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A general method is described for the synthesis of 1-aryl-2-alkyl-1,4,5,6-tetrahydropyrimidines **1**, by cyclization of *N*-acyl-*N'*-aryltrimethylenediamines **2** with trimethylsilyl polyphosphate. Precursors **2** were obtained by aminolysis of the corresponding *N*-(3-bromopropyl)amides **3**. The ^{1}H nmr spectra of tetrahydropyrimidines **1** are analyzed, discussing the influence of substituents in positions 1 and 2 of the heterocyclic ring. Alkaline hydrolysis of compounds **1**, which originates exclusively *N*-acyl-*N'*-aryltrimethylenediamines **2**, through an intermediate carbinolamine, was also studied. Cleavage of such an intermediate is discussed in the light of the stereoelectronic control theory. Reduction of compounds **1** with borane, leads regiospecifically to *N*-alkyl-*N'*-aryltrimethylenediamines **6**.

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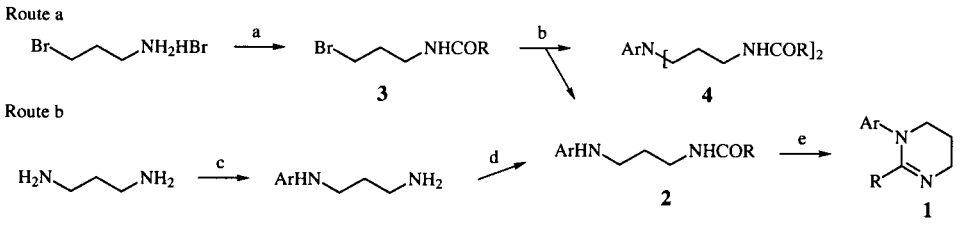
Introduction.

The synthesis of diversely substituted 1,4,5,6-tetrahydropyrimidines has been a subject of interest due to the biological activity presented by some members. The use of pyrantel and related compounds as antihelminthic agents dates from 1966 [1]. Modifications introduced in the pyrantel chemical structure allowed structure-activity relationships to be established for this family of compounds [2-6]. Other tetrahydropyrimidines have been assayed as nicotinic agonists [7], antidepressants [8] and also as bronchodilators [9] and gastric secretion inhibitors [10]. More recently, certain suitably substituted tetrahydropyrimidines have been used as M_1 selective muscarinic agonists acting at central nervous system level [11] and hold promise of therapeutic application for the treatment of Alzheimer's disease. Some of these pharmacological properties have been attributed to the fact that the cyclic amidinium group behaves as a bioisoster of the quaternary ammonium moiety of acetylcholine [12]. Besides, other publications have described numerous substances with the tetrahydropyrimidine nucleus exerting a fungicidal effect [13,14]. The compounds studied present an hydrogen atom or an alkyl substituent in position 1, but as the 1-aryl derivatives have not yet been studied for biological activity, it was of interest to develop a general method for their synthesis.

The classic synthesis method for the tetrahydropyrimidine nucleus involves the condensation of adequately substituted 1,3-diaminopropanes with carboxylic acids or their derivatives at high temperatures [15-21], but in many cases the preparation of such diamine precursors proves a limiting factor. Furthermore, global yields of the process are often conditioned by the high temperatures required for the cyclization. In previous work these drawbacks were circumvented through the development of a method for the synthesis of 1,2-diaryl-1,4,5,6-tetrahydropyrimidines [22]. In this work an extension of such a method is presented, by means of which 1-aryl-2-alkyl-1,4,5,6-tetrahydropyrimidines **1a-h** were synthesized (Table I) by ring closure of the corresponding *N*-acyl-*N'*-aryltrimethylenediamines **2**,

Scheme I

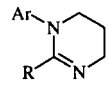


1, 2, 3, 4	Ar	R
a	*p*-ClC_6H_4	CH_3
b	*p*-ClC_6H_4	C_2H_5
c	*p*-ClC_6H_4	*iso*-C_3H_7
d	*p*-Cl C_6H_4	*tert*-C_4H_9
e	C_6H_5	*tert*-C_4H_9
f	*p*-$CH_3C_6H_4$	*tert*-C_4H_9
g	*p*-$CH_3OC_6H_4$	*tert*-C_4H_9
h	*p*-$NO_2C_6H_4$	*tert*-C_4H_9

[a] RCOCl or $(RCO)_2O/OH^-$; [b] 2 $ArNH_2$/toluene, 100-120°C, 1 hour; [c] *p*-chloronitrobenzene, 1 hour, reflux; [d] pivaloyl chloride/OH^-, room temperature; [e] trimethylsiyl polyphosphate/CH_2Cl_2, 1 hour, reflux.

Table I

1-Aryl-2-alkyl-1,4,5,6-tetrahydropyrimidines



1

Compound	Ar	R
1a	*p*-ClC_6H_4	CH_3
1b	*p*-ClC_6H_4	C_2H_5
1c	*p*-ClC_6H_4	*iso*-C_3H_7
1d	*p*-ClC_6H_4	*tert*-C_4H_9
1e	C_6H_5	*tert*-C_4H_9
1f	*p*-$CH_3C_6H_4$	*tert*-C_4H_9
1g	*p*-$CH_3OC_6H_4$	*tert*-C_4H_9
1h	*p*-$NO_2C_6H_4$	*tert*-C_4H_9

obtained from readily available strarting materials (Scheme I). The conditions in which the cyclization is carried out proved sufficiently mild so that this route seems applicable for the construction of the tetrahydropyrimidine system in more complex molecules.

Synthesis and Spectroscopic Properties.

The method implies the condensation of *N*-(3-bromopropyl)amides **3** with aromatic amines, followed by cyclization of the resulting *N*-acyl-*N'*-aryltrimethylenediamines **2** (Scheme I, route *a*). Haloamides **3** were obtained by acylation of 3-bromopropylamine hydrobromide with suitable acylating agents, with 85-90% yields in all cases. The subsequent aminolysis reaction was tested under a variety of experimental conditions, with the best results using toluene

Table II

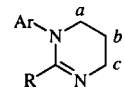
N-Acyl-N'-aryltrimethylenediamines **2d-h** [a]

Ar-NH-CH_2-CH_2-CH_2-NHCOR

Compound No.	Yield (%)	Mp (°C)	Formula	Analyses (Calcd./Found) %C	%H	%N	Mass ($M^{+\cdot}$) m/z	δ (ppm)	^{1}H nmr Multiplicity	Assignment
2d	65	84	$C_{14}H_{21}N_2ClO$	62.56	7.87	10.42	269	7.10	dd	2 *meta* H
				62.45	7.96	10.40		6.52	dd	2 *ortho* H
								6.00	bs (ex)	N*H*CO
								4.20	bs (ex)	N*H*Ar
								3.34	q	CH_2NHCO
								3.12	t	CH_2NHAr
								1.75	p	$CH_2CH_2CH_2$
								1.18	s	CH_3
2e	61	60	$C_{14}H_{22}N_2O$	71.76	9.46	11.95	234	7.22-7.09	m	2 *meta* H
				71.63	9.50	11.86		6.71	t	*para* H
								6.63	d	2 *ortho* H
								5.72	bs (ex)	N*H*CO
								4.11	bs (ex)	N*H*Ar
								3.35	q	CH_2NHCO
								3.15	t	CH_2NHAr
								1.77	p	$CH_2CH_2CH_2$
								1.17	s	CH_3
2f	63	62	$C_{15}H_{24}N_2O$	72.54	9.74	11.28	248	6.97	dd	2 *meta* H
				72.66	9.83	11.15		6.55	dd	2 *ortho* H
								6.00	bs (ex)	N*H*CO
								3.85	bs (ex)	N*H*Ar
								3.35	q	CH_2NHCO
								3.15	t	CH_2NHAr
								1.77	p	$CH_2CH_2CH_2$
								1.17	s	CH_3
2g	64	77	$C_{15}H_{24}N_2O_2$	68.15	9.15	10.60	264	6.77	dd	2 *ortho* H
				68.25	9.23	10.50		6.62	dd	2 *meta* H
								5.90	bs (ex)	N*H*CO
								4.02	bs (ex)	N*H*Ar
								3.32	q	CH_2NHCO
								3.14	t	CH_2NHAr
								1.76	p	$CH_2CH_2CH_2$
								1.18	s	CH_3
2h	82	100	$C_{14}H_{21}N_3O_3$	60.20	7.58	15.04	279	8.04	dd	2 *meta* H
				60.32	7.68	15.09		6.53	dd	2 *ortho* H
								5.95	bs (ex)	N*H*CO
								5.71	bs (ex)	N*H*Ar
								3.36	q	CH_2NHCO
								3.21	q	CH_2NHAr
								1.75	p	$CH_2CH_2CH_2$
								1.24	s	CH_3

[a] Compounds **2a-c** were described in the literature [48].

Table III
1-Aryl-2-alkyl-1,4,5,6-tetrahydropyrimidines **1a-h**



Compound No.	Yield (%)	Mp (°C)	Formula	Analyses (Calcd./Found) %C	%H	%N	Mass (M+·) m/z	Ir ν(cm-1)	1H nmr δ (ppm)	Multiplicity	Assignment
1a	77	oil	$C_{11}H_{13}ClN_2$	63.31	6.28	13.42	209	2930 (m)	7.30	dd	2 *meta* H
				63.22	6.38	13.46		1618 (s)	7.05	dd	2 *ortho* H
								1495 (s)	3.48 and 3.45	t	CH_2 *a* and *c*
								1078 (m)	1.95	p	CH_2 *b*
								835 (m)	1.70	s	CH_3
1b	81	oil	$C_{12}H_{15}ClN_2$	64.72	6.79	12.58	223	2950 (m)	7.25	dd	2 *meta* H
				64.80	6.86	12.49		1612 (s)	7.00	dd	2 *ortho* H
								1478 (s)	3.40	m	CH_2 *a* and *c*
								1060 (m)	2.00	q	CH_2CH_3
								830 (m)	1.90	p	CH_2 *b*
								0.90		t	CH_2CH_3
1c	80	oil	$C_{13}H_{17}ClN_2$	65.95	7.24	11.83	237	2960 (m)	7.30	dd	2 *meta* H
				66.13	7.32	11.90		1620 (s)	7.05	dd	2 *ortho* H
								1490 (s)	3.49 and 3.46	t	CH_2 *a* and *c*
								1080 (m)	2.34	m	$CH(CH_3)_2$
								840 (m)	1.90	p	CH_2 *b*
									1.01	d	$CH(CH_3)_2$
1d	82	88	$C_{14}H_{19}ClN_2$	67.05	7.64	11.17	251	2954 (s)	7.27	dd	2 *meta* H
				66.95	7.70	11.05		1615 (s)	6.96	dd	2 *ortho* H
								1485 (s)	3.57 and 3.36	t	CH_2 *a* and *c*
								1173 (s)	1.73	p	CH_2 *b*
								1089 (m)	1.04	s	CH_3
								849 (m)			
1e [a]	88	66	$C_{14}H_{20}N_2$	77.73	9.32	12.95	216	2954 (s)	7.30	m	2 *meta* H
				77.60	9.39	12.88		1589 (s)	7.14	t	*para* H
								1484 (s)	7.03	m	2 *ortho* H
								1170 (s)	3.56 and 3.38	t	CH_2 *a* and *c*
								748 (m)	1.73	p	CH_2 *b*
								663 (m)	1.03	s	CH_3
1f	81	69	$C_{15}H_{22}N_2$	78.21	9.63	12.16	230	2953 (s)	7.09	dd	2 *meta* H
				78.35		9.79	12.02	1620 (s)	6.92	dd	2 *ortho* H
								1508 (s)	3.53 and 3.32	t	CH_2 *a* and *c*
								1305 (m)	2.31	s	$ArCH_3$
								815 (m)	1.70	p	CH_2 *b*
									1.01	s	$C(CH_3)_3$
1g	81	60	$C_{15}H_{22}N_2O$	73.13	9.00	11.37	246	2960 (s)	6.98	dd	2 *meta* H
				73.25	9.17	11.26		1612 (s)	6.82	dd	2 *ortho* H
								1502 (s)	3.79	s	$ArOCH_3$
								1256 (s)	3.53 and 3.31	t	CH_2 *a* and *c*
								1045 (s)	1.73	p	CH_2 *b*
								849 (m)	1.00	s	$C(CH_3)_3$
1h	91	102	$C_{14}H_{19}N_3O_2$	64.35	7.33	16.08	271	2949 (m)	8.15	dd	2 *meta* H
				64.22	7.40	16.00		1592 (s)	6.96	dd	2 *ortho* H
								1490 (s)	3.52	m	CH_2 *a* and *c*
								1312 (s)	1.78	p	CH_2 *b*
								1070 (m)	1.10	s	CH_3
								849 (m)			
1i [b]									7.32	dd	C_6H_5, 2 *meta* H
									7.14-7.11	m	C_6H_5, *ortho and para* H
									7.03	dd	*p*-ClC_6H_4, 2 *meta* H
									6.73	dd	*p*-ClC_6H_4, 2 *ortho* H
									3.72-3.63	m	CH_2 *a* and *c*
									1.96	p	CH_2 *b*

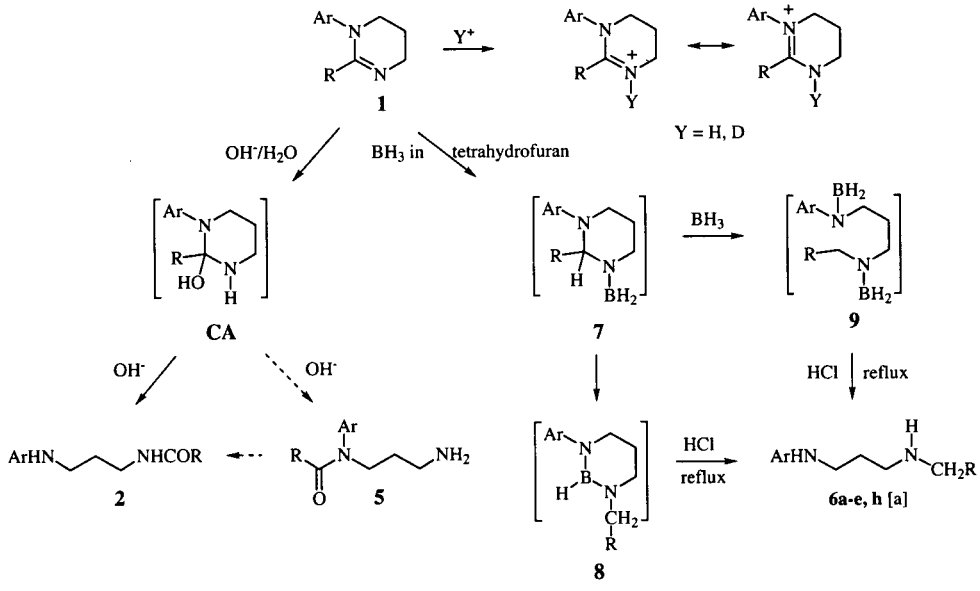
[a] Spectrum of compound **1e** run in the presence of trifluoroacetic acid-*d*: δ 7.25-7.51 (5H, m, aromatics); 3.68-3.65 (4H, m, CH_2 *a* and *c*); 2.14 (2H, p, CH_2 *b*), 1.15 (9H, s, CH_3). [b] Compound **1i** had been reported in previous work [22]. Reported data correspond to ^1H nmr spectrum of compound **1i**, run under the same conditions as compounds **1a-h**.

as the solvent in order to minimize production of *N,N*-bis(3-amidopropyl)arylamines **4**. This synthetic scheme was not applicable to derivatives having strong electron acceptors in the aryl moiety, due to low nucleophilicity of the corresponding arylamines. Thus, compound **3h** was synthesized by acylation of *N*-(*p*-nitrophenyl)trimethylenediamine, readily obtained through nucleophilic displacement of *p*-chloronitrobenzene (Scheme I, route *b*). Cyclization was performed with ethyl polyphosphate [23] and trimethylsilyl polyphosphate [24-26]. Due to its aprotic character, the latter is less prone to promote deacylation reactions, and led to better yields. Physical constants and spectroscopic data of *N*-acyl-*N'*-aryltrimethylenediamines **2a-h** and tetrahydropyrimidines **1a-h** are given in Tables II and III, respectively.

was observed when R = *tert*-butyl. In compound **1d,** the *a* and *c* methylene signals were sharply differentiated, one of the triplets being shielded and the other deshielded with respect to the mean value measured for **1a-c.** Furthermore, a small shielding effect on the *b* methylene was observed. Such findings cannot easily be explained on the basis of inductive or mesomeric effects. Distortion of molecular geometry (bond distances and angles) imposed by the *tert*-butyl substituent evidently modifies the spatial arrangement of the trimethylene chain with respect to the anisotropic groups present in the molecule, and may account for the observed shielding and deshielding effects.

Tentative assignment of *a* and *c* methylenes for 2-*tert*-butyl substituted tetrahydropyrimidines was made on the

Scheme II



1 **CA** **7** **9** **2** **5** **8** **6a-e, h [a]**

[a] Substituents Ar and R correspond to those indicated for compounds **1-4** in Scheme I.

The ^{1}H nmr spectra of the synthesized amidines **1** were analyzed to establish the influence of the substituents in positions 1 and 2 of the heterocyclic ring. To evaluate the effect of the substituent in C2, spectra of compounds **1a-d** were compared *inter se* and with the one corresponding to 1-(*p*-chlorophenyl)-2-phenyl-1,4,5,6-tetrahydropyrimidine **1i** (Ar = *p*-ClC_6H_4, R = C_6H_5) [22] (Table III). For compounds **1a-c**, *a* and *c* methylenes showed quite similar resonance frequencies, and appeared as partially or completely overlapping triplets centered at *ca.* 3.45 ppm. Replacement of the 2-alkyl by an aryl substituent (*i.e.* compound **1i**), shifted both methylene signals to lower fields approximately by the same amount (*ca.* 0.20 ppm), as a result of aromatic group anisotropy. A different effect

basis of differential shifts caused by 1-aryl substituents. For that purpose, chemical shifts of these groups were compared along the series **1d-h**. While electron donating or haloaryl substituents failed to affect substantially *a* and *c* methylene resonances, a significant downfield shift was observed in the lower frequency triplet ($\Delta\delta$ = 0.14 ppm) in 1-(*p*-nitrophenyl) derivative **1h**, which was therefore assigned as methylene *a*, due to contribution of structure **A**. Instead, the presence of the nitro group had little effect on the higher frequency signal which was thus assigned as methylene *c*. The **1e** spectrum, run in the presence of trifluoroacetic acid-*d*, showed downfield shifts of both signals, the lower frequency triplet proving more affected. This would suggest the proximity of such methylene group and N3, in contradiction to the

previous assignment. However, it has to be taken into account that in the cation (Scheme II), electron delocalization involves the entire amidinium system, thus affecting both methylene groups in an unpredictable way.

When the aromatic zone in the spectra of the 2-alkyl substituted tetrahydropyrimidines is compared with that of the corresponding 1,2-diaryl derivative **1i**, greater shielding of the 1-aryl *ortho* and *meta* hydrogen atoms is observed in the latter. This effect may be explained by considering that the steric tension caused by the presence of two aryl substituents at neighbouring positions of the heterocyclic ring leads to twisting of such groups with respect to the ring. Such spatial arrangement would cause the 1-aryl hydrogen atoms to be within the protection region of the 2-phenyl group. An alternative explanation, based on mesomeric effects, would predict an aryl substituent at C2 to participate in C=N bond electron delocalization, thus minimizing involvement of the N1 lone pair in the amidine system resonance. Therefore, electron donation (shielding effect) of N1 towards the aryl moiety would become more meaningful. However, an explanation based on anisotropy effects is more likely because an electron donating mesomeric effect should selectively influence *ortho* hydrogen atoms.

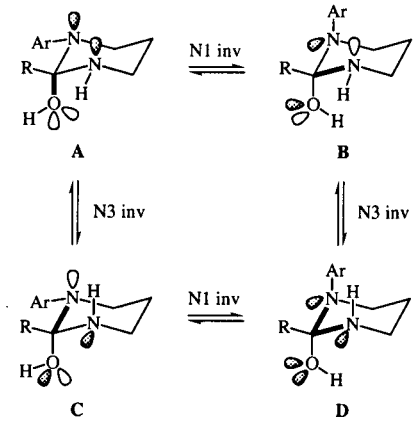
Chemical Properties.

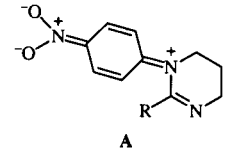
The behavior of compound **1e** was analyzed in basic aqueous medium. Alkaline hydrolysis led to the corresponding *N*-acyl-*N'*-aryltrimethylenediamine **2e**. For this type of reaction the formation is proposed of an intermediate carbinolamine **CA** (Scheme II), which would undergo selective cleavage of the N1-C2 bond. Another possibility would be initial fast cleavage of the C2-N3 bond, leading to **5** (Ar = C_6H_5, R = *tert*-C_4H_9), followed by an intramolecular aminolysis reaction, to originate the product of thermodynamic control, as observed in the alkaline hydrolysis of 1,2-diaryl-3-alkyl-1,4,5,6-tetrahydropyrimidinium salts [27] and their lower homologues [28]. Since proton transfer from the solvent to the nitrogen atom, either prior to or simultaneous with cleavage, is indispensable in reactions of this type [29,30], the first option seems unlikely since it would require proton transfer to the less basic amino group (N1).

Preferential initial cleavage of the more basic nitrogen atom bond (N3) would then seem more favorable. In fact, it would be expected that, as occurs in acyclic [30] and exocyclic amidines [31], relative basicity determines leaving group abilities, thus governing initial distribution of products [32-34]. However, our experimental observations disagree with this hypothesis, since **2e** was the only product detected. Indeed, when hydrolysis of **1e** was conducted at low temperature (0°-20°), tlc analysis only disclosed a mixture of starting and final products. On the other hand, the possibility of a **5** → **2** rearrangement occurring so fast as to preclude detection of **5** cannot be expected, since intramolecular aminolysis takes several days at room temperature to be completed for closely related compounds [27].

Selective cleavage of the C2-N3 bond can be explained bearing in mind the theory of stereoelectronic control advanced by Deslongchamps, which states that preferential cleavage of a tetrahedral intermediate occurs when there are two lone pairs antiperiplanar to a leaving group [35-37]. The intermediate carbinolamine **CA** and the changes the latter may undergo are indicated in Scheme III [38]. As a result of microscopic reversibility, initial hydroxide attack on the amidine should lead to the intermediate in conformation **A**, with the hydroxyl group axial and antiperiplanar to N1 and N3 lone pairs. Two phenomena are then possible for the initial conformer, namely ring reversal and nitrogen inversion. The former would lead to another chair conformation bearing an axial *tert*-butyl group, and can thus be excluded. Nitrogen inversion of N1, N3 or both, would lead to conformations **B**, **C** and **D** respectively. In conformation **D**, cleavage of both C-N bonds would be equally assisted by one nitrogen and one oxygen lone pairs, and would therefore lead to a mixture of products which is not observed experimentally. Steric interactions of an axial aryl group together with repulsion between the aryl group and the N3 lone pair [39,40] should strongly disfavor conformation **B**, in which cleavage of the C2-N3 bond would be assisted by two antiperiplanar electron pairs. Conformation **C**, in which steric and electronic repulsion are minimized, would lead to the observed product through cleavage of the N1-C2 bond. As a requirement for the application of the antiperiplanar hypothesis, conversion **A** → **C** should be faster than cleavage of the intermediate. Although in tertiary aliphatic amines nitrogen inversion is known to be a rather slow process [41-43], in secondary amines, the presence of an exchangeable hydrogen atom allows for alternative mechanisms for nitrogen inversion. In

Scheme III





A

particular, base or solvent catalyzed simultaneous deprotonation and reprotonation mechanisms are fast processes [44]. Therefore, an inversional change at N3 leading to conformer **C** can be expected to be faster than cleavage of the intermediate and would account for the observed results [45].

Reduction of tetrahydropyrimidines **1a-e,h** using borane as reducing agent was also studied (Scheme II). The reaction led regiospecifically to unsymmetrical *N,N'*-disubstituted 1,3-diaminopropanes **6a-e,h** with good yields. For this reaction we propose a mechanism that implies initial hydroboration of the double C=N bond, leading to the intermediate *N*-monoborane adduct **7**. As occurs in the reduction of benzothiazoles [46], this compound would undergo selective cleavage of the N1-C2 bond to originate borodiazine **8**, whose subsequent decomposition in the hydrolytic medium would yield products **6** (Scheme II). Compounds derived from boron such as **8** have been observed and characterized by ^{11}B nmr in reduction reactions of other heterocycles [46]. Alternatively, it may be supposed that selective cleavage takes place by reaction of **7** with a second molecule of borane, through the formation of **9**, similarly to what occurs in the reduction of amidines with diisobutylaluminium hydride [47].

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Bruker MSL 300 MHz spectrometer, using deuteriochloroform as the solvent. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard. Deuterium oxide was employed to confirm exchangeable protons (ex). Splitting multiplicities are reported as singlet (s), broad signal (bs), doublet (d), double doublet (dd), 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. The ir spectra were recorded on a Beckman 180A spectrometer. Samples were run as potassium bromide pellets for solids and films for oils. Analyses (tlc) were carried out on aluminium sheets Silica Gel 60 F_{254} using chloroform-methanol (9:1) as the solvent. Column chromatography was performed either on Silica Gel 60 (230-400 mesh) or on Aluminium Oxide (neutral, grade I, 70-230 mesh), with typically 30-50 g of stationary phase *per gram* of substance. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

N-(3-Bromopropyl)amides **3a-d**.

The title compounds were prepared by reaction of 3-bromopropylamine hydrobromide with a suitable acylating agent (acetic, propionic or isobutyric anhydrides and pivaloyl chloride) under Schotten Baumann conditions [48]. *N*-(3-Bromopropyl)-2,2-dimethylpropanamide **3d** had not been previously described in the literature. It was purified by column cromatography on aluminium oxide (ethyl acetate), mp 138°; ^1H nmr: δ 4.67 (2H, t, $BrCH_2$), 3.86 (2H, t, CH_2NHCO), 2.24 (2H, p, $CH_2CH_2CH_2$), 1.42 (9H, s, CH_3); ms: m/z 221 and 223 ($M^{+\cdot}$).

Anal. Calcd. for $C_8H_{16}BrNO$: C, 43.26; H, 7.26; N, 6.31. Found: C, 43.15; H, 7.20; N, 6.36.

N-Acyl-*N'*-aryltrimethylenediamines **2a-g**. General Procedure.

A mixture of the corresponding *N*-(3-bromopropyl)amide **3** (10 mmoles) and arylamine (20 mmoles) in toluene (20 ml) was heated under reflux for 1 hour protected from light. The reaction mixture was filtered to remove the precipitate, which was washed twice with toluene. The organic solutions were pooled and concentrated *in vacuo*. The crude products were purified by column chromatography using Silica Gel 60 (chloroform-ethyl acetate, 10:0 to 1:1). Compounds **2a-c** are described in the literature [48]. Yields, melting points, elemental analyses and spectroscopic data of new compounds **2d-g** are given in Table II.

The synthesis of compound **2f** was carried out under different conditions: without solvent and in benzene solution. The reaction run in the absence of a solvent led to 45% of compound **2f** and 15% of another compound, which was purified by column chromatography (Silica Gel, ethyl acetate) and identified as *N,N*-bis[3-(2,2-dimethylpropanamido)propyl]-*p*-methylaniline **4f**, mp 154°; ^1H nmr: δ 7.03 (2H, d, 2 *meta* H), 6.65 (2H, d, 2 *ortho* H); 5.88 (2H, bs, ex, NHCO), 3.32-3.24 (8H, m, $CH_2CH_2CH_2$), 2.24 (3H, s, Ar-CH_3), 1.75 (4H, p, $CH_2CH_2CH_2$), 1.16 (18H, s, $C(CH_3)_3$); ms: m/z 389 ($M^{+\cdot}$).

Anal. Calcd. for $C_{23}H_{39}N_3O_2$: C, 70.91; H, 10.09; N, 10.79. Found: C, 70.76; H, 10.18; N, 10.72.

The use of benzene as the solvent led to 51% of compound **2f** and 9% of **4f**.

N-(2,2-Dimethyl)propionyl-*N'*-(*p*-nitrophenyl)trimethylenediamine (**2h**).

Pivaloyl chloride (11 mmoles) was added to a chloroform solution of *N*-(*p*-nitrophenyl)trimethylenediamine [22] (10 mmoles), followed by 4% aqueous sodium hydroxyde solution (10 ml). The mixture was shaken for 30 minutes, after which the organic layer was separated, washed with water, treated with anhydrous sodium sulphate and filtered. The solvent was evaporated at reduced pressure to yield the crude product. Purification by column chromatography on Silica Gel 60 (ethyl acetate) afforded **2h** (82%). The physical and spectroscopic data of this compound are given in Table II.

1-Aryl-2-alkyl-1,4,5,6-tetrahydropyrimidines **1a-h**. General Procedure.

A mixture of the corresponding *N*-acyl-*N'*-aryltrimethylenediamine **2** (1g) and methylene chloride solution of trimethylsilylpolyphosphate [25] (20 ml) was heated under reflux for 5 hours. The reaction mixture was allowed to cool and then extracted with water (3 x 20 ml). Acid solutions were made alkaline with solid sodium carbonate. The mixture was extracted with methylene chloride (3 x 20 ml) and the organic layers were washed with water (5 ml) and dried over anhydrous sodium sulphate. The solution was concentrated *in vacuo* and the crude bases purified by column chromatography on Silica Gel 60 (methylene chloride-isopropylamine, 10:1) to afford compounds **1a-h**. Yields, melting points, elemental analyses and spectroscopic data of these compounds are given in Table III.

Alternatively, ethyl polyphosphate [23] was employed as a dehydrating agent, but yields were lower in all cases.

Alkaline Hydrolysis of 1-Phenyl-2-*tert*-butyl-1,4,5,6-tetrahydropyrimidine (**1e**).

Compound **1e** (1 mmole) was dissolved in aqueous sodium hydroxyde solution (10 ml) containing methanol (1 ml). The solution

was refluxed for 2 hours, after which it was extracted with methylene chloride (2 x 10 ml). The organic solution was washed with water (3 ml) and dried with anhydrous sodium sulphate. The solvent was evaporated affording compound **2e**, which was identified by comparison with an authentic sample. When the same reaction was performed at 0° (1 hour), the starting material was recovered unchanged. Hydrolysis at room temperature was monitored by tlc (chloroform-methanol 9:1, benzene-methanol 8:2 and chloroform-isopropylamine 10:1) using authentic samples of compounds **1e** and **2e** as standards. Following the reaction at different times, no spots attributable to any intermediate were detected. After 4 hours the reaction mixture contained **1e** (90 %) and **2e** (10 %).

N-Alkyl-*N'*-aryltrimethylenediamines **6a-e, h.** General Procedure.

Compounds **1a-e,h** (5 mmoles) were treated with borane in tetrahydrofurane (10 ml saturated solution) [49] and heated under reflux in a nitrogen atmosphere for 4 hours. The solvent was evaporated *in vacuo* and the residue boiled with concentrated hydrochloric acid (10 ml) for 30 minutes, after which solution was cooled. The acid solution was diluted with water (5 ml) and then made alkaline (pH = 12) with sodium hydroxide pellets. The mixture was extracted with chloroform (3 x 20 ml) and the organic layer was washed with water (5 ml) and dried with anhydrous sodium sulphate. The solution was concentrated *in vacuo* and the crude products purified by column chromatography on Silica Gel (chloroform-methanol 9:1). Compounds **6a-c** were described in the literature [48]. Yields, physical data and elemental analyses of new compounds are as follows:

N-(*p*-Chlorophenyl)-*N'*-(2,2-dimethylpropyl)trimethylenediamine (**6d**).

This compound was obtained in 80% yield, mp 82°; ^{1}H nmr: δ 7.09 (2H, dd, 2 *meta* H), 6.50 (2H, dd, 2 *ortho* H), 3.50 (1H, bs, ex, ArNH), 3.17 (2H, t, ArNHCH_2), 2.82 (2H, t, CH_2NHCH$_2$C$_4$H$_9$), 2.39 (2H, s, CH_2C$_4$H$_9$), 1.83 (2H, p, CH$_2$CH_2CH$_2$), 1.65 (1H, bs, ex, NHCH$_2$C$_4$H$_9$), 0.95 (9H, s, CH$_3$); ms: m/z 255 (M$^{+\cdot}$).

Anal. Calcd. for $C_{14}H_{23}ClN_2$: C, 65.99; H, 9.10; N, 10.99. Found: C, 66.10; H, 9.08; N, 10.90.

N-(2,2-Dimethylpropyl)-*N'*-phenyltrimethylenediamine (**6e**).

This compound was obtained as an oil (79%); ^{1}H nmr: δ 7.17 (2H, dt, 2 *meta* H), 6.69 (1H, dt, *para* H), 6.61 (2H, dd, 2 *ortho* H), 3.45 (1H, bs, ex, ArNH), 3.20 (2H, t, ArNHCH_2), 2.80 (2H, t, CH_2NHCH$_2$C$_4$H$_9$), 2.37 (2H, s, CH_2 C$_4$H$_9$), 1.84 (2H, p, CH$_2$CH_2CH$_2$), 1.33 (1H, bs, ex, NHCH$_2$C$_4$H$_9$), 0.95 (9H, s, CH$_3$); 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, 76.42; H, 11.07; N, 12.63.

N-(2,2-Dimethylpropyl)-*N'*-(*p*-nitrophenyl)trimethylenediamine (**6h**).

This compound was obtained as a yellow oil (82%); ^{1}H nmr: δ 8.05 (2H, dd, 2 *meta* H), 6.95 (1H, bs, ex, NHAr), 6.45 (2H, dd, 2 *ortho* H), 3.30 (2H, t, ArNHCH_2), 2.84 (2H, t, CH_2NHCH$_2$C$_4$H$_9$), 2.37 (2H, s, NHCH_2C$_4$H$_9$), 1.82 (2H, p, CH$_2$CH_2CH$_2$), 1.59 (1H, bs, ex, NHCH$_2$C$_4$H$_9$), 0.97 (9H, s, CH$_3$); ms: m/z 265 (M$^{+\cdot}$).

Anal. Calcd. for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.25; H, 8.86; N, 15.74.

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