N-Arylhexahydropyrimidines. Part 1. Synthesis and ^{1}H NMR Characterization of 1,3-Di and 1,2,3-Trisubstituted Derivatives

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A series of *N*-arylhexahydropyrimidines **1a-l** were synthesized by condensation of *N*-aryl-*N'*-alkyl- (or aryl)-1,3-propanediamines **2a-h** with aldehydes. Reactions with formaldehyde proceeded in hydroalcoholic solution, while condensation with aromatic aldehydes required in general the use of activated molecular sieves. ^{1}H NMR spectra of compounds **1a-l** were analyzed and the results correlated with their conformational features. Derivatives devoid of a 2-substituent **1a-g** show fast ring reversal and *N*-inversion. The presence of a 2-aryl group shifts the ring reversal equilibrium towards conformations where the 2-aryl substituent is equatorial. Differential assignment of axial and equatorial hydrogens in these compounds was made on the basis of coupling constants and chemical shift values. In compound **1k** spectral data suggest the axial orientation of the *N*-methyl group. Such findings were confirmed in the corresponding NOESY spectrum.

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Introduction.

Hexahydropyrimidines are a subject of interest due to their pharmacological activity, as some members behave as prodrugs of biologically active di [1] and polyamines [2]. Besides, some suitably substituted derivatives form stable complexes with metal ions, acting as antiamoebic [3] or decontaminating agents [4]. In organic synthesis, the hexahydropyrimidine system has been widely employed as protecting group in selective acylations [5] and additions [6] of 1,3-diamines, due to its easy cleavage in mild acid medium. Other applications include the synthesis of selectively *N*-substituted trimethylenediamines and tetrahydropyrimidinium salts through reduction [7] and dehydrogenation [8] reactions respectively.

The hexahydropyrimidine ring is also interesting from the perspective of conformational analysis. The stereochemistry of such systems was extensively studied by ^{1}H and ^{13}C NMR between 1970 and 1980 [9] and more recently by computational methods [10]. It was observed that certain chemical shifts and coupling constants in the ^{1}H NMR spectra of hexahydropyrimidines are quite sensitive to the conformation. Such parameters have been employed for the elucidation of the stereochemistry of more complex diazabicycloalkanes [11]. Data in the literature, however, are restricted to *N,N'*-dialkylhexahydropyrimidines, while *N*-aryl-*N'*-alkyl and *N,N'*-diaryl derivatives have not been studied yet.

The classic synthesis of 1,3-disubstituted hexahydropyrimidines involves the condensation of adequately substituted 1,3-propanediamine derivatives with carbonyl compounds. Alternative synthetic methods involve reduction of cyclic urea derivatives [12] or dihydropyrimidines [13], leading to 2 or 3-unsubstituted hexahydropyrimidines respectively. In previous work we attempted the synthesis of 1,2-diaryl-3-methylhexahydropyrimidines by reduction of the corresponding cyclic amidinium salts [14]. However, treatment of 1,4,5,6-tetrahydropyrimidinium salts with metal hydride complexes led, in all cases, to acyclic overreduction products, through selective cleavage of the hexahydropyrimidine nucleus.

In the present work hexahydropyrimidines **1a-l** were synthesized by the classical method (Scheme I). One limitation of this procedure was the preparation of the corresponding unsymmetrically *N,N'*-disubstituted 1,3-propanediamines **2**. According to their substitution patterns, such compounds were synthesized employing two alternative procedures developed in previous work [15,16].

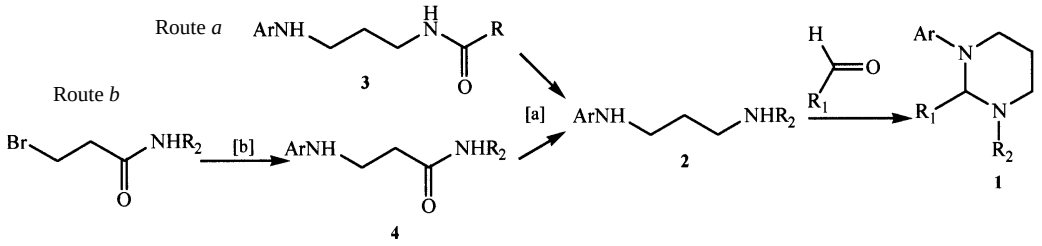
The assignment of ^{1}H NMR spectra of compounds **1** is discussed and some spectral parameters are correlated with their stereochemical and conformational features.

Synthesis.

Unsymmetrically substituted diamines **2a-e,h** were synthesized by the sequences depicted in Scheme I, in which one of the amino groups is generated by aminolysis of a bromo derivative and the other by reduction of an amide. Route *a*, involves reduction of *N*-acyl-*N'*-aryltrimethylenediamines **3** [15]. This route led to good yields of the desired diamines **2b,e-h** in the case of benzamides and alkanamides (**3,** R= aryl or alkyl). Instead, reduction of formamides **3** (R=H) with borane led to low yields of the corresponding *N*-methyl derivatives, due to incomplete decomposition of boron derivatives in the reaction work-up. A second limitation of Route *a*, is that it cannot be employed for the synthesis of derivatives in which the amino moiety generated by reduction of the amide contains a secondary or tertiary alkyl or an aryl substituent. Thus, diamines **2a,d** were synthesized with high yields by reduction of the corresponding 3-arylaminopropanamides **4** (Scheme I, Route *b*) [16].

Condensation of precursors **2a-h** with aldehydes led to the corresponding hexahydropyrimidines **1a-l** (Scheme I). It was observed that optimum reaction conditions depended strongly on the type of carbonyl compound employed and also on the stability towards hydrolysis of

Scheme I



Compd.	Ar	R_1	R_2
1a, 2a	*p*-ClC_6H_4	H	CH_3
1b, 2b	*p*-ClC_6H_4	H	C_2H_5
1c, 2c	*p*-ClC_6H_4	H	C_3H_7
1d, 2d	*p*-ClC_6H_4	H	*iso*-C_3H_7
1e, 2e	*p*-ClC_6H_4	H	*iso*-$C_3H_7CH_2$
1f, 2f	C_6H_5	H	C_6H_5
1g, 2g	*p*-ClC_6H_4	H	*p*-ClC_6H_4
1h, 2h	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	$C_6H_5CH_2$
1i	C_6H_5	*p*-$NO_2C_6H_4$	C_6H_5
1j	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4
1k	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	CH_3
1l	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	C_2H_5

[a] BH_3/tetrahydrofurane, reflux, 3 hs.; [b] 2 $ArNH_2$, 100-120ºC, 1 hour.

the resulting cyclic aminals. It is widely accepted that compounds of this type undergo hydrolysis through carbocation-iminium ions (Scheme II) [17]. The stability of such intermediates is enhanced by electron donor substituents on the carbocationic carbon and by *N*-alkyl groups, whereas *N*-aryl substituents do not provide stabilization. Thus, *N,N'*-diaryl and 2-unsubstituted cyclic aminals are more resistant towards hydrolysis [18].

Reaction of *N*-aryl-*N'*-alkyl- (or aryl)-1,3-propanediamines with formaldehyde was performed in hydroalcoholic solution at room temperature and led to high yields of 2-unsubstituted hexahydropyrimidines **1a-g**. These compounds were easily purified by column chromatography using neutral alumina as stationary phase, while attempts of chromatographic purification employing silica gel led to partial hydrolysis. Condensation of *N,N'*-diaryl-1,3-propanediamines **2f,g** with *p*-nitrobenzaldehyde took place without difficulties in anhydrous ethanol, where the resulting hexahydropyrimidines **1i,j** were insoluble. In contrast, reaction of *N*-(*p*-chlorophenyl)-*N'*-methyl-1,3-propanediamine **2a** with *p*-nitrobenzaldehyde under the same conditions did not lead to the desired products and unreacted starting materials were recovered. The condensation also failed when carried out in anhydrous benzene solution, with azeotropic distillation of water, or in the presence of *p*-toluenesulphonic acid. The synthesis of 2-aryl derivatives **1h,k,l** was accomplished by employing a physical dehydrating agent in an aprotic low boiling point anhydrous solvent. The condensation was carried out by stirring at room temperature equimolar amounts of the reagents in anhydrous dichloromethane solution, in the presence of activated molecular sieves [19]. The reaction was monitored in cellulose tlc plates until disappearance of the starting materials (48 hours) and the products were purified chromatographically employing the same stationary phase. Instead, purification on neutral alumina or silica gel led to complete hydrolysis of the aminals. Attempts to extend this methodology to the condensation of *N*-(*p*-chlorophenyl)-*N'*-methyl-1,3-propanediamine with aliphatic aldehydes were unsuccessful. Reaction of **2a** with acetaldehyde led to intensely coloured materials resulting from autocondensation of the carbonyl compound, while condensation with pivaldehyde, devoid of α-hydrogens, did not take place due perhaps to its low reactivity.

Spectral Properties and Conformational Features.

The stereochemistry of the hexahydropyrimidine nucleus involves two different processes, namely ring reversal and *N*-inversion (Scheme III). Variable temperature NMR experiments [9h,i] on hexahydropyrimidines indicate that both ring reversal and *N*-inversion are fast processes at room temperature, although their coalescence temperatures are substantially different. In 1,2,3-trialkyl derivatives, ring inversion becomes slow in the NMR timescale below –40 ºC, while slowing of *N*-inversion requires temperatures below –100 ºC [9i]. In *N,N'*-dialkylhexahydropyrimidines the absence of a 2-substituent lowers the energy barrier for ring reversal and *N*-inversion [9h]. Although *N*-arylhexahydropyrimidines have not been studied, literature indicates that in acyclic [20] and six membered cyclic [21,22] tertiary arylamines, the nitrogen atom has substantial sp^3 character. Thus, in *N*-arylhexa-

hydropyrimidines **1** the aryl substituent could in principle be axial or equatorial, as depicted in Scheme III. Due to partial conjugation, *N*-inversion is much faster for aryl than for alkylamines [23].

^{1}H NMR spectra of hexahydropyrimidines **1a-l** under study show differences according to their conformational behavior, which is in turn related to the presence or absence of a 2-substituent.

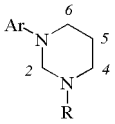
Like *N*,*N'*-dialkylhexahydropyrimidines [9h], derivatives **1a-g** (Table I) show isochronicity of the geminal protons on the trimethylene portion and on C2 due to fast ring reversal and *N*-inversion at room temperature. The assignment of the ^{1}H NMR spectra of compounds **1a-e** was made on the basis of the 1,3-diaryl derivative **1g**, taken as model compound. Thus, in all cases, the lower frequency triplet was assigned to methylene H4 and the higher frequency triplet to methylene H6. For compound **1a**, such assignment was confirmed by means of the corresponding HMBC spectrum. When hexahydropyrimidines **1a,b,d** are compared *inter se*, an increasing deshielding of methylenes H2 and H4 is observed. This trend would be related to a decreasing hyperconjugative effect along the series *N*-methyl-ethyl-isopropyl, which was previously observed for *N*-alkylpiperidines [24].

The introduction of a substituent in position 2 of the hexahydropyrimidine ring shifts the ring inversion equilibrium towards a preferred conformation in which the 2-substituent is equatorial (Scheme II, set A) [9a-e,h,i,n]. Due to this conformational bias, in 1,2,3-trisubstituted derivatives **1h-l** the geminal protons on the trimethylene portion appear anisochronous (Table II). According to the nature of both *N*-substituents, these compounds show spectral patterns of different complexity, which will be analyzed separately.

1,3-Diaryl-2-(*p*-nitrophenyl)hexahydropyrimidines **1i,j** show two separate signals corresponding to axial and equatorial hydrogens on C4,C6 and two higher field resonances corresponding to C5 protons (Table II). Differential assignment of axial and equatorial hydrogens in the trimethylene portion was made on the basis of their coupling constants and chemical shift values, listed in Table II. For hydrogens on C4, C6, ^{2}J (H,H) correspond to the geminal coupling constants. Both multiplets show two further vicinal splittings, J_2 and J_3. The difference between such coupling constants is greater for the lowest frequency signals, which were thus assigned to the axial protons ($H4_a$, $H6_a$). Differential assignment of C5 hydrogens was performed on the basis of their chemical shift values. Unlike cyclohexane, where axial hydrogens resonate at higher fields than their equatorial partners, in azaheterocycles β-axial hydrogens show the highest resonance frequencies [26,9n]. Thus, in our case, the multiplets

Table I

^{1}H NMR Spectra of 1,3-Disubstituted Hexahydropyrimidines **1a-g**



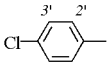
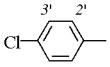
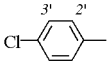
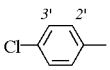
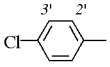
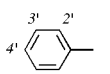
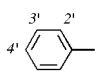
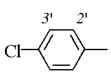
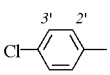
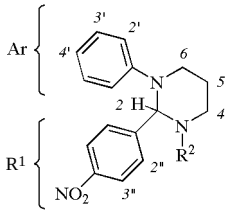
Compd.	Ar	R	H4	H6	H5	H2	Ar	R
1a		CH_3	2.60 (t)	3.26 (t)	1.75 (p)	3.79 (s)	*2':* 6.87 (dd) *3':* 7.19 (dd)	2.30 (s)
1b		CH_2CH_3 *a b*	2.66 (t)	3.26 (t)	1.75 (p)	3.86 (s)	*2':* 6.87 (dd) *3':* 7.19 (dd)	*a:* 2.49 (q) *b:* 1.15 (t)
1c		$CH_2CH_2CH_3$ *a b c*	2.67 (t)	3.26 (t)	1.74 (p)	3.86 (s)	*2':* 6.87 (dd) *3':* 7.18 (dd)	*a:* 2.36-2.41 (m) *b:* 1.57 (m) *c:* 0.93 (t)
1d		$CH(CH_3)_2$ *a b*	2.73 (t)	3.24 (t)	1.73 (p)	3.94 (s)	*2':* 6.86 (dd) *3':* 7.18 (dd)	*a:* 2.84 (m) *b:* 1.11 (d)
1e		$CH_2CH(CH_3)_2$ *a b c*	2.63 (t)	3.25 (t)	1.71 (p)	3.83 (s)	*2':* 6.87 (dd) *3':* 7.17 (dd)	*a:* 2.18 (d) *b:* 1.80 (m) *c:* 0.93 (d)
1f			3.37 (t)		1.80 (p)	4.59 (s)	*2':* 7.01 (dd) *3':* 7.27 (dt) *4':* 6.83 (dt)	
1g			3.39 (t)		1.83 (p)	4.56 (s)	*2':* 6.93 (dd) *3':* 7.23 (dd)	

Table II

^{1}H NMR Spectra of 1,2,3-Trisubstituted Hexahydropyrimidines **1h-l**



Compd.	H2	$H4_a$	$H6_a$	$H4_e$	$H6_e$	$H5_a$	$H5_e$	Ar	R^2	R^1
1i	6.42 (s)	3.35 (ddd) [a]		3.60 (ddd) [b]		1.80-2.21 (m)	1.42-1.61 (m)	*2', 4':* 6.75-6.82 (m), *3':* 7.21 (dt)		*3":* 8.13 (dd) *2":* 7.54 (dd)
1j	6.32 (s)	3.37 (ddd) [c]		3.54 (ddd) [d]		1.99-2.09 (m)	1.51-1.58 (m)	*2':* 6.75 (dd) *3':* 7.27 (dd)		*3":* 8.21 (dd) *2":* 7.55 (dd)
1k	5.25 (s)	3.03 (ddd) [e]	3.26 (ddd) [f]	2.62 (ddd) [g]	3.60 (ddd) [h]	2.12-2.22 (m)	1.36-1.44 (m)	*2':* 6.82 (dd) *3':* 7.17 (dd)	2.54 (s)	*3":* 8.16 (dd) *2":* 7.64 (dd)
1l	5.58 (s)	2.86-2.97 (m) [i]	3.26 (ddd) [j]	2.70-2.82 (m) [i]	3.65-3.76 (m)	2.07-2.22 (m)	1.17-1.25 (m)	*2':* 6.77 (dd) *3':* 7.18 (dd)	CH_2: 2.70-2.82 (m) [i] and 2.86-2.97 (m) [i] CH_3: 1.13 (t)	*3":* 8.18 (dd) *2":* 7.67 (dd)
1h	5.45 (s)	3.07 (ddd) [k]	3.29 (ddd) [l]	2.89 (d, b. s.)	3.78 (d, b.s)	2.22-2.37 (m)	1.25-1.29 (m)	*2':* 6.69 (dd) *3':* 7.17 (dd)	*2":* 7.66 (dd) *3":* 8.17 (dd)	CH_2: 3.87 (d) [m] and 4.08 (d) [m] C_6H_5: 7.29-7.33 (m)

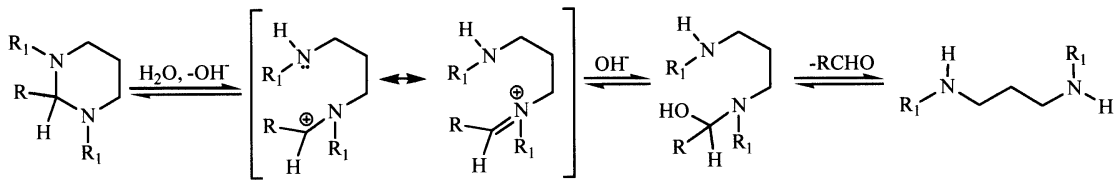
[a] J_1: 12.4 Hz, J_2: 7.8 Hz, J_3: 4.5 Hz; [b] J_1: 12.4 Hz, J_2: 6.9 Hz, J_3: 5.4 Hz; [c] J_1: 12.7 Hz, J_2: 7.9 Hz, J_3: 4.4 Hz; [d] J_1: 12.7 Hz, J_2: 6.7 Hz; J_3: 5.4 Hz; [e] J_1: 13.5 Hz, J_2: 10.2 Hz, J_3: 3.7 Hz; [f] J_1: 13.1 Hz, J_2: 10.0 Hz, J_3: 3.5 Hz; [g] J_1: 13.5 Hz, J_2= J_3: 4.1 Hz; [h] J_1: 13.1 Hz, J_2= J_3: 4.4 Hz; [i] overlapping signals; [j] J_1: 13.2 Hz, J_2: 11.8 Hz, J_3: 3.4 Hz; [k] J_1: 14.1 Hz, J_2: 12.4 Hz, J_3: 3.3 Hz; [l] J_1: 14.1 Hz, J_2: 11.5 Hz, J_3: 3.3 Hz; [m] J_1:13.2 Hz.

centered at *ca.* 2.00 ppm were assigned to $H5_a$, while the remaining signals were attributed to $H5_e$.

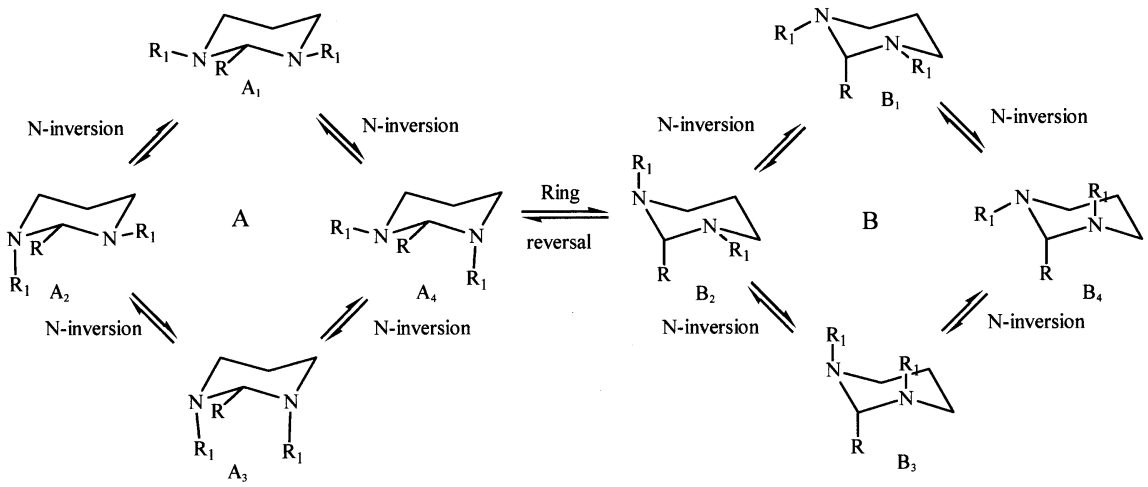
The trimethylene portion of the unsymmetrically substituted hexahydropyrimidine **1k** displays four separate signals corresponding to axial and equatorial hydrogens on C4 and C6, and two higher field resonances corresponding to C5 protons. Differential assignment of axial and equatorial hydrogens was made on the basis of their coupling constants and chemical shift values (Table II). For both hydrogens on C4 and C6, ^{2}J (H,H) correspond to the geminal coupling constants, and were used to pair the corresponding geminal protons. By comparison with the same signals in the symmetrical derivative **1i**, the pair with higher chemical shift was assigned as $H6_a$-$H6_e$ and the remaining pair as $H4_a$-$H4_e$. Two additional splittings were present in all four signals, J_2 and J_3. For one of the signals within each pair, J_2 shows values which are characteristic of trans-diaxial coupling. Thus, the multiplets centered at 3.26 and 3.03 ppm were assigned respectively as $H6_a$ and $H4_a$, while the remaining signals, centered at 3.60 and 2.62 ppm, were respectively attributed to $H6_e$ and $H4_e$. Following the same criterion as for compound **1i** the multiplet centered at 2.20 ppm was assigned to $H5_a$, and the signal centered at 1.40 ppm to $H5_e$.

On the basis of the spectral parameters discussed before and some literature data, we attempted to disclose some stereochemical and conformational features of compound **1k**. Previously reported spectral data indicate that in 1,3-dialkyl-2-phenylhexahydropyrimidines the ring inversion equilibrium is highly biased towards conformations with the 2-phenyl equatorial (Scheme II, set A) [9n]. Taking into account these data, we assume the same preference for the 2-*p*-nitrophenyl group. The preferential orientation of the *N*-methyl substituent was tentatively established on the basis of the geminal coupling constant of C4 methylene and of H2 chemical shift. The influence of heteroatom lone

Scheme II

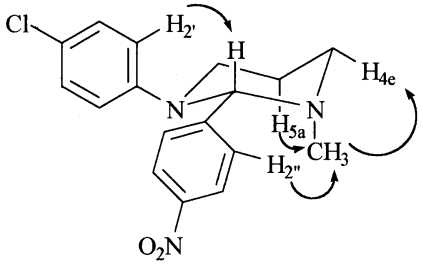


Scheme III



pairs on the magnitude of geminal H-H coupling constants of adjacent methylene groups has been well established in a variety of nitrogen and oxygen heterocycles [27], including hexahydropyrimidines. In such systems, the presence of one or more axially oriented lone pairs causes a decrement in the absolute value of geminal coupling constants, as a consequence of lone pair-$\sigma^*_{C\text{-}H}$ electron delocalization. This hyperconjugative interaction leads also to differential shielding of the adjacent axial hydrogen antiperiplanar to the lone pair (H2). In our case, the value of the geminal coupling constant of C4 methylene (13.6 Hz) suggests the absence of an antiperiplanar lone pair and therefore the axial orientation of the *N*-methyl substituent. In fact, in *N*-alkylpiperidines this constant is ~11.5 Hz in the equatorial conformer and ~13.6 Hz in the axial conformer [27a]. To confirm the proposed orientation of the *N*-methyl, the chemical shift of H2 in **1k** (δ=5.25 ppm) was compared with the corresponding signal in the homologous 1,2-diaryl-3-methylimidazolidine (δ=4.25 ppm) [18], in which this hydrogen is *cis* with respect to the *N*-methyl [28]. The observed chemical shift difference (1 ppm) would indicate a shielding effect of the *trans* lone pair in the imidazolidine, which does not operate in the hexahydropyrimidine as a consequence of the *trans* orientation of H2 and *N*-methyl. In order to confirm the proposed orientation of the substituents in hexahydropyrimidine **1k** we performed the corresponding NOESY spectrum. Relevant correlations are shown in Scheme IV. Correlations of the *N*-methyl group with $H5_a$ and $H4_e$ indicate the axial disposition of the former, while its correlation with H2" confirms the relative *cis* orientation of both groups. Besides, correlation of H2 and the *ortho* hydrogens of the *N*-aryl (H2') suggest a *cis* relationship between them.

Scheme IV



The trimethylene portion of the ^{1}H NMR spectra of 1,2-diaryl-3-alkylhexahydropyrimidines **1h,l** has approximately the same pattern as that of the 3-methyl derivative **1k**. Thus, assignment of the corresponding resonances was made by comparison with the latter (Table II). When the *N*-methyl group is replaced by a CH_2X type substituent, both methylene hydrogens are anisochronous. Diasterotopicity of *N*-methylene hydrogens in these compounds is attributed to the presence of a stereogenic centre (C2) in the molecule.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer. HMBC spectrum of compound **1a** and NOESY spectrum of compound **1k** were performed in a Bruker AVANCE DRX300 spectrometer (mixing time for the NOESY spectrum=0.5 seconds). Deuteriochloroform was used as the solvent, and the standard concentration of the samples was 20mg/mL. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Coupling constants (J values) are given in Hz. Splitting multiplicities are reported as singlet (s), broad signal (bs), doublet (d), double doublet (dd), double double doublet (ddd), triplet (t), double triplet (dt), quartet (q), pentet (p) and multiplet (m). Mass spectra (electron impact) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. Tlc analyses were carried out either on aluminium sheets Alumina 60 F_{254} using chloroform as the solvent or on aluminium Cellulose F sheets using *n*-pentane. Column chromatography was performed either on Aluminium Oxide (neutral, grade

I, 70-230 mesh) or on Cellulose microcrystalline, with typically 30-50 g of stationary phase *per gram* substance. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

N,N'-Diaryl-1,3-propanediamines **2f,g** were obtained according to the literature procedure (mp **2f** 39-41 °C, lit. [29] 40-41 °C and **2g** 79-80 °C, lit. [29] 78-79 °C). *N*-Aryl-*N'*-alkyl (or aralkyl)-1,3-propanediamines **2b,c,e,h** were obtained by reduction of the corresponding *N*-aryl-*N'*-acyl-1,3-propanediamines [15]. *N*-Aryl-*N'*-alkyl-1,3-propanediamines **2a,d** were obtained by reduction of the corresponding 3-arylaminopropanamides [16].

1,3-Disubstituted Hexahydropyrimidines **1a**-**g**. General Procedure.

A solution of 1,3-propanediamine **2a-f** (5 mmol) in methanol (50 mL) was treated with 37% aqueous formaldehyde (5 mmol). The solution was stirred at room temperature for 2 hours, after which it was treated with 20% aqueous sodium carbonate (10 mL). The mixture was extracted with methylene chloride (3 x 30 mL) and the organic layers were washed with water (5 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude products were purified by column chromatography on neutral alumina (grade I) using chloroform as mobile phase, to yield compounds **1a-g**. ^{1}H NMR data of compounds **1a-g** are given in Table I. Yields, mass spectra and elemental analyses of new compounds are as follows:

1-(*p*-Chlorophenyl)-3-methylhexahydropyrimidine (**1a**).

This compound was obtained as an oil (84%); ms: m/z 210 ($M^{+\cdot}$).

Anal. Calcd for $C_{11}H_{15}N_2Cl$: C, 62.70; H, 7.18; N, 13.29. Found: C, 62.59; H, 7.22; N, 13.25.

1-(*p*-Chlorophenyl)-3-ethylhexahydropyrimidine (**1b**).

This compound was obtained as an oil (85%); ms: m/z 224 ($M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{17}N_2Cl$: C, 64.13; H, 7.62; N, 12.47. Found: C, 64.05; H, 7.70; N, 12.42.

1-(*p*-Chlorophenyl)-3-propylhexahydropyrimidine (**1c**).

This compound was obtained as an oil (87%); ms: m/z 238 ($M^{+\cdot}$).

Anal. Calcd for $C_{13}H_{19}N_2Cl$: C, 65.40; H, 8.02; N, 11.73. Found: C, 65.33; H, 8.10; N, 11.75.

1-(*p*-Chlorophenyl)-3-isopropylhexahydropyrimidine (**1d**).

This compound was obtained as an oil (86%); ms: m/z 238 ($M^{+\cdot}$).

Anal. Calcd for $C_{13}H_{19}N_2Cl$: C; 65.40, H; 8.02, N; 11.73. Found: C, 65.35; H, 8.07; N, 11.67.

1-(*p*-Chlorophenyl)-3-(2-methylpropyl)hexahydropyrimidine (**1e**).

This compound was obtained as an oil (85%); ms: m/z 252 ($M^{+\cdot}$).

Anal. Calcd for $C_{14}H_{21}N_2Cl$: C, 66.52; H, 8.37; N, 11.08. Found: C, 66.45; H, 8.35; N, 11.01.

1,3-Diphenylhexahydropyrimidine (**1f**) (89%) was synthesized employing the same procedure, mp 86-87 °C (from ethanol) (lit., [29] 87 °C).

1,3-Di-(*p*-chlorophenyl)hexahydropyrimidine (**1g**).

This compound was obtained in 91% yield, mp 84-86 ºC (methanol/water); ms: m/z 306 ($M^{+\cdot}$).

Anal. Calcd for $C_{16}H_{16}N_2Cl_2$: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.61; H, 5.12; N, 9.08.

1,3-Diaryl-2-(*p*-nitrophenyl)hexahydropyrimidines (**1i,j**). General Procedure.

A stirred solution of *N,N'*-diaryl-1,3-propanediamine **2i,j** (5 mmol) in anhydrous ethanol (50 mL) was treated with *p*-nitrobenzaldehyde (5 mmol). After 2 hours a solid precipitated, which was filtered and washed with anhydrous ethanol to yield compounds **1i,j**. ^{1}H NMR data of these compounds are given in Table II. Yields, mass spectra and elemental analyses of new compounds are as follows:

1,3-Diphenyl-2-(*p*-nitrophenyl)hexahydropyrimidine (**1i**).

This compound was obtained in 81% yield, yellow crystals; mp 89-90 ºC (anhydrous ethanol); ms: m/z 359 ($M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.65; H, 5.80; N, 11.60.

1,3-Di(*p*-chlorophenyl-2-(*p*-nitrophenyl)hexahydropyrimidine (**1j**).

This compound was obtained in 83% yield, yellow crystals; mp 160-162 ºC (anhydrous ethanol); ms: m/z 427 ($M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{19}Cl_2N_3O_2$: C, 61.69; H, 4.47; N, 9.81. Found: C, 61.78; H, 4.41; N, 9.73.

1,2-Diaryl-3-alkylhexahydropyrimidines (**1h,k,l**). General Procedure.

The aldehyde (5 mmol) was added to a solution of diamine **2a,b,h** (5 mmol) in anhydrous dichlorometane (50 mL). Previously activated 3 Å molecular sieves [19] (4 g) were added to the solution, which was stirred at room temperature protected from moisture. The reaction was monitored by tlc (cellulose microcrystalline, *n*-pentane) until disappearance of the starting materials (approximately 48 hours), after which molecular sieves were separated by filtration. The solvent was removed *in vacuo* and the crude products purified by column chromatography, using cellulose microcrystalline (*n*-pentane). ^{1}H NMR data of compounds **1h,k,l** are given in Table II. Yields, mass spectra and elemental analyses are as follows:

1-(*p*-Chlorophenyl)-2-(*p*-nitrophenyl)-3-methylhexahydropyrimidine (**1k**).

This compound was obtained as an oil (74%); ms: m/z 331 ($M^{+\cdot}$).

Anal. Calcd for $C_{17}H_{18}N_3O_2Cl$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.65; H, 5.40; N, 12.69.

1-(*p*-Chlorophenyl)-3-ethyl-2-(*p*-nitrophenyl)hexahydropyrimidine (**1l**).

This compound was obtained as an oil (76%); ms: m/z 345 ($M^{+\cdot}$).

Anal. Calcd for $C_{18}H_{20}N_3O_2Cl$: C, 62.52; H, 5.83; N, 12.15. Found: C, 62.40; H, 5.79; N, 12.24.

1-(*p*-Chlorophenyl)-3-benzyl-2-(*p*-nitrophenyl)-hexahydropyrimidine (**1h**).

This compound was obtained as an oil (78%); ms: m/z 407 ($M^{+\cdot}$).

Anal. Calcd for $C_{23}H_{22}ClN_3O_2$ C, 67.73; H, 5.44; N, 10.30. Found: C, 67.60; H, 5.47; N, 10.41.

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