HETEROCYCLES, Vol. 63, No. 11, 2004, pp. 2557 - 2572
Received, 26th July, 2004, Accepted, 6th October, 2004, Published online, 8th October, 2004

1-ARYL-3-ALKYL-1,4,5,6-TETRAHYDROPYRIMIDINIUM SALTS. PART 2.[1] REACTIONS WITH NUCLEOPHILES

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Abstract- The reactivity of 1-aryl-3-alkyl-1,4,5,6-tetrahydropyrimidinium salts (**1**) towards nucleophiles was studied. Hydrolysis of salts (**1**) afforded initially compounds (**2**, kinetic products) through the corresponding amidinium hydroxides (**4**). The regioselectivity of the reaction was analyzed considering the relative leaving group abilities and the stereoelectronic control theory. Amino amides (**2a-c**) in the reaction medium underwent spontaneous formyl migration, affording compounds (**3**, thermodynamic products). Reduction of salts (**1**) with sodium borohydride led to acyclic trimethylenediamines (**5**) or to the corresponding hexahydropyrimidines (**6**), according to the reaction conditions. Aminolysis of compound (**1f**) with isopropylamine yielded an acyclic formamidine (**7f**).

INTRODUCTION

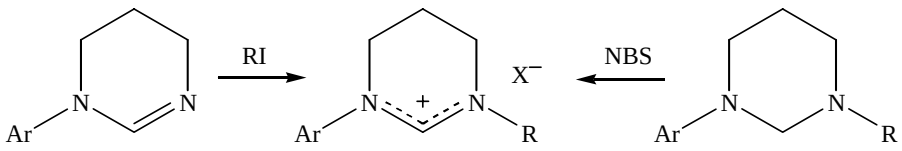
Cyclic formamidinium salts have been studied as models of the coenzyme N^5,N^{10}-methenyltetrahydrofolic acid, involved in biochemical transfer of one carbon units at the oxidation level of formic acid.[2] In biological systems, such transfer occurs through N^{10}-formyltetrahydrofolic acid, which plays a key role in *de novo* synthesis of purinic nucleotides.[3] In an attempt to mimic the biological processes, transference of C2 unit to several nucleophilic reagents was investigated in cyclic amidinium salts in which C2 is linked to two nitrogen atoms of different basicities, as occurs in the natural cofactor.[4,5] Besides, such compounds have been employed as synthetic intermediates for the preparation of selectively substituted alkylenediamine derivatives.[4,6-8] The major part of the research in this area is devoted to 1*H*-4,5-dihydroimidazolium salts,[4,6] while six membered homologues have been less studied.[7,8] Recently, 2-unsubstituted derivatives were used by Alder *et al.* for the synthesis of stable heteroatomic carbene

complexes,[9] potentially useful as catalysts. They have also found application as models to evaluate the relative importance of steric and stereoelectronic effects in nucleophilic additions to nitrogen heterocycles.[10] Continuing ongoing research on tetrahydropyrimidines and their salts,[1,7,8,11] we have examined the reaction of a series of 1-aryl-3-alkyl-1,4,5,6-tetrahydropyrimidinium salts (**1**) with different nucleophiles, leading to selectively substituted cyclic and acyclic 1,3-propanediamine derivatives. Alkaline hydrolysis, reduction and aminolysis of compounds (**1**) were investigated, analysing the relative influence of steric and electronic effects on reactivity. The isolation and spectral characterization of ionic reaction intermediates in alkaline hydrolysis is presented, as well as a theoretical study based upon the stereoelectronic control theory.

RESULTS AND DISCUSSION

Compounds (**1a-d,f**) were synthesized by alkylation of the corresponding 1,4,5,6-tetrahydropyrimidines (Scheme 1, route a). When this procedure was not applicable (compound **1e**), dehydrogenation of the corresponding hexahydropyrimidine was used.[1]

Scheme 1



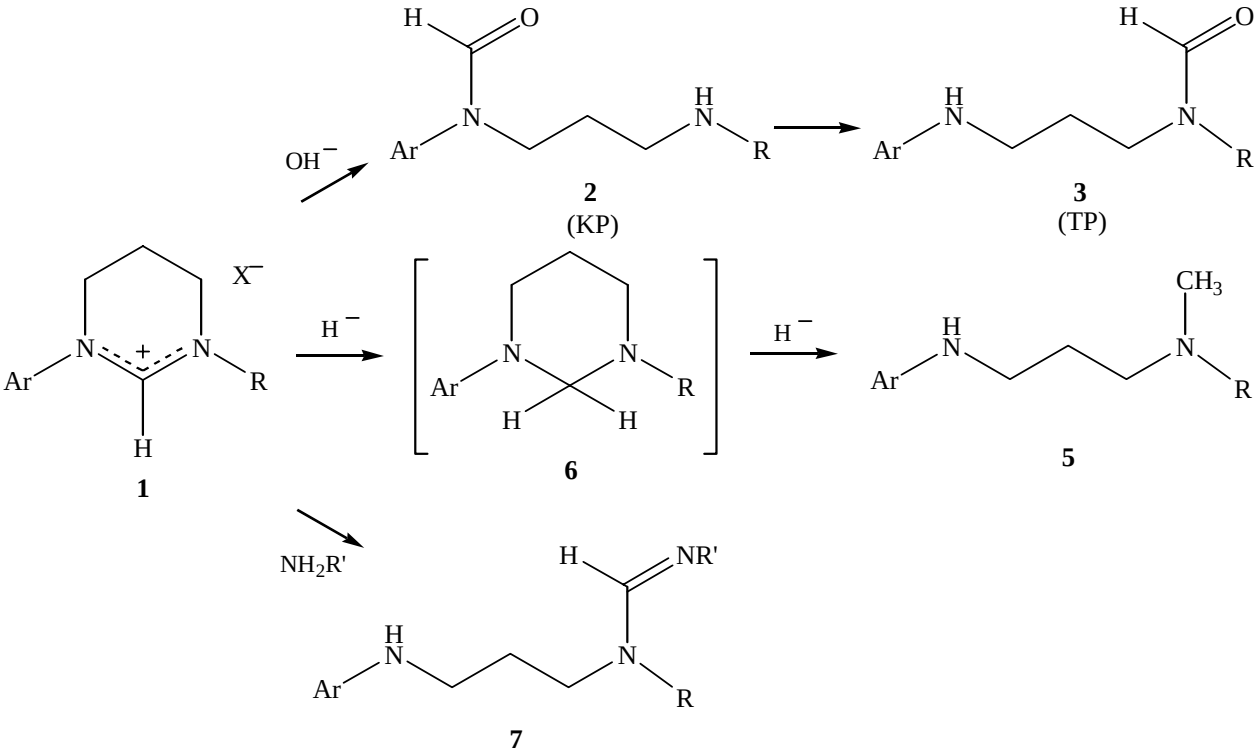
Compd	Ar	R	X	Route
1a	C_6H_5	CH_3	I	a
1b	4-ClC_6H_4	CH_3	I	a
1c	4-$CH_3C_6H_4$	CH_3	I	a
1d	2,4,6-$(CH_3)_3C_6H_2$	CH_3	I	a
1e	4-ClC_6H_4	*tert*-C_4H_9	Br	b
1f	4-$NO_2C_6H_4$	CH_3	I	a

Reactions of compounds (**1**) with different nucleophiles are summarized in Scheme 2.

Treatment of compounds (**1a-c**) with an excess 10% aqueous sodium hydroxide solution led initially to the corresponding *N*-aryl-*N*-formyl-*N´*-alkyltrimethylenediamines (**2**) which, in the reaction medium,

underwent spontaneous formyl migration affording *N*-alkyl-*N*-formyl-*N´*-aryltrimethylenediamines (**3**) (Scheme 2). A similar behavior was previously observed in 1,2-diaryl-3-methyltetrahydropyrimidinium[7] and dihydroimidazolium[6] salts. The accepted reaction mechanism involves initial addition of hydroxide ion to C2 leading to a carbinolamine (CA), followed by selective N3-C2 cleavage, originating aminoamide (**2**) (kinetic product). As a consequence of intramolecular formyl migration, in neutral or alkaline medium, compounds (**2a-c**) rearrange to the isomeric aminoamides (**3**) (thermodynamic products), probably through the same reaction intermediate.[12] It was observed that the nature of the substituent on the aryl ring influenced the reaction rates, which were retarded by electron releasing groups (see EXPERIMENTAL).

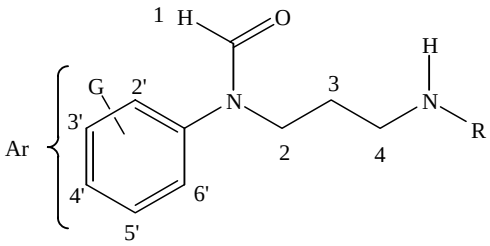
Scheme 2



In contrast, alkaline hydrolysis of **1f** yielded exclusively compound (**3f**), while salts (**1d,e**) afforded amino amides (**2d,e**), which did not undergo formyl migration. Compound (**2d**) was stable in the reaction medium, while **2e** was hydrolysed yielding *N*-(*p*-chlorophenyl)-*N´-tert*-butyltrimethylenediamine. Spectral data of compounds (**2**) and (**3**) are listed in Tables 1 and 2, respectively.

To gain further insight into the reaction mechanism and in order to detect the intermediate carbinolamines, for compounds (**1a-e**) conversion **1→2** was monitored chromatographically. In addition to salts (**1**) and amino amides (**2**), in variable amounts according to the reaction progress, a third spot with R_f *ca.* 0.2 was evidenced in all cases, presumably corresponding to the reaction intermediates.

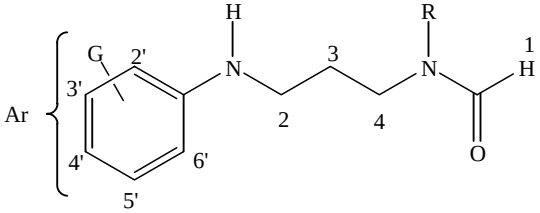
Table 1



Compd	G	R	1	2	3	4	Ar	R
2a	H	CH_3	8.38 (s)	3.90 (t) [a]	1.70-1.77 (m)	2.58 (t) [b]	3',5'=7.42-7.48 (m) 2',6'=7.25-7.29 (m) 4'=7.17-7.20 (m)	2.40 (s)
2b	4-Cl	CH_3	8.31 (s)	3.85 (t) [a]	1.76-1.80 (m)	2.63 (t) [b]	2',3',5',6'=7.13 (d) [c] and 7.37 (d) [c]	2.41 (s)
2c	4-CH_3	CH_3	8.32 (s)	3.85 (t) [a]	1.78-1.83 (m)	2.57 (t) [d]	2',6'=7.20 (d) [e] 3',5'=7.05 (d) [f] 4-CH_3=2.23 (s)	2.44 (s)
2d	2,4,6-(CH_3)$_3$	CH_3	7.98 (s)	3.61 (t) [g]	1.68-1.76 (m)	2.59 (t) [b]	3',5'=6.93 (s) 2,6-(CH_3)$_2$=2.29 (s) 4-CH_3=2.19 (s)	2.39 (s)
2e	4-Cl	$C(CH_3)_3$	8.34 (s)	3.88 (t) [a]	1.68-1.72 (m)	2.54 (t) [a]	2',3',5',6'=7.37 (dd) and 7.13 (dd) [h]	1.07 (s)

[a] J=7.1 Hz, [b] J=6.9 Hz, [c] J=8.7 Hz, [d] J=6.8 Hz, [e] J=8.6 Hz, [f] J=8.3 Hz, [g] J=7.8 Hz, [h] J_1=6.7 Hz, J_2=2.1 Hz.

Table 2

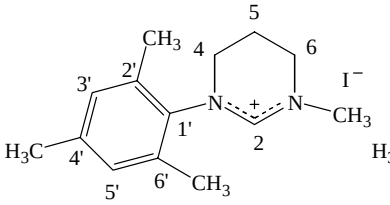


Compd [a]	G	R	1	2	3	4	Ar	R
3a	H	CH_3	8.07 (s)	3.14 (t) [b]	1.80-1.91 (m)	3.45 (t) [b]	6.59-6.65 (m) 6.66-6.73 (m) 7.14-7.21(m)	2.94 (s)
3b	4-Cl	CH_3	8.07 (s)	3.11 (t) [c]	1.76-1.89 (m)	3.43 (t) [d]	7.09-7.14 (m) 6.50-6.56 (m)	2.94 (s)
3c	4-CH_3	CH_3	8.07 (s)	3.11 (t) [e]	1.79-1.89 (m)	3.43 (t) [b]	6.97-7.01 (d) [f] 6.51-6.58 (m) 4-CH_3=2.24 (s)	2.93 (s)
3f [g]	4-NO_2	CH_3	8.03-8.09 (m) [h]	3.21 (c) [i]	1.76-1.84 (m)	3.44 (t) [j]	8.03-8.09 (m) [h] 6.54 (d) [k]	2.96 (s)

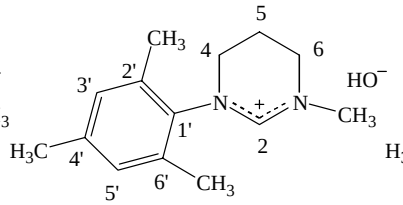
[a]=The reported signals correspond to the major *E/Z* diasteromer. [b] J=6.7 Hz, [c] J=6.8 Hz, [d] J=6.5 Hz, [e] J=6.6 Hz, [f] J=5.6 Hz, [g] N*H* 5.63 ppm, [h] overlapping signals, [i] J=6.4 Hz, [j] J=6.3 Hz, [k] J=9.2 Hz.

Chromatographic separation of such species was unsuccessful due to complete conversion to amino amides (**2**). Isolation of the intermediate was then attempted by elution of the less reactive mesityl derivative (**1d**) through a column containing anionic exchange resin (IRA 400, OH^-) in dry methanol. TLC analysis of the eluate evidenced a sole product with the same R_f as the third species previously detected during hydrolysis. A comparison of the ^{1}H NMR spectrum of the isolated species with salt (**1d**) and the corresponding hexahydropyrimidine (**6d**) taken as model compounds (Table 3), allowed us to assign the structure of tetrahydropyrimidinium hydroxide (**4d**) to the isolated intermediate. Such compound underwent slow conversion to amino amide (**2d**) on standing. Treatment of compounds (**1a-c**) with the exchange resin led to analogous results, although due to their higher reactivity, partial conversion to the corresponding amino amides (**2**) during work-up could not be avoided.

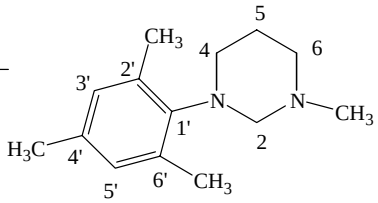
Table 3



1d



4d



6d

^{1}H NMR

Compd	2	4	5	6	Ar	R
1d	8.27 (s)	3.63 (t) [a]	2.36-2.44 (m)	3.75 (t) [b]	3',5'=6.91 (s) 2,6-$(CH_3)_2$=2.29 (s) 4-CH_3=2.26 (s)	3.56 (s)
4d	8.69 (s)	3.56 (t) [b]	2.34-2.39 (m)	3.67 (t) [c]	3',5'=6.92 (s) 2,6-$(CH_3)_2$=2.28 (s) 4-CH_3=2.26 (s)	3.60 (s)
6d	3.67 (s)	3.06 (t) [d]	1.78-1.84 (m)	2.62 (t) [a]	3',5'=6.81 (s) 2,6-$(CH_3)_2$=2.30 (s) 4-CH_3=2.24 (s) [e]	2.31 (s) [e]

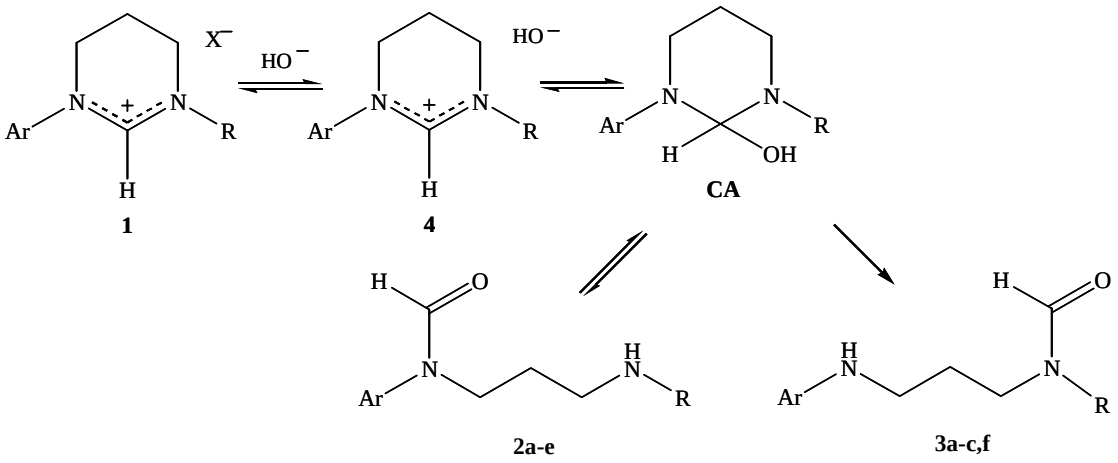
[a] J=5.7 Hz, [b] J=5.8 Hz, [c] J=5.9 Hz, [d] J=5.4 Hz, [e] Exchangeable assignment.

On the basis of our experimental results, alkaline hydrolysis of tetrahydropyrimidinium salts (**1**) involves initial anion exchange originating amidinium hydroxide (**4**). Previous to its cleavage, this ionic species must undergo hydroxide attack leading to the corresponding carbinolamine (Scheme 3), which was not evidenced spectroscopically maybe due to its low concentration.

In order to rationalize the regioselective cleavage of the intermediate carbinolamine to the kinetic product some factors must be considered, namely the relative leaving abilities of both groups (N1 and N3) and the selective stabilization of the transition state leading to the observed product. It is accepted that, due to

their strong basicity, nitrogen anions (RR´N$^-$) are poor nucleofuges and require proton transfer previous or simultaneous to their departure.[13] Selective cleavage with liberation of the most basic amine may then be the consequence of a thermodynamically favored proton transfer from the solvent to the more basic nitrogen (N3), which thus becomes the best leaving group.[14]

Scheme 3



Selective cleavage of C2-N3 bond can also be explained taking into account the stereoelectronic control theory advanced by Deslongchamps, which states that preferential cleavage of a tetrahedral intermediate is favored when there are two lone pairs antiperiplanar to a leaving group.[15] As a first approximation to evaluate the applicability of stereoelectronic control in our system, we studied the relative stabilities of the different conformations of the tetrahedral intermediate proposed for compound (**1a**) (Scheme 4). We assumed in our analysis an early transition state, resembling more the intermediate carbinolamine than its hydrolysis product. For this purpose, geometries corresponding to each conformation were optimised employing the *ab initio* 6-31G* method.[16] Heats of formation, as well as relative energies of conformations **A-H** are listed in Table 4.

As a result of microscopic reversibility, initial hydroxide attack on the amidinium system should lead to the intermediate in conformation **A**, with the hydroxyl group axial and antiperiplanar to N1 and N3 lone pairs, as in such conformation the inverse reaction (cleavage of C2-OH bond) is assisted by two antiperiplanar lone pairs. A similar preference was previously observed in the formation of related tetrahedral intermediates derived from the addition of hydride and carbon nucleophiles to 1,3-dimethyl-5-phenyltetrahydropyrimidinium salts.[10] Two processes are then possible for conformer **A**, namely ring reversal and/or nitrogen inversion (Scheme 4). Ring reversal would lead to conformations **E-H**, with the hydroxyl equatorial, which are disfavored by the anomeric effect.[17] This is in accordance with the results of our theoretical study, which predicts higher relative energies for such structures. Among the remaining conformations (**A-D**), conformer **D** can be discarded due to its high energy content derived from the steric

congestion associated to the presence of three axial substituents. Regarding structures **A-C**, the theoretical study predicts an energy difference in favour of conformation **C**, in which cleavage of C2-NCH_3 bond is assisted by two antiperiplanar lone pairs (one from oxygen and another from N1) (Scheme 4). However, the calculated ΔΔHf value is smaller than 1 Kcal mol^{-1} and could not, by itself, account for the observed regioselectivity, which would mainly be determined by relative basicities.

Scheme 4

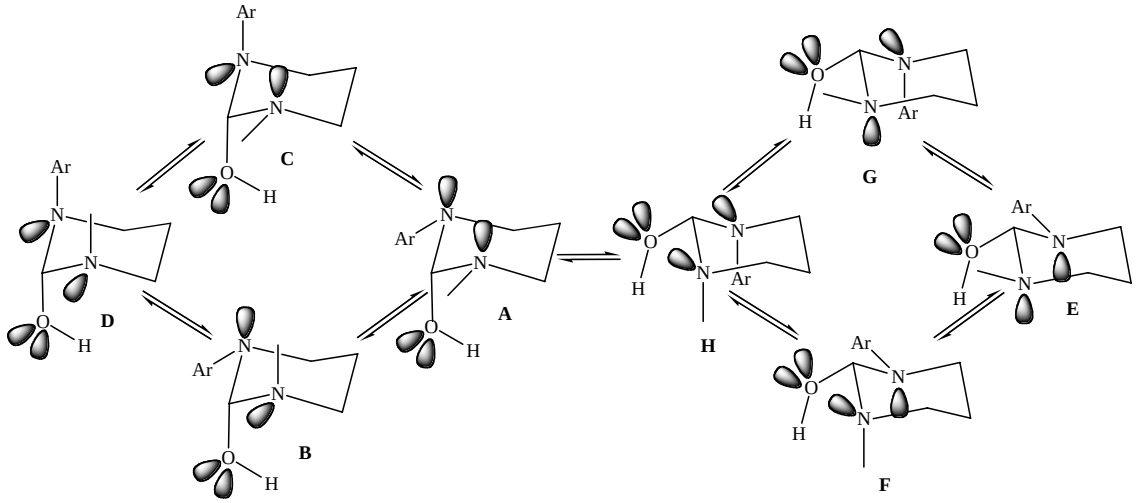


Table 4

Conformation	**ΔHf 6-31G***	**Relative Energies** [a] **(Kcal/mol)**
A	-609.605977	0.577
B	-609.605569	0.834
C	-609.608997	0
D	-609.596966	6.23
E	-609.603844	1.91
F	-609.597023	6.196
G	-609.600848	3.796
H	-609.588141	11.77

[a] With respect to conformation C

As previously said, kinetic products (**2a-c**) in the reaction medium undergo formyl migration affording amino amides (**3a-c**). Instead, for compounds (**2d,e**) such migration does no take place. It is accepted that rearrangement **2→3** results from intramolecular aminolysis and involves the formation of a tetrahedral intermediate.[12] Reaction rates would thus be enhanced by increasing nucleophilicity of the alkylamine and by higher reactivity of the amide carbonyl. The lower reactivity of compound (**2c**) with respect to **2a,b** would then be related to the electron releasing effect of the 4-methyl group, which renders the amide carbonyl less reactive. In line with this, the absence of formyl migration in the mesityl derivative (**2d**) can

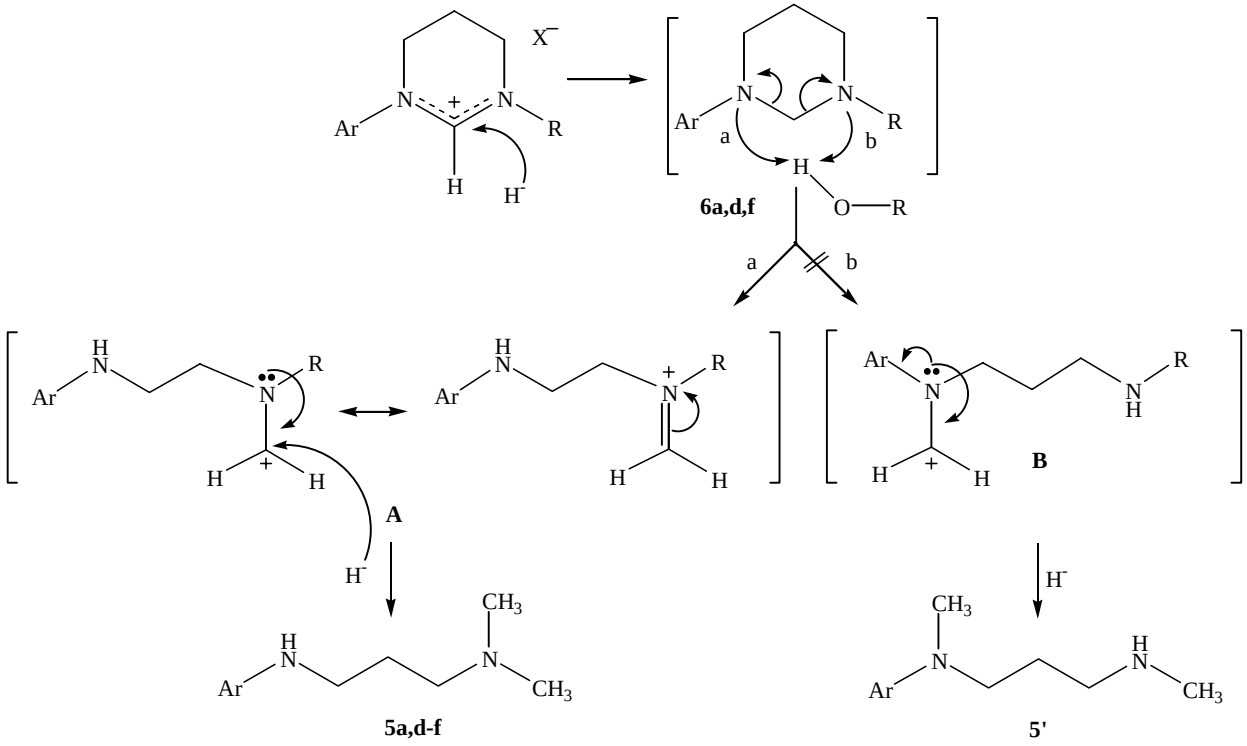
be attributed to a steric effect of the 2',6'-methyls, which forces the aryl substituent out of the plane of the amide group, inhibiting *N*-aryl electron delocalization and enhancing competitive N-CO resonance, thus rendering the amide moiety less reactive. The same rationale explains the stability towards amide hydrolysis observed for this compound. For compound (**2e**) formyl migration did not take place, even after prolonged reaction times. Steric hindrance of the *N*-*tert*-butyl substituent may impede nucleophilic attack to the amide, thus preventing tetrahedral intermediate formation. In this case, competitive amide hydrolysis leading to *N*-(4-chlorophenyl)-*N´*-*tert*-butyltrimethylenediamine was observed.

At variance with salts (**1a-e**), hydrolysis of compound (**1f**) afforded aminoamide (**3f**) as the only product, although TLC analysis evidenced an intermediate species which could not be isolated. This might be interpreted as the result of an initial cleavage towards a kinetic product followed by very fast formyl migration, attributable to the presence of a strongly electron withdrawing substituent which enhances the electrophilicity of the amide group. However, an alternative mechanism involving initial N1-C2 bond cleavage cannot be excluded.

Reduction of tetrahydropyrimidinium salts (**1a,d-f**) with an excess sodium borohydride in ethanol invariably led to the corresponding *N*-alkyl-*N´*-aryl-*N*-methyltrimethylenediamines (**5**) as the only products (Scheme 5). A similar behavior was previously observed in 1,2-diaryl-3-methyltetrahydropyrimidinium salts.[8] When reduction was carried out by gradually adding an equimolar amount of the reagent, salts (**1a,d,f**) afforded exclusively the corresponding hexahydropyrimidines (**6**) (Scheme 5), while compound (**1e**) originated a mixture of overreduction product (**5e**) and unreacted starting material. It is accepted that reduction of *N,N´*-disubstituted cyclic aminals occurs *via* intermediate iminium ions and requires previous proton transfer from the solvent to one of the nitrogen atoms.[18] Due to the asymmetric substitution of salts (**1**), in our case two isomeric diamines could, in principle, be expected (Scheme 5). However, our experimental results indicate that reduction of the hexahydropyrimidines is regioselective and would involve the more stabilized iminium ions **A**. The observed regioselectivity would thus be the consequence of two thermodynamically opposite processes, as it involves unfavorable proton transfer to the less basic amine and its subsequent liberation affording the most stable *N*-alkyliminium cation. The proposed reaction mechanism can also account for the unusual stability towards reduction of 2-unsubstituted hexahydropyrimidines (**6a,d,f**) with respect to the corresponding 2-aryl derivatives, which cannot be prepared by mild reduction of the corresponding amidinium salts.[8] The observed difference would be related to the additional stabilization of the intermediate iminium cations provided by the aryl substituent on C2 in the latter. Finally, overreduction of 3-*tert*-butyl derivative (**1e**) under mild conditions can be attributed to the instability of the intermediate

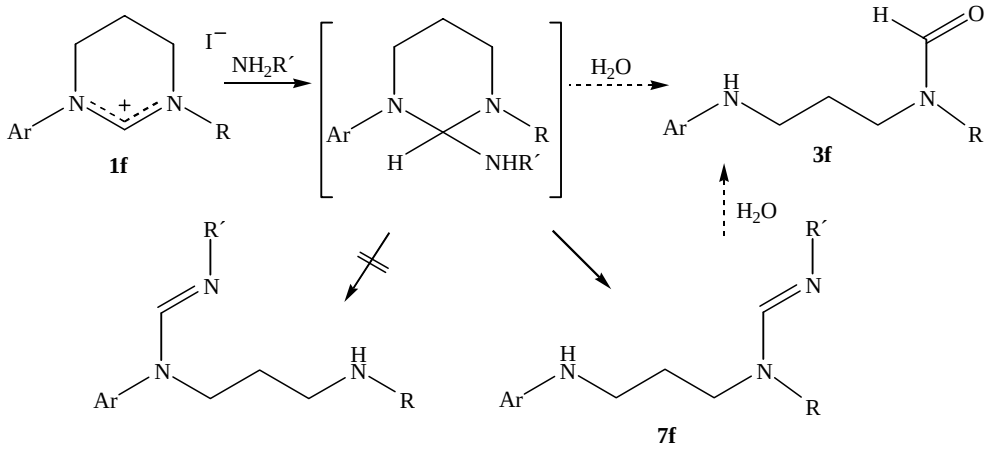
hexahydropyrimidine. Such characteristic would be related to its lability towards hydrolysis, which also involves an intermediate iminium cation.[19]

Scheme 5



Aminolysis of tetrahydropyrimidinium salts (**1**) was initially attempted by treatment of compound (**1c**) with an excess isopropylamine in dry methanol, but no reaction was observed. The same reaction was then conducted with the more reactive 4-nitro derivative (**1f**). TLC analysis of the reaction progress showed initial conversion of the substrate into a spot of lower R_f, which was then partially transformed to the corresponding hydrolysis product (**3f**). On the basis of its spectral data, the isolated compound was identified as the acyclic formamidine (**7f**).

Scheme 6



Accepting that aminolysis of amidinium salts involves initial formation of an intermediate cyclic triamine followed by prototropic ring opening, the experimentally observed product would result from regioselective C2-NAr cleavage with liberation of the less basic amine (Scheme 6). Compound (**3f**) could result from hydrolysis either of the cyclic orthoamide or of the acyclic formamidine (**7f**). Amino amides (**3b,f**) were obtained as the only products when salts (**1b,f**) were treated with sodium methoxide in methanol.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer with deuteriochloroform as the solvent unless otherwise indicated. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. J values are given in Hz. MS (EI) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out on aluminium silica gel 60 F_{254} sheets. Column chromatographies were performed on silica gel 60 (0.040-0.063 mm). Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

1,3-Disubstituted 1,4,5,6-tetrahydropyrimidinium salts (1) were synthesized by two methodologies previously reported.[1] Compounds (**1a,c,f**)[20] and (**1b,e**)[1] were described in the literature. Yields and physical data of new compounds are as follows.

1-(2,4,6-Trimethylphenyl)-1,4,5,6-tetrahydropyrimidine was obtained as an oil (78%);^{1}H NMR: δ 1.99-2.02 (m, 2H, C-CH_2-C), 2.22 (s, 6H, 2,6-CH_3), 2.28 (s, 3H, 4-CH_3), 3.33 (t, J=5.8 Hz, 2H, CH_2N), 3.44 (t, J=5.1 Hz, 2H, CH_2N), 6.91 (s, 1H, CH), 6.92 (s, 2H, aromatics); MS: m/z 202 ($M^{+\cdot}$). Anal. Calcd for $C_{13}H_{18}N_2$: C; 77.18, H; 8.97, N; 13.85. Found: C; 77.22, H; 8.94, N; 13.88.

1-(2,4,6-Trimethylphenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium iodide (1d) was obtained in 88% yield; mp 156-158^{o}C (dry isopropanol); ^{1}H NMR spectrum is reported in Table 3; ^{13}C NMR δ 18.55, 19.19, 20.99, 43.75, 45.56, 45.91, 130.08, 134.69, 136.37, 140.15, 153.63; MS: m/z 202 ($M^{+\cdot}$-ICH_3). Anal. Calcd for $C_{14}H_{21}N_2I$: C; 48.83, H; 6.10, N; 8.14. Found: C; 48.76, H; 6.03, N; 8.10.

Alkaline hydrolysis. General procedure

An aqueous solution of the corresponding tetrahydropyrimidinium salt (**1**) (50 mg in 10 mL) was treated with 1 mL (2.5 mmol) of 10% aqueous sodium hydroxide solution at 0 °C. After complete disappearance of the starting material was observed by TLC (chloroform:methanol 8:2), the reaction mixture was extracted with methylene chloride (2 x 10 mL). The organic phases were pooled, washed with water, dried over sodium sulfate and filtered. The solvent was then eliminated *in vacuo* at rt. Compounds (**2a-e**)

and (**3a-c,f**) were purified by flash chromatography employing mixtures of chloroform:methanol (10:0 to 8:2). ^{1}H NMR spectral data of compounds (**2**) and (**3**) are listed in Tables 1 and 2, respectively. Physical data and elemental analyses are as follows.

***N*-Phenyl-*N*-formyl-*N´*-methyltrimethylenediamine (2a)**

This compound was obtained as an oil, MS: m/z 192 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{16}N_2O$: C; 68.72, H; 8.39, N; 14.57, Found: C; 68.67, H; 8.46, N; 14.61.

***N*-(4-Chlorophenyl)-*N*-formyl-*N´*-methyltrimethylenediamine (2b)**

This compound was obtained as an oil, MS: m/z 226 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{15}N_2OCl$: C; 58.28, H; 6.67, N; 12.36, Found: C; 58.35, H; 6.62, N; 12.30.

***N*-Formyl-*N*-(4-methylphenyl)-*N´*-methyltrimethylenediamine (2c)**

This compound was obtained as an oil, MS: m/z 206 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_{18}N_2O$: C; 69.87, H; 8.80, N; 13.58, Found: C; 69.81, H; 8.88, N; 13.52.

***N*-Formyl-*N*-(2,4,6-trimethylphenyl)-*N´*-methyltrimethylenediamine (2d)**

This compound was obtained as an oil, MS: m/z 234 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{22}N_2O$: C; 71.76, H; 9.46, N; 11.95, Found: C; 71.69, H; 9.51, N; 11.88.

***N*-(4-Chlorophenyl)-*N*-formyl-*N´*-tert-butyltrimethylenediamine (2e)**

This compound was obtained as an oil, MS: m/z 268 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{21}N_2OCl$: C; 62.56, H; 7.88, N; 10.42, Found: C; 62.61, H; 7.85, N; 10.47.

***N*-Formyl-*N*-methyl-*N´*-phenyltrimethylenediamine (3a)**

This compound was obtained as an oil, MS: m/z 192 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{16}N_2O$: C; 68.72, H; 8.39, N; 14.57, Found: C; 68.79, H; 8.43, N; 14.61.

***N*-Formyl-*N*-methyl-*N´*-(4-chlorophenyl)trimethylenediamine (3b)**

This compound was obtained as an oil, MS: m/z 226 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{15}N_2OCl$: C; 58.28, H; 6.67, N; 12.36, Found: C; 58.33, H; 6.69, N; 12.30.

***N*-Formyl-*N*-methyl-*N´*-(4-methyl)phenyltrimethylenediamine (3c)**

This compound was obtained as an oil, MS: m/z 206 ($M^{+\cdot}$); Anal. Calcd for $C_{12}H_{18}N_2O$: C; 69.87, H; 8.80, N; 13.58, Found: C; 69.92, H; 8.85, N; 13.49.

***N*-Formyl-*N*-methyl-*N´*-(4-nitro)phenyltrimethylenediamine (3f)**

This compound was obtained as an oil, MS: m/z 237 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{15}N_3O_3$: C; 55.69, H; 6.37, N; 17.71, Found: C; 55.72, H; 6.42, N; 17.77.

The progress of the hydrolysis reactions was monitored chromatographically. For compounds (**1a-e**), in addition to salts (**1**), TLC analysis evidenced initially the corresponding tetrahydropyrimidinium hydroxides (**4a-e**) (R_f *ca.* 0.2), followed by amino amides (**2a-e**), and finally compounds (**3a-c**). In the

case of salt (**1f**), inmediately after the addition of the nucleophile TLC analysis showed the presence of aminoamide (**3f**) and a spot with R_f *ca.* 0.2 which could not be isolated.

Reaction time required for the complete disappearance of salts (**1**) was as follows: (**1a,e**) 60 min.; (**1b,f**) 40 min; (**1c**) *ca.* 5 h, (**1d**) *ca.* 24 h.

Isolation of the reaction intermediates. General procedure

A solution of the corresponding compound (**1**) in anhydrous methanol was eluted through a column loaded with the anion exchange resin (IRA 400/OH^-) suspended in the same solvent. The eluate was evaporated *in vacuo* at rt.

1-(2,4,6-Trimethylphenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium hydroxide (4d) was obtained as an oil; ^{1}H NMR spectral data are reported in Table 3; ^{13}C NMR: δ 17.93, 19.26, 20.96, 43.01, 45.38, 130.03, 136.56, 136.66, 139.93, 154.70; Anal. Calcd for $C_{13}H_{20}N_2O$: C; 70.87, H; 9.15, N; 12.72. Found: C; 70.91, H; 9.22, N; 12.75.

Compounds (**4a-c**) were isolated as mixtures containing small amounts of the corresponding aminoamides (**2**).

1-Phenyl-3-methyl-1,4,5,6-tetrahydropyrimidinium hydroxide (4a) ^{1}H NMR: δ 2.39-2.42 (m, 2H, C-CH_2-C), 3.41 (t, J=5.6 Hz, 2H, CH_2N), 3.54 (s, 3H, NCH_3), 3.98 (t, J=5.6 Hz, 2H, CH_2N), 7.32 (t, J=6.2 Hz, 1H, aromatics), 7.42-7.48 [a] (m, 2H, aromatics), 7.59 (d, J=8.2 Hz, 2H, aromatics), 8.57 (s, 1H, CH). [a]: signals partially overlapping with the corresponding amino amide (**2**).

1-(4-Chlorophenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium hydroxide (4b) ^{1}H NMR: δ 2.30-2.32 (m, 2H, C-CH_2-C), 3.56 (s, 3H, NCH_3), 3.58 (t, J=5.9 Hz, 2H, CH_2N), 3.89 (t, J=5.6 Hz, 2H, CH_2N), 7.40 (d, J=8.9 Hz, 2H, aromatics), 7.55 (d, J=8.9 Hz, 2H, aromatics), 9.32 (s, 1H, CH).

1-(4-Methylphenyl)-3-methyl-1,4,5,6-tetrahydropyrimidinium hydroxide (4c) ^{1}H NMR: δ 2.34 (s, 3H, 4-CH_3), 2.35-2.37 (m, 2H, C-CH_2-C), 3.57-3.61 (m, 5H, NCH_3 and CH_2N), 3.88 (t, J=5.6 Hz,2H, CH_2N), 7.22 (d, J=8.7 Hz, 2H, aromatics), 7.43 (d, J=8.7 Hz, 2H, aromatics), 9.15 (s, 1H, CH).

Attempted rearrangement of compounds (2d,e)

A solution of the corresponding amino amide (**2**) (40 mg in 10 mL) was treated with 1 mL (2.5 mmol) of 10% aqueous sodium hydroxide solution was left at rt for 1 week. TLC analysis of the reaction progress evidenced slow conversion of **2e** in a compound which was isolated and characterized as *N*-*tert*-butyl-*N*-(4-chlorophenyl)trimethylenediamine by comparison with an authentic sample.[20] No additional spots were detected. In the same conditions, compound (**2d**) was recovered unreacted.

Reduction of tetrahydropyrimidinium salts with sodium borohydride

Sodium borohydride 0.19 g (5 mmol) was added to a solution of the corresponding salt (**1**) (6 mmol) in dry ethanol (20 mL) at rt. The reaction was continued until evolution of gas stopped. The solvent was then evaporated *in vacuo* and the residue treated with water (5 mL) and extracted with methylene chloride (2 x 20 mL). The organic layers were combined, washed with water (5 mL), dried with sodium sulfate and filtered. The solvent was then evaporated *in vacuo*, affording compounds (**5**), which were purified by flash chromatography (chloroform:methanol 10:0 to 8:2). Yields and physical data and elemental analyses are as follows.

***N,N*-Dimethyl-*N´*-phenyl-1,3-propanediamine (5a)**

This compound was obtained as an oil (82%); ^{1}H NMR: δ 1.76-1.80 (m, 2H, C-CH_2-C), 2.24 (s, 6H, $N(CH_3)_2$), 2.39 (t, J=6.8 Hz, 2H, C$H_2$$N(CH_3)_2$), 3.17 (t, J=6.8 Hz, 2H, CH_2NAr), 6.61 (dd, J=8.8 and 0.9 Hz, 2H, aromatics), 6.68 (dt, J=6.9 and 0.9 Hz,1H, aromatics), 7.14-7.17 (m, 2H, aromatics); MS: m/z 178 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{18}N_2$: C; 74.11, H; 10.18, N; 15.71. Found: C; 74.18, H; 10.25, N; 15.67.

***N,N*-Dimethyl-*N´*-(2,4,6-trimethylphenyl)-1,3-propanediamine (5d)**

This compound was obtained as an oil (91%);^{1}H NMR: δ 1.77-1.81 (m, 2H, C-CH_2-C), 2.21 (s, 3H, 4-$CH_3C_6H_2$), 2.23 (s, 6H, CH_3), 2.25 (s, 6H, CH_3), 2.39 (t, J=5.8 Hz, 2H, C$H_2$$N(CH_3)_2$), 3.21 (t, J=5.8 Hz, 2H, CH_2NAr), 6.81 (s, 2H, aromatics); MS: m/z 220 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{24}N_2$: C; 76.31, H; 10.98, N; 12.71. Found: C; 76.38, H; 10.96, N; 12.75.

***N-tert*-Butyl-*N´*-(4-chlorophenyl)-*N*-methyl-1,3-propanediamine (5e)**

This compound was obtained as an oil (86%);^{1}H NMR: δ 1.10 (s, 9H, $C(CH_3)_3$), 1.79-1.83 (m, 2H, C-CH_2-C), 2.29 (s, 3H, NCH_3), 2.60 (t, J=6.2 Hz, 2H, C$H_2$$NC(CH_3)_3$), 3.15 (t, J=6.2 Hz, 2H, CH_2NAr), 6.50 (d, J=8.7 Hz, 2H, aromatics), 7.10 (d, J=8.7 Hz, 2H, aromatics); MS: m/z 254 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{23}N_2Cl$: C; 65.99, H; 9.10, N; 10.99. Found: C; 66.03, H; 9.13, N; 10.95.

***N,N*-Dimethyl-*N´*-(4-nitrophenyl)-1,3-propanediamine (5f)**

This compound had mp 59-61 ºC (ethanol/water) (88%);^{1}H NMR: δ 1.78-1.84 (m, 2H, C-CH_2-C), 2.26 (s, 6H, $N(CH_3)_2$), 2.44 (t, J=5.9 Hz, 2H, C$H_2$$N(CH_3)_2$), 3.29 (q, J=6.4 Hz, 2H, CH_2NAr), 5.30 (br s, exchangeable, 1H, NH), 6.47 (d, J=9.2 Hz, 2H, aromatics), 8.06 (d, J=9.2 Hz, 2H, aromatics); MS: m/z 223 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{17}N_3O_2$: C; 59.17, H; 7.67, N; 18.82. Found: C; 59.23, H; 7.73, N; 18.78.

When the reaction was carried out by adding 1.2 mmol (0.045 g) of sodium borohydride in portions and keeping the reaction mixture at –5 °C, and after the same work-up procedure, salts (**1a,d,f**) afforded exclusively the corresponding hexahydropyrimidines (**6**) with the following yields: **6a** 79%, **6d** 82%, **6f** 85%. Under the same reaction conditions, salt (**1e**) afforded a mixture of diamine (**5e**) and unreacted starting material.

1-Phenyl-3-methylhexahydropyrimidine (6a)

This compound was obtained as an oil; ^{1}H NMR: δ 1.74-177 (m, 2H, C-CH_2-C), 2.31 (s, 3H, NCH_3), 2.60 (t, J=5.5 Hz, 2H, CH_2NCH_3), 3.28 (t, J=5.6 Hz, 2H, CH_2NAr), 3.82 (s, 2H, NCH_2N) 6.96 (d, J=8.7 Hz, 2H, aromatics), 6.83, (t, J=7.2 Hz, 1H, aromatic), 7.25-7.29 (m, 2H, aromatics); MS: m/z 176 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{16}N_2$: C; 74.96, H; 9.15, N; 15.89. Found: C; 75.01, H; 9.20, N; 15.86.

1-(2,4,6-Trimethyl)phenyl-3-methylhexahydropyrimidine (6d)

This compound was obtained as an oil; ^{1}H NMR: δ 1.80-1.83 (m, 2H, C-CH_2-C), 2.24 (s, 3H, 4-CH_3), 2.30 (s, 6H, 2,6-CH_3), 2.31 (s, 3H, NCH_3), 2.62 (t, J=5.6 Hz, 2H, CH_2NCH_3), 3.06 (t, J=5.4 Hz, 2H, CH_2NAr), 3.67 (s, 2H, NCH_2N) 6.81 (s, 2H, aromatics), MS: m/z 218 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{22}N_2$: C; 77.01, H; 10.16, N; 12.83. Found: C; 77.05, H; 10.13, N; 12.79.

1-(4-Nitrophenyl)-3-methylhexahydropyrimidine (6f)

This compound was obtained as an oil; ^{1}H NMR: δ 1.75-178 (m, 2H, C-CH_2-C), 2.32 (s, 3H, NCH_3), 2.69 (t, J=5.6 Hz, 2H, CH_2NCH_3), 3.52 (t, J=5.6 Hz, 2H, CH_2NAr), 4.01 (s, 2H, NCH_2N) 6.86 (d, J=9.4 Hz, 2H, aromatics), 8.12 (d, J=9.4 Hz, 2H, aromatics); MS: m/z 221 ($M^{+\cdot}$); Anal. Calcd for $C_{11}H_{15}N_3O_2$: C; 59.71, H; 6.83, N; 18.99. Found: C; 59.78, H; 6.80, N; 18.93.

Aminolysis with isopropylamine

A solution of **1f** 1.10 g, (5 mmol) in dry methanol (5 mL) was treated with isopropylamine 0.59 g, (10 mmol). After disappearance of the starting material was disclosed by TLC, the solution was evaporated *in vacuo* and the residue purified by flash chromatography (chloroform:methanol:isopropylamine 100:0:0 to 90:9:1) affording a mixture of compounds (**7f**) and (**3f**) (*ca.* 40% and 60%, respectively). Under the same reaction conditions, salt (**1c**) was recovered unreacted.

***N*-(*N*-Isopropylformimidoyl)-*N*-methyl-*N´*-(4-nitrophenyl)-1,3-propanediamine (7f)**

This compound was obtained as an oil; ^{1}H NMR (CD_3OD): δ 1.29 (d, J=6.6 Hz, 2H, CH(CH_3)$_2$), 2.02-2.06 (m, 2H, C-CH_2-C), 3.03 (s, 3H, NCH_3), 3.29 (t, J=7.0 Hz, 2H, CH_2N), 3.66 (t, J=7.0 Hz, 2H, CH_2N), 3.75-3.78 (m, 1H, CH(CH_3)$_2$), 6.70 (d, J=9.2 Hz, 2H, aromatics), 8.05 (d, J=9.2 Hz, 2H, aromatics), 8.15 (s, 1H, CH); MS: m/z 278 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{22}N_4O_2$: C; 60.41, H; 7.97, N; 20.13. Found: C; 60.36, H; 8.03, N; 20.18.

Reaction with sodium methoxide

A solution of the corresponding salt (**1b,f**) (5 mmol) in dry methanol (20 mL) was treated with an excess sodium methoxide in the same solvent. After disappearance of the starting material, TLC analysis of the reaction mixture evidenced as the only products the corresponding aminoamides (**3b,f**), which were identified by comparison with authentic samples.

ACKNOWLEDGEMENTS

This work was supported by the Universidad de Buenos Aires and by CONICET.

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