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NOVEL SYNTHESIS OF SUBSTITUTED C-PHENYLPIPERAZINES BY ADDITION OF BENZYLAMINE OR METHYLAMINE TO β-NITROSTYRENE

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Abstract *- Addition of benzylamine or methylamine to 4-chloro-β-nitrostyrene* ***2*** *allowed the successful obtention of 1-phenylethylene-1,2-diamines* ***5,6*** *The intermediate nitrocompounds* ***3,4*** *were isolated and then reduced in acidic conditions Selective ethylation of primary amine group to* ***11,12*** *followed by cyclization with 1,2-dibromopropionitrile or ethyl 1,2-dibromopropionate led to substituted 6-phenylpiperazines* ***13-18****. The stereoisomers were separated and unambiguously identified by a spectroscopic study*

Introduction

Much of our synthetic work has been focussed on the preparation of heterocyclic amines [1] We have extended these studies to the synthesis of various substituted C-phenylpiperazines in order to evaluate their pharmacological properties

A few examples of C-phenylpiperazines synthesis have been previously described in the literature However these methods are not suitable for compounds possessing the substitution patterns necessary for a structure-activity relationship study [2] This is especially the case when nitrogen atoms are substituted by different groups and for C-alkylation of the piperazine ring system Thus, we investigated a new method to achieve the desired compounds We report here the synthesis and the stereochemical assignments of substituted 6-phenylpiperazines **13-18** obtained in this new way

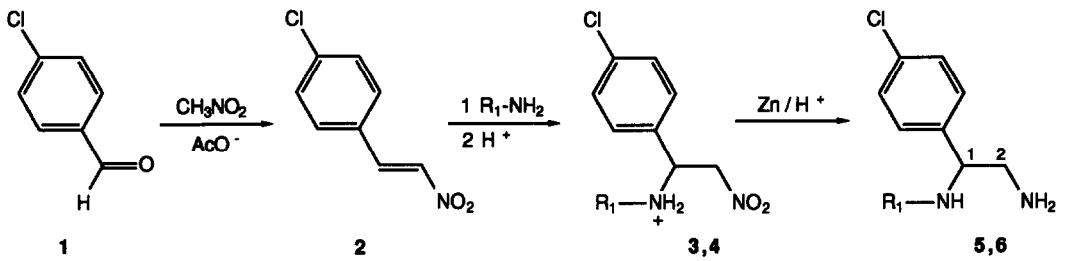
Synthesis of 1-phenylethylene-1,2-diamines

It is known that weak amine bases like aniline or phenylhydrazine can be added to β-nitrostyrene according to a *Michael* reaction However, attempts to obtain addition compounds with strong amine bases like benzylamine or methylamine were unsuccessful because of the great tendency of β-nitrostyrenes to form a polymer or to be hydrolysed in basic media [3] We report here a solution to overcome these difficulties

We easily prepared 1-phenylethylene-1,2-diamines **5,6** by addition of a strong amine, for example benzylamine or methylamine, to 4-chloro-β-nitrostyrene **2** This latter compound was obtained from 4-chlorobenzaldehyde **1** by condensation with nitromethane in the usual manner [4]

The resulting nitroamino intermediates **3,4** were only stable as salts In fact, in the presence of base, these latter compounds immediately underwent a retro *Michael* reaction to give back the starting primary amine and β-nitrostyrene Thus, after addition of excess primary amines to **2**, the addition compounds **3,4** could be stabilized by addition of concentrated hydrochloric acid and isolated as salts before polymerisation or hydrolysis occurred

The weak solubility of compounds **3,4** in water allowed the separation of these salts from those of benzylamine or methylamine which were dissolved in a small amount of water Upon reduction of the nitro group under strong acidic conditions, the 1-phenylethylene-1,2-diamines **5,6** were obtained with good yields (Scheme 1) This is therefore a particularly useful method for unsymmetrical vicinal diamination, which is difficult to prepare in other ways.

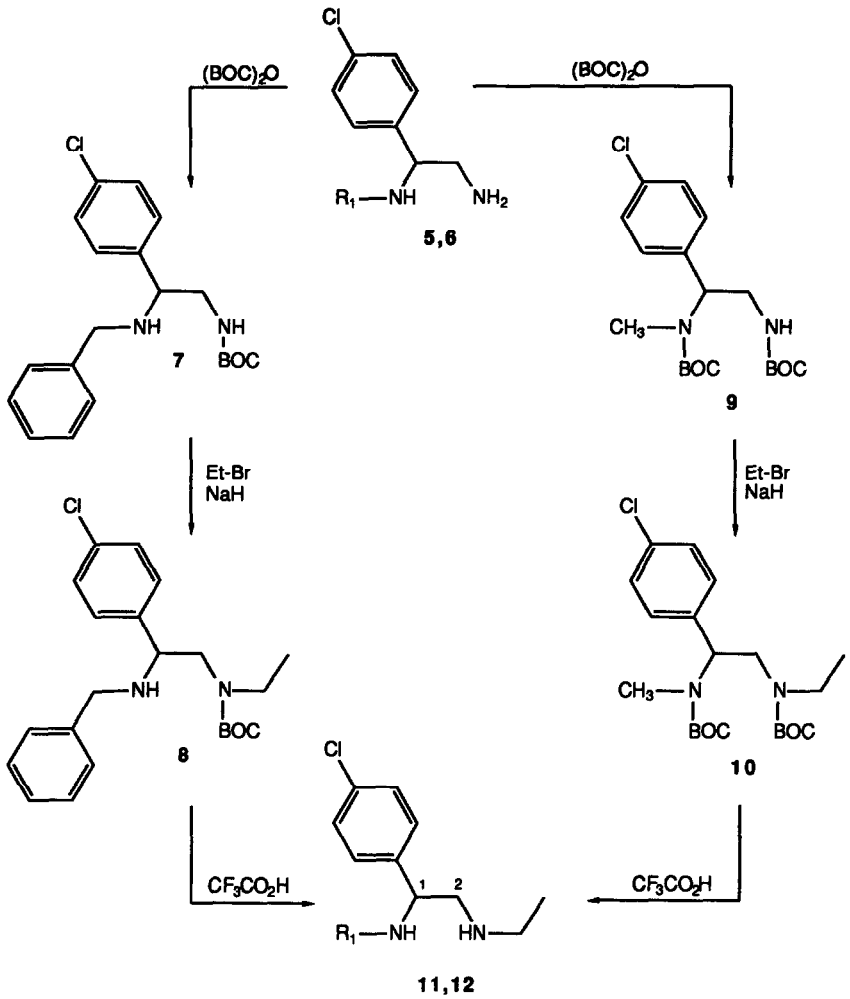


1 **2** **3,4** **5,6**

Scheme 1 Synthesis of 1-phenyl-1,2-diamines **5** (R_1 = benzyl) and **6** ($R_1 = CH_3$)

A convenient way of obtaining secondary amines from the primary amine group, without contamination by primary or tertiary amines, involved previous treatment of **5,6** with di-*tert*-butyl dicarbonate (BOC) to lead to carbamates **7,9** In the case of compound **7**, the weaker nucleophilicity of the benzylamino group compared to the methylamino group did not require its conversion into secondary BOC derivative (Scheme 2)

Then the resulting derivatives **7,9** were reacted with bromoethane in the presence of sodium hydride to give **8,10** Treatment of these compounds with diluted trifluoroacetic acid readily removed the *tert*-butoxycarbonyl group to provide essentially quantitative yields of the desired *N*-benzyl-*N'*-ethyl-2-(4-chlorophenyl)ethylene-1,2-diamines **11,12**



Scheme 2 Alkylation of the primary amine of **5** to **11** (R_1 = benzyl) and **6** to **12** (R_1 = CH_3)

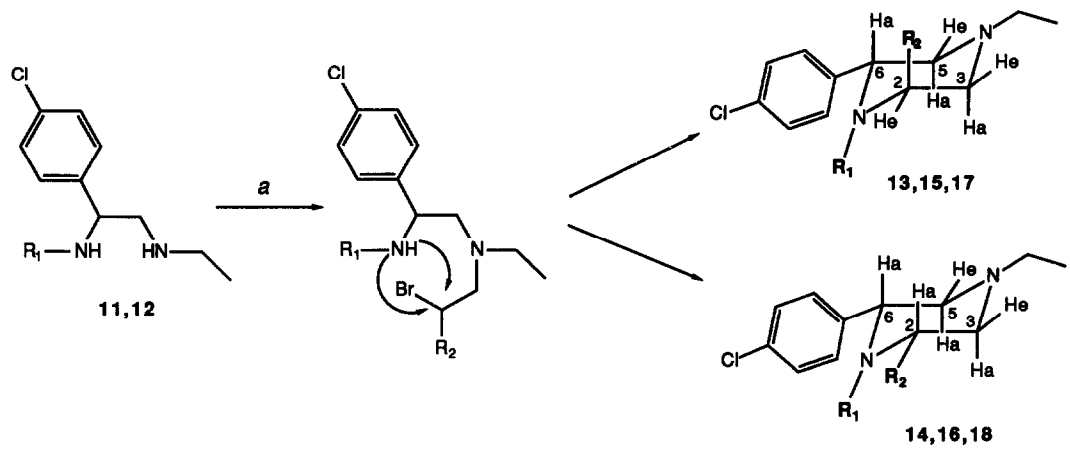
Synthesis of C-phenylpiperazines

For the 2-C-substituted phenylpiperazines, the preferred reagents of cyclization appeared to be 2,3-dibromopropionitrile or ethyl 2,3-dibromopropionate, allowing the introduction of a nitrile or an ethoxycarbonyl group, respectively

The resulting 6-phenylpiperazines **13-18** were identified as 2-C-substituted derivatives A mixture of two structural stereoisomers was obtained, where the nitrile or ethoxycarbonyl group adopted an axial or an equatorial orientation, while the phenyl ring had an equatorial position for both isomers

All these structural features were determined unambiguously by a ^{1}H-n m r study The two respective isomers were separated by column chromatography, in a 2 1 ratio, leading to the main diastereoisomers **13,15,17** having R_2 in axial position and to the minor epimers **14,16,18** exhibiting R_2 in equatorial orientation (Table 1)

Table I Synthesis of substituted 6-phenylpiperazines **13-18**



Compound	Reagent *a*	R_1	R_2	Yield %[b]
13	Br-CH_2-CHBr-CN	benzyl	CN	40
14	Br-CH_2-CHBr-CN	benzyl	CN	26
15	Br-CH_2-CHBr-CN	CH_3	CN	38
16	Br-CH_2-CHBr-CN	CH_3	CN	23
17	Br-CH_2-CHBr-CO_2Et	benzyl	CO_2Et	40
18	Br-CH_2-CHBr-CO_2Et	benzyl	CO_2Et	24

[b] Global yield of the pure isomer isolated after the final purification by column chromatography

The 200 MHz n m r spectral data of compounds **15,16** defined the stereochemistry of phenyl ring and nitrile substituents Both the compounds **15,16** exhibited an equatorial assignment of the 4-chlorophenyl ring This was confirmed by the appearance of a double doublet with a large (J = 11 0 Hz) and small (J = 3 1 Hz) coupling constants at δ 3 81 for **15** and δ 3 55 for **16** These signals were assigned to H_6 in an axial orientation because of the large constant coupling due to the axial-axial interaction between H_{6ax} and H_{5ax}

From spin-decoupling experiments, we deduced that the signals at δ 3 93, 3 14 and 2 45 were mutually coupled and assigned to H_2 and 2 x H_3 respectively in the n m r spectrum of **15**

Thus, the axial assignment of the nitrile group was confirmed by the appearance of a triplet (J = 2 6 Hz) at δ 3 93 corresponding to proton H_{2eq} coupled to H_{3eq} and H_{3ax}

In addition, the H_{3eq} exhibited a double triplet (J = 11 4 Hz, J = 2 6 Hz) at δ 3 14 by coupling to H_{3ax} and H_{2eq}, H_{5eq} This latter high long-range coupling is attributed to the "W-conformation" of the equatorial protons of 3-C and 5-C Thereby, the absence of such a coupling constant in the signal of H_2 resulted in favour of the 2-C position of the nitrile group In contrast, the proton H_{3ax} exhibited a double doublet (J = 9 8 Hz, J = 2 6 Hz) at δ 2 45, due to the coupling to H_{3eq} and H_{2eq}

For compound **16**, the equatorial assignment of the nitrile group was determined in the same manner as **15**, especially by the appearance of a double doublet (J = 10 6 Hz, J = 3 2 Hz) at δ 3 17 and assigned to proton H_{2ax} coupled to H_{3ax} and H_{3eq} The stereochemistry of compound **13,14** and **17,18** was defined by spectral comparison with **15** and **16**

Considering the product ratios, the preferred orientation of the cyclization is probably subject to steric hindrance In the transition state (table 1), the phenyl ring takes an equatorial position Then the R_2 group adopts an orientation leading preferentially to the axial isomer because of the lower steric interaction between the phenyl ring and the nitrile group leading to a *trans*-chair conformation

Conclusion

Our results have shown that strong amines can add to 4-chloro-β-nitrostyrene The reduction of the resulting addition compounds under acidic conditions yields 1-phenylethylene-1,2-diamines, and thus constitutes a new and potentially valuable procedure for vicinal diamination These diamines can be used for the preparation of various substituted C-phenylpiperazines

Experimental section

^{1}H-NMR spectra were recorded at 200 MHz with a Brucker AC 200 Spectrometer in $CDCl_3$ or DMSO-d_6 as solvents Chemical shifts are in δ, parts per million (ppm) and coupling constants (J) are given in Hertz Multiplicities are abbreviated as follows s singlet, d doublet, t triplet, q quartet, m multiplet, br broad Infrared spectra were recorded on a Beckman IR 4230 Spectrometer Melting points (uncorrected) were taken on a Kofler hot stage apparatus Combustion analysis were performed at the Service de Microanalyse de l'U L.P at Strasbourg All tlc were performed on Merck silica gel F-254 plates (ether/hexane, 60 40)

4-Chloro-β-nitrostyrene **2**

A mixture of 4-chlorobenzaldehyde **1** (25 g, 177 5 mmoles), anhydrous ammonium acetate (15 g, 195 mmoles), nitromethane (40 ml, 656 mmoles), acetic anhydride (3 5 ml, 3 0 mmoles) in glacial acetic acid (110 ml) was refluxed for 1h 30 The reaction flask was cooled in an ice bath and the precipitate was isolated by filtration, washed with acetic acid/water (50 50) and dried. Recrystallization from ethanol gave 23 9 g (73 %) of pale yellow needles **2**, mp 111-112 °C (lit 111-112 °C)[4] I r (KBr) cm^{-1} 1640 ($\nu_{C=C}$), 1335 (ν_{NO_2}) ^{1}H-NMR ($CDCl_3$) δ 7 57 (d, J = 13 6, 1H, H_α), 7 97 (d, J = 13 6, 1H, H_β), 7 48 (m, 4H, Ar-H)

Benzyl[1-(4-chlorophenyl)-2-nitroethyl]amine, hydrochloride **3**

To a stirred solution of 4-chloro-β-nitrostyrene **2** (22.5 g, 122 5 mmoles) in tetrahydrofuran (80 ml) pure benzylamine (66 5 ml, 600 mmoles) was added dropwise over 5 mn The reaction mixture was stirred at room temperature for 20 mn, then diluted with water (250 ml) and acidified with concentrated hydrochloric acid The resulting precipitate was isolated by filtration, washed with THF/water (50 50) and air dried Recrystallization from ethanol gave 28 g (70%) of **3** as hydrochloride, mp 230°C (dec) I r (KBr) cm^{-1} 2490-2830 (ν_{N+H}), 1552 (ν_{NO_2}) ^{1}H-NMR (DMSO-d_6) δ 5 62 (m, 1H, C<u>H</u>-CH_2-NO_2), 5 29-5 36 (m, 2H, CH_2-NO_2), 4 21 (m,1H, Ar-CH-N), 7 23-7 32 (m, 9H, Ar-H) Anal calcd for $C_{15}H_{15}ClN_2O_2$, HCl C, 55 08, H, 4 89, N, 8 57 Found C, 55 11, H, 4 87, N, 8 54

[1-(4-chlorophenyl)-2-nitroethyl](methyl)amine, hydrochloride **4**

In accordance with the method presented above, this compound was prepared from **2** (22 5 g, 122 5 mmoles) and 40% aqueous methylamine (54 3 ml, 600 mmoles), but no water was added at the end of the reaction before acidification because of the greater solubility of the hydrochloride to afford 16 9 g (55 %) of **4**, mp 235°C (dec) I r (KBr) cm^{-1} 2490-2830 (ν_{N+H}), 1550 (ν_{NO_2}) ^{1}H-NMR ($CDCl_3$) δ 2 42 (s, 3H, CH_3), 5 08 (t, 1H, CH), 5 25 (dd, J =14 2 and 7 6, 1H, CH_a-NO_2), 5 48 (dd, J = 6 0 and 14 2, 1H, CH_b-NO_2), 7 57 (d, J = 8 6, 2H, Ar-H), 7 68 (d, J = 8 6, 2H, Ar-H) Anal calcd for $C_9H_{11}ClN_2O_2$, HCl C, 43 08, H, 4 78, N, 11 16 Found C, 42 99, H, 4 81, N, 11 18

N-Benzyl-1-(4-chlorophenyl)ethylene-1,2-diamine **5**

Powdered zinc (20 g) was added portionwise at 0-5°C to a stirred suspension of **3** (20 g, 61 mmoles) in a mixture of ethanol (100 ml) and concentrated HCl (100 ml) over 20 mn The mixture was stirred at room temperature for 40 mn The excess zinc was removed by filtration The filtrate

was concentrated *in vacuo*, diluted with water (150 ml), treated with a large excess of concentrated ammonia solution and extracted with CH_2Cl_2 The organic phases were washed with water, dried ($MgSO_4$) and evaporated to give 17.4 g (84 %) of the crude amine **5** as an oil. It could be purified by recrystallization of the dihydrochloride from absolute ethanol, mp 204-206°C I r ($CHCl_3$) cm^{-1} 3500-3100 (ν_{NH_2}) ^{1}H-NMR ($CDCl_3$) δ 3 55 (d, J = 13 1, 1H, H_a benzyl), 3 70 (d, J =13 1, 1H, H_b benzyl), 3 62-3 74 (m, 1H, H_1), 2 90 (m, 2H, H_2), 7 21-7 37 (m, 9H, Ar-H) Anal. calcd for $C_{15}H_{15}ClN_2$, 2 HCl C, 60 44, H, 6 37, N, 9 40 Found C, 60 40, H, 6.39, N, 9 37

1-(4-Chlorophenyl)-*N*-methylethylene-1,2-diamine **6**

In accordance with the method presented above, this compound was prepared from **4** (15 g, 59 5 mmoles) to afford 10 4 g (95 %) of **6** as an oil Purification of the dihydrochloride could be carried out from absolute ethanol, mp 238-240°C I r ($CHCl_3$) cm^{-1} 3500-3100 (ν_{NH_2}). ^{1}H-NMR ($CDCl_3$) δ 1 54 (s, 3H, NH, NH_2), 2 29 (s, 3H, CH_3), 2 77 (dd, J = 7 2 and 12 2, 1H, H_2); 2 89 (dd, J = 5 4 and 12 1, 1H, H_2), 3 46 (t, J = 5 4, 1H, H_1), 7 21-7 34 (m, 4H, Ar-H) Anal. calcd for $C_9H_{13}ClN_2$, 2 HCl C, 48 68, H, 4 78, N, 11 16 Found C, 48 72, H, 4 81, N,11 13

tert-Butyl *N*-[2-benzylamino-2-(4-chlorophenyl)ethyl]carbamate **7**

A solution of compound **5** (15 g, 57 5 mmoles) and di-*tert*-butyl dicarbonate (13 8 g, 128 mmoles) in dichloromethane (150 ml) was stirred at room temperature for 30 mn Then the solvent was evaporated under reduced pressure to give a solid residue which was recrystallized from ether to obtain 20 5 g (90 %) of **7**, mp 106°C I r (KBr) cm^{-1} 3340 (ν_{NH}), 1705 (ν_{CO}) ^{1}H-NMR ($CDCl_3$) δ 1 70 (s, 1H, NH), 1 41 (s, 9H, $C(CH_3)_3$), 3 27 (t, J = 5 8, 2H, $C\underline{H}_2NHCO$); 3,54 (d, J =13 2, 1H, H_a benzyl); 3 68 (d, J =13 2, 1H, H_b benzyl), 3 79 (t, J = 6 2, 1H, $C\underline{H}$-CH_2), 4 75 (m, 1H, NHCO), 7 20-7 36 (m, 9H, Ar-H) Anal calcd for $C_{20}H_{25}ClN_2O_2$ C, 66 60, H, 6 93, N, 7 77. Found C, 66 57, H,6 91 , N, 7 78

tert-Butyl *N*-[2-benzylamino-2-(4-chlorophenyl)ethyl]-*N*-ethylcarbamate **8**

A solution of **7** (10 g, 27 5 mmoles) in *N,N*-dimethylformamide (20 ml) was added to a suspension of sodium hydride (1 14 g, 45 5 mmoles) in DMF (12 ml) The reaction mixture was stirred at room temperature for 30 mn and ethylbromide (0,62 ml, 8 mmoles) was added The mixture was stirred at 70°C for 2 h, then diluted with water (100 ml) and extracted with ethylacetate The organic phases were collected, washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give 5 9 g (57 %) of **6** as an oil, which was used in the next step without further purification I r (KBr) cm^{-1} 1670 (ν_{CO}) ^{1}H-NMR ($CDCl_3$) δ. 0 92 (t, J = 7 2, 3H, $C\underline{H}_3CH_2N$), 1 35 (s, 9H, $C(CH_3)_3$), 1 96 (s, 1H, NH), 2 95-3 16 (m, 3H, $C\underline{H}_a$-N-$C\underline{H}_2$-CH_3), 3 40-3 51 (m, 2H ,

H_a benzyl, CH_b-NCO); 3 63 (m, 1H, H_b benzyl), 3 81 (t, J = 6.1, 1H, C<u>H</u>-CH_2N), 7.21-7.43 (m, 9H, Ar-H) Anal. calcd for $C_{22}H_{29}ClN_2O_2$ C, 67 97, H, 7 46, N, 7 21 Found C, 67 95; H, 7 49, N, 7 18

tert-Butyl *N*-[2-*tert*-butoxycarbamido-1-(4-chlorophenyl)ethyl]-*N*-methylcarbamate **9**

In accordance with the method presented above, this compound was prepared from **6** (10 g, 54 mmoles), but two equivalents of di-*tert*-butyl dicarbonate (20 6 g, 113 mmoles) were used to afford 18 6 g (90 %) of **9** as an oil I r ($CHCl_3$) cm^{-1} 3330 (ν_{NH}), 1672 (ν_{CO}) ^{1}H-NMR ($CDCl_3$) δ 1,44 (s, 9H, $C(CH_3)_3$), 1,49 (s, 9H, $C(CH_3)_3$), 2,58 (s, 3H, CH_3N), 3,62 (br s, 2H, CH_2N), 4,54 (br s, 1H, C<u>H</u>-CH_2), 5,40 (br s, 1H, NH), 7,16-7,34 (m, 4H, Ar-H) Anal calcd for $C_{19}H_{29}ClN_2O_4$ C, 59 32, H, 7 54, N, 7 28 Found C, 59 31, H, 7 51, N, 7 30

tert-Butyl *N*-[2-(*N*-ethyl-*tert*-butoxycarbamido)-1-(4-chlorophenyl)ethyl]-*N*-methylcarbamate **10**

In accordance with the method presented above, this compound was prepared from **9** (15 g, 39 mmoles) to afford 9 6 g (60 %) of **10** as an oil I r ($CHCl_3$) cm^{-1} 1670 (ν_{CO}) ^{1}H-NMR ($CDCl_3$) δ 1,16 (t, J = 7 2, 3H, C<u>H</u>$_3$-CH_2), 1,46 (s, 18H, 2x$OC(CH_3)_3$), 2,62 (s, 3H, CH_3N), 3,17-3,36 (m, 4H, CH-C<u>H</u>$_2$-N and CH_3-C<u>H</u>$_2$-N), 4,35 (t, J = 8 6, 1H, CH), 7,19-7,38 (m, 4H, Ar-H) Anal calcd for $C_{21}H_{33}ClN_2O_4$ C, 61 11, H, 7 99, N, 6 79 Found C, 61 15, H, 7 81 , N, 6 76

N-Benzyl-1-(4-chlorophenyl)-*N'*-ethylethylene-1,2-diamine **11**

Compound **8** (10 g, 27 5 mmoles) was dissolved in trifluoroacetic acid (15 ml) The solution was stirred at room temperature for 30 mn Then, the acid was evaporated *in vacuo* and the residue dissolved in chloroform (150 ml) The mixture was cooled at 0°C and strong ammonia solution (25 ml) was added under stirring After 10 mn the organic layer was separated, washed with water and dried ($MgSO_4$) The solvent was evaporated under reduced pressure to give 6 6 g (90 %) of crude product **7** as an oil, which was used in the next step without further purification I r ($CHCl_3$) cm^{-1} 3320 (ν_{NH}) ^{1}H-NMR ($CDCl_3$) δ 1 00 (t, J = 7 8, 3H, C<u>H</u>$_3$-CH_2N), 1 61 (s, 2H , 2xNH) , 2 52 (q, J = 7 8, 2H, CH_3-C<u>H</u>$_2$N), 2 66-2 72 (m, 2H, H_2), 3 45 (d, 1H, H_a benzyl), 3 61-3 69 (m, 2H, H_a benzyl and H_1), 7 14-7 30 (m, 9H, Ar-H) Anal calcd for $C_{17}H_{19}ClN_2$. C, 56 75, H, 5 84, N, 7 79 Found C, 56 78, H, 6 81, N, 7 82

1-(4-Chlorophenyl)-*N'*-ethyl-*N*-methylethylene-1,2-diamine **12**

Following the procedure described for **11**, compound **10** (15 g, 36 mmoles) was hydrolysed to give 7 7 g (97 %) of **12** as an oil I r ($CHCl_3$) cm^{-1} 3320 (ν_{NH}) ^{1}H-NMR ($CDCl_3$) δ 1 07 (t, J = 7 0, 3H, C<u>H</u>$_3$-CH_2), 1 51 (s, 2H, 2xNH), 2 27 (s, 3H, CH_3N), 2 58-2 79 (m, 4H, H_2 and

CH_3-$C\underline{H}_2N$), 3 56 (dd, J = 5 3 and 8 2, 1H, H_1), 7 22-7 33 (m, 4H, Ar-H) Anal calcd for $C_{11}H_{17}ClN_2$, 2HCl C, 46 23, H, 6 65; N, 6 79 Found: C, 46 20, H, 6 67, N, 6 76

1-Benzyl-6-(4-chlorophenyl)-4-ethylpiperazine-2-carbonitriles **13,14**

2,3-Dibromopropionitrile (4 7 g, 22 mmoles) in benzene (15 ml) was added dropwise to a solution of the diamine **11** (6 g, 20 mmoles) and diisopropylethylamine (0 13 g, 50 mmoles) in benzene (55 ml) at 0 °C The mixture was stirred at room temperature for 10 h Then, after filtration, the solution was concentrated *in vacuo* The residue was extracted with CH_2Cl_2, the organic layers were washed with water then dried ($MgSO_4$) The solvent was evaporated to give a mixture of nitriles **13,14** which was chromatographied on silica gel column, using ether/cyclohexane (80.20) as eluent, to afford in first 2 7 g (40 %) of the *trans* -isomer **13**, mp 104-105°C I r (KBr) cm^{-1} 2215 ($\nu_{C\equiv N}$) ^{1}H-NMR ($CDCl_3$) δ. 1 05 (t, J = 7.2, 3H, $C\underline{H}_3$-CH_2), 2 10 (t, J = 11.0, 1H, H_{5ax}), 2.30 (dd, J = 11 4 and 2 8, 1H, H_{3ax}), 2 39-2 47 (m, 2H, $C\underline{H}_2$-CH_3), 2 90 (dt, J = 11 3 and 2 1, 1H, H_{5eq}), 3 04 (dt, J = 2 1 and 11 3, 1H, H_{3eq}), 3 17 (d, J = 14 3, 1H, H_a benzyl), 3.73-3 89 (m, 3H, H_b benzyl, H_{6ax}, H_{2eq}), 7 25-7 41 (m, 9H, Ar-H) Anal calcd for $C_{20}H_{22}ClN_3$ C, 70 71, H, 6 47, N, 12 37 Found C, 70 68, H, 6 45, N, 12 39

Further elution gave 1 7 g (26 %) of the *cis* -isomer **14**, mp 95°C I r (KBr) cm^{-1} 2218 ($\nu_{C\equiv N}$) ^{1}H-NMR ($CDCl_3$) δ 1 00 (t, J = 7 4, 3H, $C\underline{H}_3$-CH_2), 2 03 (t, J = 11 0, 1H, H_{5ax}), 2 38 (q, J = 7 4, 2H, $C\underline{H}_2$-CH_3), 2 50 (t, J = 7 0, 1H, H_{3ax}), 2 75 (dt, J = 11 4 and 2 4, 1H, H_{5eq}), 3 14 (dt, J = 11 4 and 2 4, 1H, H_{3eq}), 3 49-3 60 (m, 2H, H_{6ax}, H_{2ax}), 3 80 (d, J = 14.8, 1H, H_a benzyl), 4 00 (d, J = 14 8, 1H, H_b benzyl), 7 11-7 44 (m, 9H, Ar-H) Anal calcd for $C_{20}H_{22}ClN_3$ C, 70 71, H, 6 47, N, 12 37 Found C, 70 73, H, 6 43, N, 12 35

4-Ethyl-6-(4-chlorophenyl)-1-methylpiperazine-2-carbonitriles **15,16**

Following the procedure described for **13,14**, the diamine **12** (7 g, 32 mmoles) was allowed to react with 2,3-dibromopropionitrile (7 7 g, 35 mmoles) to lead to a mixture of **15,16** Separation of the isomers on silica gel column chromatography, using ether/cyclohexane (80 20) as eluent, gave 3 2 g (38 %) of the *trans* isomer **15**, mp 97-98°C I r (KBr) cm^{-1} 2216 ($\nu_{C\equiv N}$) ^{1}H-NMR ($CDCl_3$) δ 1 07 (t, J = 7 2, 3H, $C\underline{H}_3$-CH_2), 2 01 (t, J = 11 4, 1H, H_{5ax}), 2 15 (s, 3H, CH_3N), 2 39-2 48 (m, 3H, $C\underline{H}_2$-CH_3, H_{3ax}), 2 83 (dt, J = 9 2 and 2 2, 1H, H_{5eq}), 3 14 (dt, J = 11 4 and 2 6, 1H, H_{3eq}), 3 49 (dd, J = 10 2 and 3 2, 1H, H_{6ax}), 3 93 (t, J = 2 6, 1H, H_{2eq}), 7 27-7 29 (m, 4H, Ar-H) Anal calcd for $C_{14}H_{18}ClN_3$ C, 63 78, H, 6 83, N, 15 94 Found C, 63 75, H, 6 79, N, 6 86

Further elution gave 1 9 g (23 %) of the *cis* isomer **16** as an oil I r (KBr) cm^{-1}. 2218 ($\nu_{C\equiv N}$) ^{1}H-NMR ($CDCl_3$) δ 1 06 (t, J = 7 2, 3H, $C\underline{H}_3$-CH_2N), 2 04 (t, J = 10 6, 1H, H_{3ax}), 2 24 (s, 3H, CH_3N), 2 39-2 53 (m, 3H, $C\underline{H}_2$-CH_3, H_{5ax}), 2 79 (dt, J = 9 0 and 2 8, 1H, H_{3eq}), 3 13-3 22 (m, 2H,

H_{2ax}, H_{5eq}); 3.37 (dd, J = 11.0 and 3 1, 1H, H_{6ax}), 7 27-7 3 (m, 4H, Ar-H). Anal calcd for $C_{14}H_{18}ClN_3$ C, 63 78; H, 6 83; N, 15 94 Found· C, 63 79, H, 6 85, N, 6 81

Ethyl 1-benzyl-4-ethyl-(4-chlorophenyl)piperazine-2-carboxylates **17,18**

A solution of ethyl 2,3-dibromopropionate (2.4 g, 11 0 mmoles) in benzene (8 ml) was added dropwise to a mixture of diamine **11** (3 g, 10 mmoles) and diisopropylethylamine (3 23 g, 25 mmoles) in benzene (6 ml) at 0°C The mixture was allowed to stand at room temperature for 10 h under continuous stirring Then, after filtration, the filtrate was evaporated *in vacuo* , water (25 ml) was added and the mixture extracted with CH_2Cl_2 The organic layers were washed with water then dried ($MgSO_4$) The solvent was evaporated to give a mixture of isomers **17** and **18** These were separated on silica gel chromatography column Elution was performed with ether/hexan (80 20) to afford 1.5 g (40 %) of the *trans*-isomer **17**, mp 108-109°C I r (KBr) cm^{-1} 1718 (ν_{CO}) ^{1}H-NMR ($CDCl_3$) δ 1 00 (t, J = 7 2, 3H, $C\underline{H}_3$-CH_2N), 1 26 (t, J = 7 4, 3H, $C\underline{H}_3$-CH_2O), 2 05 (t, J = 10 8, 1H, H_{5ax}); 2 18-2 28 (m, 2H, CH_3-$C\underline{H}_2N$ and H_{3ax}), 2 34-2 47 (m, 1H, CH_3-$C\underline{H}_2N$), 2.86 (dt, J = 11 6 and 3 4, 1H, H_{5eq}); 3 26 (dt, J = 11 3, and J = 2 3, 1H, H_{3eq}), 3 47 (t, J = 2 1, 1H, H_{2eq}), 3 63 (d, J = 14 8, 1H, H_a benzyl), 3 72 (d, J = 14 8, 1H, H_b benzyl), 4 10-4 30 (m, 2H, CH_3-$C\underline{H}_2O$), 4.66 (dd, J = 9 8 and 3 6; 1H, H_{6ax}), 7 18-7 47 (m, 9H, Ar-H) Anal calcd for $C_{22}H_{27}ClN_2O_2$ C, 68.32, H, 6 98, N, 7 25 Found C, 68 35, H, 7 02, N, 7 21

Further elution gave 0 9 g (24 %) of the *cis*-isomer **18** as an oil I r (KBr) cm^{-1}. 1717 (ν_{CO}) ^{1}H-NMR ($CDCl_3$) δ· 1 02 (t, J = 7.2, 3H, $C\underline{H}_3$-CH_2N), 1 24 (t, J = 7 4, 3H, $C\underline{H}_3$-CH_2O), 2 06 (t, J = 11 0, 1H, H_{5ax}), 2 28 (t, J = 7 0, 1H, H_{3ax}), 2 35 (q, J = 7 2, 2H, CH_3-$C\underline{H}_2N$), 2 79 (dt, J = 11 2 and 2.6, 1H, H_{5eq}), 3 02 (dt, J = 11 4 and 2 4, 1H, H_{3eq}), 3 44-3 60 (m, 3H, H_a benzyl, H_{6ax}, H_{2ax}), 3 70 (d, J = 14 8, 1H, H_b benzyl), 4 01-3 88 (m, 2H, CH_3-$C\underline{H}_2O$), 7 02-7 46 (m, 9H, Ar-H) Anal calcd for $C_{22}H_{27}ClN_2O_2$ C, 68 32; H, 6 98, N, 7 25 Found C, 68 28; H, 6 99; N, 7 28

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