7.17-7.35 (m, 10H, benzene H) ppm; Anal. Calcd. for  $C_{20}H_{26}N_2$ : C, 81.58; H, 8.90; N, 9.52. Found: C, 81.42; H, 8.91; N, 9.36.

5c: colorless prisms (from AcOEt); mp 155-157°C; ms: m/z 295 ( $M^+ + 1$ ), 203 ( $M^+ - CH_2C_6H_5$ );  $^1H$ -nmr:  $\delta$  1.98 (dd,  $J = 9.8$  and  $11.5$  Hz, 2H, piperazine H), 2.28 (s, 6H, 2 x  $CH_3$ ), 2.30-2.40 (m, 4H, piperazine H), 2.58 (dd,  $J = 2.2$  and  $11.5$  Hz, 2H, 2 x  $CH_aC_6H_5$ ), 3.14 (m, 2H, 2 x  $CH_bC_6H_5$ ), 7.13-7.30 (m, 10H, benzene H) ppm; Anal. Calcd. for  $C_{20}H_{26}N_2$ : C, 81.58; H, 8.90; N, 9.52. Found: C, 81.61; H, 8.93; N, 9.56.

Benylation of 2,5-Diisobutyl- (7a,b,c) and 2,5-Diisopropylpiperazines (8a,b,c) --- NaH (240 mg, 10 mmol) and benzyl bromide (855 mg, 5 mmol) were successively added to a DMF solution (30 ml) of the mixture of cis and trans isomers (7a,b,c)

(396 mg, 2 mmol) and the reaction mixture was stirred at room temperature for 2 h. After adding MeOH, the solvent was removed by evaporation in vacuo. The residue was triturated with water and extracted with  $\text{CHCl}_3$ . The products were purified by HPLC using a mixture of hexane and AcOEt as an eluant, to separate the cis- (9a,b) (195 mg, 19%) and trans-isomers (9c) (826 mg, 79%) from each other. Compounds 8a,b,c (340 mg, 2 mmol) were benzylated in the same manner as before, and the products were separated from each other to give the cis- (10a,b) (144 mg, 21%) and trans-isomers (10c) (418 mg, 60%).

9a,b: colorless oil; bp 150-170°C/0.13 torr; ms: m/z 378 ( $\text{M}^+$ ), 321 ( $\text{M}^+$ - $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 287 ( $\text{M}^+$ - $\text{CH}_2\text{C}_6\text{H}_5$ );  $^1\text{H-nmr}$ :  $\delta$  0.79 (d, J = 6.2 Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.87 (d, J = 6.2 Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.40-1.54 (m, 6H, 2 x  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.41-2.58 (m, 6H, piperazine H), 3.33 (d, J = 13.7 Hz, 2H, 2 x  $\text{CH}_a\text{C}_6\text{H}_5$ ), 3.92 (d, J = 13.7 Hz, 2H, 2 x  $\text{CH}_b\text{C}_6\text{H}_5$ ), 7.20-7.41 (m, 10H, benzene H) ppm; Anal. Calcd. for  $\text{C}_{26}\text{H}_{38}\text{N}_2$ : C, 82.48; H, 10.12; N, 7.40. Found: C, 82.65; H, 10.15; N, 7.12.

9c: colorless prisms (from MeOH); mp 117-120°C; ms: m/z 378 ( $\text{M}^+$ ), 321 ( $\text{M}^+$ - $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 287 ( $\text{M}^+$ - $\text{CH}_2\text{C}_6\text{H}_5$ );  $^1\text{H-nmr}$ :  $\delta$  0.78 (d, J = 6.2 Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.83 (d, J = 6.2 Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.22-1.56 (m, 6H, 2 x  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.99 (dd, J = 9.0 and 11.6 Hz, 2H,  $\text{C}_3^-$  and  $\text{C}_6\text{-ax}$ . H), 2.35-2.45 (m, 2H,  $\text{C}_2^-$  and  $\text{C}_5\text{-H}$ ), 2.78 (dd, J = 3.0 and 11.6 Hz, 2H,  $\text{C}_3^-$  and  $\text{C}_6\text{-eq}$ . H), 3.17 (d, J = 13.6 Hz, 2H, 2 x  $\text{CH}_a\text{C}_6\text{H}_5$ ), 4.00 (d, J = 13.6 Hz, 2H, 2 x  $\text{CH}_b\text{C}_6\text{H}_5$ ), 7.20-7.35 (m, 10H, benzene H) ppm; Anal. Calcd. for  $\text{C}_{26}\text{H}_{38}\text{N}_2$ : C, 82.48; H, 10.12; N, 7.40. Found: C, 82.54; H, 10.18; N, 7.40.

10a,b: pale yellow viscous oil; bp 155°C/0.09 torr; ms: m/z 350 ( $\text{M}^+$ ), 307 ( $\text{M}^+$ - $\text{CH}(\text{CH}_3)_2$ );  $^1\text{H-nmr}$ :  $\delta$  0.77 (d, J = 6.8 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 0.90 (d, J = 6.8 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 2.18 (m, J = 3.3 and 6.7 Hz, 2H,  $\text{C}_2^-$  and  $\text{C}_5\text{-H}$ ), 2.32 (m, 2H, 2 x  $\text{CH}(\text{CH}_3)_2$ ), 2.39 (dd, J = 3.3 and 13.0 Hz, 2H,  $\text{C}_3^-$  and  $\text{C}_6\text{-eq}$ . H), 2.74 (dd, J = 6.7 and 13.0 Hz, 2H,  $\text{C}_3^-$  and  $\text{C}_6\text{-ax}$ . H), 3.38 (d, J = 13.3 Hz, 2H, 2 x  $\text{CH}_a\text{C}_6\text{H}_5$ ), 4.03 (d, J = 13.3 Hz, 2H, 2 x  $\text{CH}_b\text{C}_6\text{H}_5$ ), 7.21-7.38 (m, 10H, benzene H) ppm; Anal. Calcd. for  $\text{C}_{24}\text{H}_{34}\text{N}_2$ : C, 82.23; H, 9.78; N, 7.99. Found: C, 82.15; H, 9.76; N, 7.89.

10c: colorless needles (from MeOH); mp 145-147°C; ms: m/z 350 ( $\text{M}^+$ ), 307 ( $\text{M}^+$ - $\text{CH}(\text{CH}_3)_2$ );  $^1\text{H-nmr}$ :  $\delta$  0.77 (d, J = 6.7 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 0.90 (d, J = 6.7 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 1.94 (dd, J = 10.6 and 11.2 Hz, 2H,  $\text{C}_3^-$  and  $\text{C}_6\text{-ax}$ . H), 2.15-2.35 (m, 4H, 2 x  $\text{CH}(\text{CH}_3)_2$ ,  $\text{C}_2^-$  and  $\text{C}_5\text{-H}$ ), 2.72 (dd, J = 2.3 and 11.2 Hz, 2H,  $\text{C}_3^-$  and  $\text{C}_6\text{-eq}$ . H), 3.00 (d, J = 13.3 Hz, 2H, 2 x  $\text{CH}_a\text{C}_6\text{H}_5$ ), 4.13 (d, J = 13.3 Hz, 2H, 2 x

$\text{CH}_2\text{C}_6\text{H}_5$ ), 7.20-7.32 (m, 10H, benzene H) ppm; Anal. Calcd. for  $\text{C}_{24}\text{H}_{34}\text{N}_2$ : C, 82.23; H, 9.78; N, 7.99. Found: C, 82.19; H, 9.85; N, 7.88.

Preparation of (2R,5S)-2,5-Dibenzyl-1,4-dimethylpiperazine (5c)---Compound 6 (3.9 g, 12.1 mmol), prepared from D- and L-phenylalanine in the reported manner<sup>7</sup>, was dissolved in THF (460 ml), and  $\text{LiAlH}_4$  (1.35 g, 35.5 mmol) was added to the solution. After being refluxed for 12 h, the reaction mixture was worked up as usual and the resulting product was purified by column chromatography (40 g) using a mixture of hexane and AcOEt as a developer to give 5c (2.02 g, 57%). 5c: colorless prisms (from AcOEt); mp 154-157°C; ms: m/z 295 ( $\text{M}^+$ +1), 203 ( $\text{M}^+$ - $\text{CH}_2\text{C}_6\text{H}_5$ );  $^1\text{H}$ -nmr:  $\delta$  1.99 (dd, J = 9.8 and 11.5 Hz, 2H, piperazine H), 2.28 (s, 6H, 2 x  $\text{CH}_3$ ), 2.31-2.39 (m, 4H, piperazine H), 2.60 (dd, J = 2.2 and 11.5 Hz, 2H, 2 x  $\text{CH}_2\text{C}_6\text{H}_5$ ), 3.15 (m, 2H, 2 x  $\text{CH}_2\text{C}_6\text{H}_5$ ), 7.13-7.32 (m, 10H, benzene H) ppm; Anal. Calcd. for  $\text{C}_{20}\text{H}_{26}\text{N}_2$ : C, 81.58; H, 8.90; N, 9.52. Found: C, 81.76; H, 8.89; N, 9.53.

Preparation of (3S, 6S)-1,4-Dibenzyl-3,6-diisobutyl- (13) and Diisopropylpiperazine-2,5-diones (14) --- NaH (600 mg, 25 mmol) and benzyl bromide (6.84 g, 40 mmol) were successively added to a DMF solution (750 ml) of 11 (1.13 g, 5 mmol), prepared from L-leucine in the reported manner<sup>8</sup>. The mixture was heated at 50°C for 4 h and worked up as usual. The resulting product was purified by HPLC to give 13 (1.54 g, 76%). Compound 12 (460 mg, 2 mmol) was submitted to the reaction in the same method to give 14 (690 mg, 79%).

13: colorless prisms (from MeOH); mp 204-207°C; ms: m/z 406 ( $\text{M}^+$ ); ir (KBr): 1640 (C=O), 1660 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr:  $\delta$  0.96 (d, J = 6.7 Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.96 (d, J = 6.4 Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.55-2.10 (m, 6H, 2 x  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 3.80-4.05 (br m, 2H, piperazine H), 3.85 (d, J = 14.9 Hz, 2H, 2 x  $\text{CH}_2\text{C}_6\text{H}_5$ ), 5.29 (d, J = 14.9 Hz, 2H, 2 x  $\text{CH}_2\text{C}_6\text{H}_5$ ), 7.15-7.35 (m, 10H, benzene H) ppm;  $[\alpha]_D^{20}$  -141.1° (c = 1.009,  $\text{CHCl}_3$ ); Anal. Calcd. for  $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_2$ : C, 76.81; H, 8.43; N, 6.89. Found: C, 76.93; H, 8.42; N, 7.11.

14: colorless prisms (from MeOH); mp 155-156°C; ms: m/z 378 ( $\text{M}^+$ ), 335 ( $\text{M}^+$ - $\text{CH}(\text{CH}_3)_2$ ); ir (KBr): 1660 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr:  $\delta$  1.17 (d, J = 6.6 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 1.18 (d, J = 6.8 Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 2.10-2.22 (m, 2H, 2 x  $\text{CH}(\text{CH}_3)_2$ ), 3.58 (d, J = 9.5 Hz, 2H, piperazine H), 3.78 (d, J = 15.0 Hz, 2H, 2 x  $\text{CH}_2\text{C}_6\text{H}_5$ ), 5.49 (d, J = 15.0 Hz, 2H, 2 x  $\text{CH}_2\text{C}_6\text{H}_5$ ), 7.06-7.32 (m, 10H, benzene H) ppm;  $[\alpha]_D^{20}$  -212.90° (c = 0.093,  $\text{CHCl}_3$ ); Anal. Calcd. for  $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2$ : C, 76.15; H, 7.99; N, 7.40. Found: C, 76.25; H, 8.02; N, 7.43.



Preparation of (2S,5S)-1,4-Dibenzyl-2,5-diisobutyl- (9a) and Diisopropyl-piperazines (10a) --- A solution of 13 (812 mg, 2 mmol) and  $\text{LiAlH}_4$  (456 mg, 12 mmol) in THF (30 ml) was refluxed for 24 h. The reaction mixture was worked up as usual to give a pale yellow oil, which was purified by HPLC using a mixture of hexane and AcOEt as a developer to give 9a (517 mg, 68%). Compound 14 (323 mg, 1 mmol) was reduced in the same manner to give 10a (187 mg, 63%) as an oil.

9a: colorless viscous oil; bp ca.  $150^\circ\text{C}/0.13$  torr; ms:  $m/z$  378 ( $\text{M}^+$ ), 321 ( $\text{M}^+ - \text{CH}_2\text{CH}(\text{CH}_3)_2$ );  $^1\text{H-nmr}$ :  $\delta$  0.75 (d,  $J = 6.2$  Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 0.83 (d,  $J = 6.2$  Hz, 6H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.35-1.50 (br m, 6H,  $2 \times \text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.35-2.56 (m, 6H, piperazine H), 3.29 (d,  $J = 13.7$  Hz, 2H,  $2 \times \text{CH}_a\text{C}_6\text{H}_5$ ), 3.92 (d,  $J = 13.7$  Hz, 2H,  $2 \times \text{CH}_b\text{C}_6\text{H}_5$ ), 7.19-7.37 (m, 10H, benzene H) ppm;  $[\alpha]_D^{20} +100.2^\circ$  ( $c = 1.030$ ,  $\text{CHCl}_3$ ); Anal. Calcd. for  $\text{C}_{26}\text{H}_{38}\text{N}_2$ : C, 82.48; H, 10.12; N, 7.40. Found: C, 82.67; H, 10.17; N, 7.49.

10a: pale yellow viscous oil; bp  $145-150^\circ\text{C}/0.1$  torr; ms:  $m/z$  350 ( $\text{M}^+$ ), 307 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ );  $^1\text{H-nmr}$ :  $\delta$  0.80 (d,  $J = 6.8$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 0.92 (d,  $J = 6.8$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 2.20 (m,  $J = 3.3$  and  $6.8$  Hz, 2H,  $\text{C}_2$ - and  $\text{C}_5$ -H), 2.35 (m,  $J = 6.8$  Hz, 2H,  $2 \times \text{CH}(\text{CH}_3)_2$ ), 2.42 (dd,  $J = 3.3$  and  $13.0$  Hz, 2H,  $\text{C}_3$ - and  $\text{C}_6$ -eq. H), 2.76 (dd,  $J = 6.7$  and  $13.0$  Hz, 2H,  $\text{C}_3$ - and  $\text{C}_6$ -ax. H), 3.40 (d,  $J = 13.4$  Hz, 2H,  $2 \times \text{CH}_a\text{C}_6\text{H}_5$ ), 4.06 (d,  $J = 13.4$  Hz, 2H,  $2 \times \text{CH}_b\text{C}_6\text{H}_5$ ), 7.22-7.41 (m, 10H, benzene H) ppm;  $[\alpha]_D^{20} +135.60^\circ$  ( $c = 0.090$ ,  $\text{CHCl}_3$ ); Anal. Calcd. for  $\text{C}_{24}\text{H}_{34}\text{N}_2$ : C, 82.23; H, 9.78; N, 7.99. Found: C, 81.96; H, 9.54; N, 8.13.

Hydrogenation of 3,6-Dialkyl-2-hydroxypyrazines (15, 16, and 17) --- An EtOH solution (40 ml) of 16 (1.04 g, 5 mmol) was stirred in an autoclave of  $120 \text{ kg/cm}^2$  at room temperature for 14 h in the presence of  $\text{PtO}_2$  (50 mg). The reaction mixture was worked up as described before to give a pale brown solid, which was submitted to column chromatography (17 g). The fractions eluted with  $\text{CH}_2\text{Cl}_2$  gave the trans isomers (19c,d) (40 mg, 4%) and the cis isomers (19a,b) (818 mg, 77%), successively. Compounds 15 (1.104 g, 4 mmol) and 17 (905 mg, 5 mmol) were hydrogenated under the same conditions. The trans isomers (18c,d and 20c,d) were obtained in 9 (101 mg) and a few % yields, respectively. On the other hand, the cis compounds (18a,b and 20a,b) were produced in 83 (934 mg) and 69% (642 mg) yields, respectively.

18a,b: colorless needles (from hexane); mp  $108-109^\circ\text{C}$ ; ms:  $m/z$  280 ( $\text{M}^+$ ), 189 ( $\text{M}^+ - \text{CH}_2\text{C}_6\text{H}_5$ ); ir (KBr):  $1650$  (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$ :  $\delta$  1.63 (br s, 1H, NH), 2.61 (dd,  $J = 8.9$  and  $13.3$  Hz, 1H,  $\text{CHC}_6\text{H}_5$ ), 2.74 (dd,  $J = 5.6$  and  $13.3$  Hz, 1H,  $\text{CHC}_6\text{H}_5$ ),

2.91 (m, 1H, piperazine H), 2.96-3.06 (m, 2H, piperazine H and  $\text{CHC}_6\text{H}_5$ ), 3.29 (dd,  $J = 3.6$  and  $13.6$  Hz, 1H, piperazine H), 3.56 (m, 1H, piperazine H), 3.65 (dd,  $J = 3.6$  and  $9.2$  Hz, 1H,  $\text{CHC}_6\text{H}_5$ ), 5.74 (br s, 1H, CONH), 7.08-7.38 (m, 10H, benzene H) ppm; Anal. Calcd. for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$ : C, 77.11; H, 7.19; N, 9.99. Found: C, 77.17; H, 7.17; N, 10.02.

19a,b: colorless needles (from hexane); mp  $114-115^\circ\text{C}$ ; ms:  $m/z$  212 ( $\text{M}^+$ ), 155 ( $\text{M}^+ - \text{CH}_2\text{CH}(\text{CH}_3)_2$ ); ir (KBr):  $1660$  (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$ :  $\delta$  0.90-0.98 (m, 12H,  $2 \times \text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.32 (m, 1H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.44 (m, 1H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.54-1.85 (m, 4H,  $2 \times \text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 2.78 (dd,  $J = 6.0$  and  $13.1$  Hz, 1H,  $\text{C}_5\text{-H}$ ), 3.01 (dd,  $J = 4.4$  and  $13.1$  Hz, 1H,  $\text{C}_5\text{-H}$ ), 3.42 (dd,  $J = 3.6$  and  $10.3$  Hz, 1H, piperazine H), 3.46 (m, 1H, piperazine H) ppm; Anal. Calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}$ : C, 67.88; H, 11.39; N, 13.19. Found: C, 68.08; H, 11.61; N, 13.15.

20a,b: colorless prisms (from hexane); mp  $92-93^\circ\text{C}$ ; ms:  $m/z$  184 ( $\text{M}^+$ ), 141 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ ); ir (KBr):  $1650$  (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$ :  $\delta$  0.92 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ), 0.93 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ), 0.98 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ), 1.02 (d,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 1.87 (m,  $J = 6.8$  Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.45 (m,  $J = 3.8, 6.9$  and  $13.8$  Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.92-3.10 (m, 3H, piperazine H), 3.28 (d,  $J = 3.8$  Hz, 1H, piperazine H) ppm; Anal. Calcd. for  $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}$ : C, 65.17; H, 10.94; N, 15.20. Found: C, 65.03; H, 10.95; N, 15.13.

Reduction of cis-3,6-Dialkylpiperazin-2-ones (18a,b and 19a,b) with  $\text{LiAlH}_4$  -- A mixture of 19a,b (848 mg, 4 mmol) and  $\text{LiAlH}_4$  (760 mg, 20 mmol) in THF (30 ml) was stirred at room temperature for 14 h. The reaction mixture was worked up as usual and purified by distillation under a reduced pressure to give 7a,b (702 mg, 87%) as an oil, bp  $110-113^\circ\text{C}/3$  torr, which was further benzylated. Compounds 18a,b (140 mg, 0.5 mmol) were also reduced in the same manner as above to afford compounds 4a,b (113 mg, 85%) as an oil.

Benylation of cis-3,6-Diisopropylpiperazin-2-ones (20a,b) --- Benzylation of 20a,b (368 mg, 2 mmol) was achieved using the corresponding amounts of the reagents as described in the case of benzylation of 7a,b,c. After being heated at  $50^\circ\text{C}$  for 4 h, the reaction mixture was worked up as usual to give 21a,b (654 mg, 90%) as a pale yellow oil, which was purified by distillation.

21a,b: colorless oil; bp  $155-160^\circ\text{C}/0.06$  torr; ms:  $m/z$  364 ( $\text{M}^+$ ), 321 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ ); ir (neat):  $1640$  (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$ :  $\delta$  0.69 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ), 0.91 (d,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 1.11 (d,  $J = 6.8$  Hz, 3H,  $\text{CH}_3$ ), 1.19 (d,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ), 2.21 (m,  $J = 6.8$  Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.29 (dd,  $J = 4.3$  and  $13.0$  Hz,

1H, C<sub>5</sub>-H), 2.42 (m, J = 7.0 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.87 (dd, J = 5.9 and 13.0 Hz, 1H, C<sub>5</sub>-H), 2.95-3.00 (br m, 2H, piperazine H), 3.29 (d, J = 13.4 Hz, 1H, CHC<sub>6</sub>H<sub>5</sub>), 3.82 (d, J = 14.8 Hz, 1H, CHC<sub>6</sub>H<sub>5</sub>), 3.87 (d, J = 13.4 Hz, 1H, CHC<sub>6</sub>H<sub>5</sub>), 5.60 (d, J = 14.8 Hz, 1H, CHC<sub>6</sub>H<sub>5</sub>), 7.20-7.35 (m, 10H, benzene H) ppm; Anal. Calcd. for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O: C, 79.08; H, 8.85; N, 7.69. Found: C, 78.89; H, 8.90; N, 7.85.

Reduction of cis-1,4-Dibenzyl-3,6-diisopropylpiperazin-2-ones (21a,b) with LiAlH<sub>4</sub>

--- A mixture of 21a,b (360 mg, 1 mmol) and LiAlH<sub>4</sub> (5 mmol) in THF (10 ml) was refluxed for 14 h. The reaction mixture was worked up as usual and purified by distillation to give 10a,b (270 mg, 78%) as an oil.

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