Nucleophilic Addition to Substituted 1*H*-4,5-Dihydroimidazolium Salts

Alejandra Salerno, Vanina Ceriani and Isabel A. Perillo*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica,
Universidad Nacional de Buenos Aires, Junín 956, Buenos Aires, República Argentina

Received November 13, 1996

1*H*-4,5-Dihydroimidazolium salts **1** react readily with nucleophilic reagents originating cyclic products which may be stable or become transformed into acyclic compounds maintaining the structural ethylenediamine unit. With methylmagnesium iodide compound **1e** affords the expected imidazolidine, but in the case of substituted 1-aryl-3-methyl-2-phenyl salts **1b-d** the *N*-aryl-*N'*-methylethylenediamines **3b-d** and acetophenone (**4**) were isolated, the process representing the transfer of the C-2 unit to a nucleophilic carbon. With alkaline cyanides salts **1** react efficiently affording α,α-diaminonitriles **5**. In these compounds the cyano group may be readily substituted by nucleophiles (hydroxyl anion, species with nucleophilic carbon and reagents that act by hydride ion transfer), in a way similar to the salts but with better yields.

J. Heterocyclic Chem., **34**, 709 (1997).

The reaction of compounds **1** with aliphatic or arylalkyl amines probably involves decomposition of an intermediate orthoamide to yield, through the expulsion of the more basic amine, a benzimidoyl derivative (presumably *N*-aryl-*N*-(*N*-alkylbenzimidoyl)-*N'*-methylethylenediamines resulting from kinetic control detected by chromatography and spectroscopy. They then isomerize to the thermodynamically more stable *N*-(*N*-alkylbenzimidoyl)-*N'*-aryl-*N*-methylethylendiamines **9**.

Introduction.

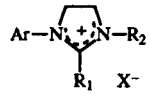
1*H*-4,5-Dihydroimidazolium salts with different types of substitution have been used as suitable models of the coenzyme N^5,N^{10}-methenyltetrahydrofolic acid promoting biochemical transfer of one carbon unit at the oxidation level of formic acid [1-3]. Thus, in attempts to mimic the biological process chemically reproducing the transfer of C-2, the reactions of various models with suitable nucleophilic reagents have been studied [4-13]. By analogy with the natural cofactor, in which the transferable carbon is linked to two nitrogen atoms with dissimilar electronic features [14], the results on asymmetrically *N*-substituted salts are noteworthy, particularly the reports of Pandit on 1-methyl-3-tosyl or acetyl derivatives [4,5], those of Saunders on 1-benzyl-3-methyl derivatives [6,7] and those of Benkovic on a complex imidazolinium salt derived from a tetrahydroquinoxaline analog model of the natural cofactor [8-10].

Furthermore, the value of 1*H*-4,5-dihydroimidazolium salts as synthetic precursors has been demonstrated [6,7,15-18]. In this connection, as part of our studies on substituted 1,2-diaryl-3-methyl salts we have reported that alkaline hydrolysis under conditions of kinetic control leads to *N*-aroyl-*N*-aryl-*N'*-methylethylenediamines which in neutral or alkaline media rearrange giving stable *N*-aroyl-*N'*-aryl-*N*-methylethylenediamines, compounds **6** (see below) [15-17]. On the other hand, the reaction with reducing agents acting *via* hydride transfer leads to imidazolidines or *N,N,N'*-trisubstituted ethylenediamines, compounds **7** and **8** (see below), depending on the type of reagent and on the substituents on the heterocyclic ring [18].

In order to provide an in depth study on such type of salts and to explore their usefulness as synthetic tools to obtain cyclic and acyclic compounds having the structural ethylenediamine unit (>N-CH_2-CH_2-N<), we have examined the reactions of a series of asymmetric 1,2-diaryl-3-methyl-1*H*-4,5-dihydroimidazolium salts **1a-d**, as well as the symmetric 1,3-diphenyl counterpart **1e** (Table I) with diverse nucleophilic reagents.

Table I

1*H*-4,5-Dihydroimidazolium Salts



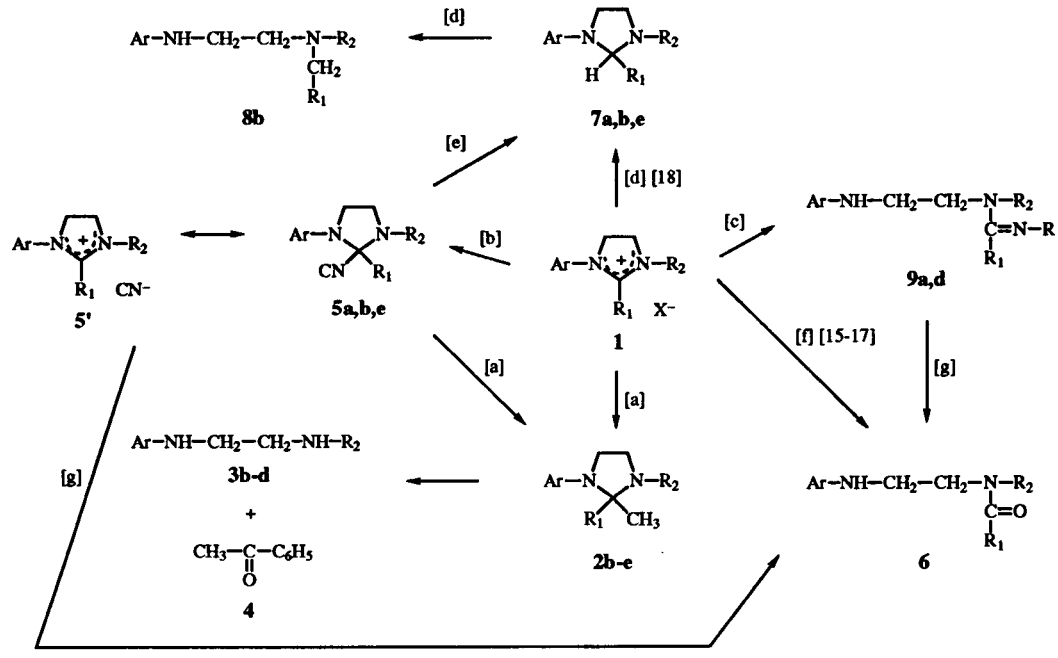
Compound	Ar	R_1	R_2	X^-
1a	*p*-$NO_2C_6H_4$	C_6H_5	CH_3	I^-
1b	C_6H_5	C_6H_5	CH_3	I^-
1c	*p*-$CH_3C_6H_4$	C_6H_5	CH_3	I^-
1d	*p*-$CH_3OC_6H_4$	C_6H_5	CH_3	I^-
1e	C_6H_5	H	C_6H_5	Cl^-

Results and Discussion.

Reactions of salts **1a-e** with Grignard reagents, potassium cyanide and amines are presented in Scheme I.

The reaction of a suspension of salts **1b-d** with methylmagnesium iodide in tetrahydrofuran leads in all cases to a first product presumed to be the 2,2-disubstituted imidazolidines **2b-d**, the one which was detected but could not be isolated. Work-up of the reactions leads with fair yields to *N*-aryl-*N'*-methylethylenediamines **3b-d** and acetophenone (**4**), the process representing the transfer of a phenyl substituted one-carbon unit from the salt to a reagent with a nucleophilic carbon. As secondary products, small quantities of the corresponding 1,2-diaryl-1*H*-4,5-dihydroimidazoles

Scheme I



Compounds 1-9	Ar	R_1	R_2
a	*p*-$NO_2C_6H_4$	C_6H_5	CH_3
b	C_6H_5	C_6H_5	CH_3
c	*p*-$CH_3C_6H_4$	C_6H_5	CH_3
d	*p*-$CH_3OC_6H_5$	C_6H_5	CH_3
e	C_6H_5	H	C_6H_5

[a] CH_3MgI/THF; [b] KCN; [c] R-NH_2 (R = i-C_3H_7, CH_2–C_6H_5); [d] $NaBH_4$/EtOH; [e] $LiAlH_4$/THF or $NaBH_4$/silica gel ($CHCl_3$) or EtOH; [f] NaOH/H_2O; [g] H_2O.

(demethylated product) are obtained, resulting from methyl activation in the course of SN_2 displacements. From the reaction of **1e** with methylmagnesium iodide, the expected 1,3-diphenyl-2-methylimidazolidine (**2e**) was isolated.

The behavior of salts **1** with alkaline cyanides was studied using as substrate compounds **1a,b,e**. The reaction of nitrophenyl derivative **1a** with potassium cyanide in anhydrous ethanol at room temperature afforded a yellow solid that crystallized in the reaction medium and to which the structure of the α,α-diaminonitrile **5a** was assigned by elemental analysis and spectroscopic data. On the other hand, in the case of the salts **1b** and **1e**, *N*-benzoyl-*N*-methyl-*N'*-phenylethylenediamine (**6b**) and *N*-formyl-*N,N'*-diphenylethylenediamine (**6e**) alone, respectively, were obtained under the same conditions. These products may have originated by alkaline hydrolysis of the starting salt or else from the expected products **5b,e** as a result of the alkaline medium generated by the relatively basic nature of the cyanide and traces of moisture which was difficult to eliminate from the reaction medium. In order to avoid hydrolytic processes, the reaction was carried out using potassium cyanide adsorbed on aluminum oxide [19,20] in a non-hydroxylic solvent (anhydrous methylene chloride). Under these conditions products **5b** and **5e** were obtained. Good results were also achieved by rapidly agitating a solution of the salt in a mixture of water and ether, in order to extract the products **5** as soon as they were formed. This would indicate that hydrolysis occurs preferably on the reaction product.

The uv spectral study of **5a** indicates that its structure varies according to the nature of the solvent (Table II). In non-polar or poorly polar solvents, the compound appears to have predominantly the covalent structure proposed for **5**. Thus, in solvents such as *n*-hexane, carbon tetrachloride, benzene and even chloroform and tetrahydrofuran, absorptions are similar to those of *N*-methyl-*N'*-(*p*-nitrophenyl)-ethylenediamine (**3a**) and 1-methyl-2-phenyl-3-(*p*-nitrophenyl)imidazolidine (**7a**), which absorb at a wavelength close to the visible range (λ *ca.* 350 nm) due to the presence of the *p*-nitroaniline moiety (Table II). In protic polar solvents, the presence of a maximum at about 300 nm coincides with salt **1a** and discloses its strong ionic character. Since only a single species is detected by chromatography, the cyano product may be considered as a hybrid resonating between limiting covalent **5** and ionic **5'** structures. In terms of valence bonds, the contribution of the ionic structure is responsible for the different degree of ionic character of the C-CN bond and would be consistent with the increase in

Table II

UV Spectroscopy Data for Compounds **1a**, **3a**, **5a** and **7a** in Different Solvents

Compound	Solvents (Dielectric Constant)						
	n-hexane (D = 1.89)	carbon tetrachloride (D = 2.24)	benzene (D = 2.28)	chloroform (D = 4.80)	1-butanol (D = 17.80)	methanol (D = 33.0)	water (D = 39.0)
	λmáx (nm) log ε	λmáx (nm) log ε	λmáx (nm) log ε	λmáx (nm) log ε	λmáx (nm) log ε	λmáx (nm) log ε	λmáx (nm) log ε
5a	[a]	348 3.95	352 4.17	356 4.30	295 4.03	295 4.03	[b]
1a	[a]	[a]	[a]	300 4.13	304 4.13	309 3.98	318 4.10
3a [15]	[a]	358 3.94	379 4.07	388 4.09	399 4.12	389 4.11	400 4.08
7a [15]	335 3.88	345 3.90	355 4.22	360 3.99	360 4.24	361 4.29	365 4.25

[a] The insolubility of the species in the solvent do not allow the uv spectrum to be observed. [b] The uv spectrum could not be determined due to the ease of hydrolysis of this compound.

such character upon increasing solvent polarity [21], as shown by the hypsochromic shift observed. In terms of molecular orbital theory, the same finding could be described as the result of an orbital interaction n → σ* between the non-linked electron pair of the heteroatom and the vacant σ* orbital of the C-CN bond [21,22].

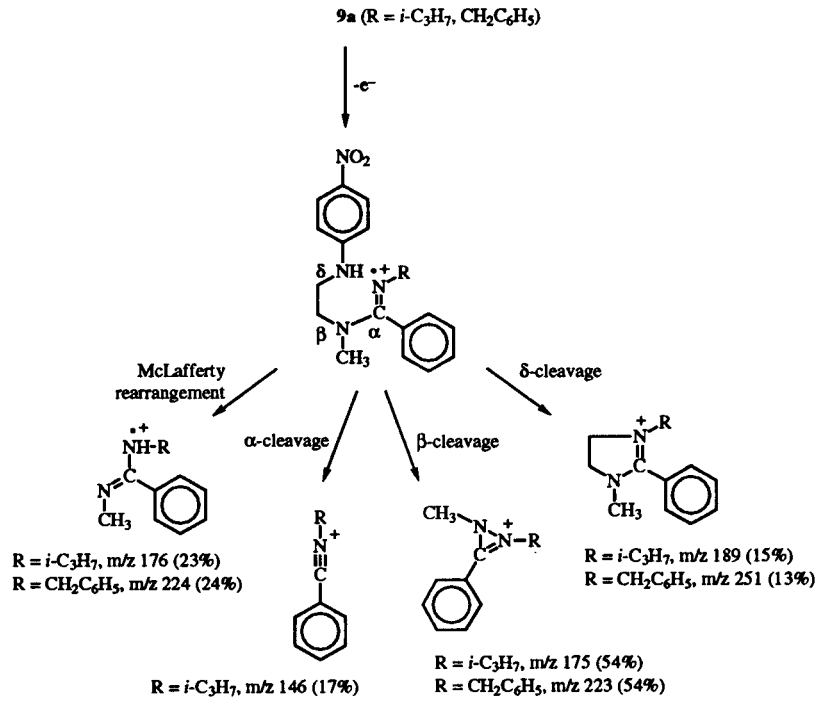
The ^{1}H nmr spectra of **5a** and **5b** in deuteriochloroform are also compatible with the covalent structure. While as a result of the planar (or almost planar) character of the salts methylene hydrogen atoms in compounds **1** are observed as symmetrical multiplets (AA'BB' system) centered on δ = 4.7-4.9 ppm [15,16], the signals corresponding to the methylenes of **5a** and **5b** appear as more shielded complex multiplets (δ *ca.* 3.2-4.3 ppm). This is typical of the 1,2-diaryl-3-methylimidazolidines where the four hydrogen atoms are dissimilar [18]. Likewise, chemical shifts of N-CH_3 hydrogen atoms of cyanoaminals (δ *ca.* 2.35 ppm) are similar to those of the corresponding imidazolidines (δ = 2.40) [18] and differ from those of the salts (δ = 3.25) [15-17] in which a marked paramagnetic shift arising from low electron density on the nitrogen atom is observed.

Gaseous and solid state spectra also indicate a covalent structure. The ir spectrum of **5a** in potassium bromide fails to present the strong absorption at 1620-1669 cm^{-1}, corresponding to stretching C-N of the amidinium system [15-17] [24]. In the mass spectrum under electron impact, the base peak corresponds to the M^+ ion (m/z = 308), which is remarkably stable [26].

Some chemical properties of compounds **5a,b,e** obtained were studied. Reaction with mineral acids was found to regenerate salts **1**. On the other hand, the cyano group may be readily substituted by several types of nucleophiles providing cyclic compounds which may undergo subsequent transformation. Hydrolysis may be carried out simply by treatment with water and leads, as in compounds **1**, to the acyclic *N*-acylethylenediamines **6** probably through the carbinolamine (**A**, Nu = OH) [28]. With reducing agents acting *via* hydride transfer (lithium aluminum hydride in tetrahydrofuran and sodium borohydride under different conditions), imidazolidines **7** (**A**, Nu = H) are obtained in good yields, though in the case of **7b** with sodium borohydride in ethanol partial over-reduction may be observed. Likewise, **5b** and **5e** reacts efficiently with methylmagnesium iodide producing as main products **3b** and **4** in the first case and **2e** in the second, with better yields that in the case of the corresponding salts [29]. This is probably due to the greater solubility of the compounds **5** in ethers which allows working in homogeneous media. Thus, the preparation of compounds **5** and their subsequent reaction with nucleophiles is a valuable synthetic alternative when direct attack of the nucleophile on the salt is hindered by the low solubility of the latter in the reaction solvent.

When compound **1a** was treated with aromatic or secondary aliphatic amines in various reaction conditions, it remained unchanged. On the other hand, the reaction with an excess of primary aliphatic or arylalkyl amines (isopropylamine and benzylamine), led in each case to single products which were isolated as yellow crystalline solids. Assuming that the aminolysis of the salt could proceed in a way similar to hydrolysis [15-17], three possible structures were considered for these compounds: the cyclic triamino derivative **I** (**A**, Nu = NHR), corresponding to the simple adduct analogous to the carbinolamine of hydrolysis, or the two possible acyclic benzimidoyl derivatives **II** and **III** resulting from the rupture of one of the C-N bonds. The orthoamide structure **I** was ruled out on the basis of chemical and spectroscopic evidence [31]. The appearance of a band at 1635 cm^{-1} in the ir spectrum and a signal at 165 ppm in the ^{13}C nmr spectrum discloses the presence of a C=N group and validates the open structure of a benzimidoyl derivative **II** or **III** consistent with data corresponding to ^{1}H nmr spectra in which methylene hydrogens present as triplets characteristic of a AA'BB' pattern, typical of open chain compounds. The presence in this

Scheme II

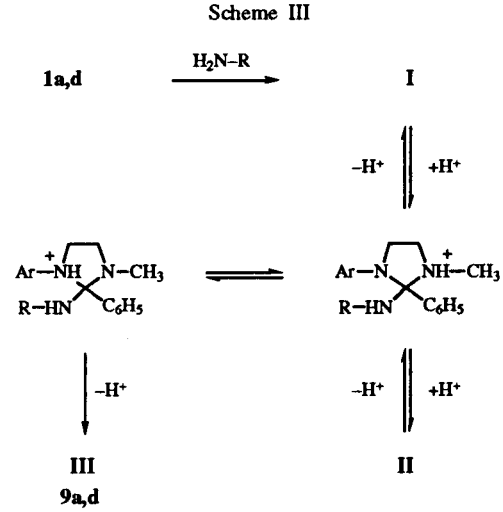


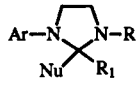
spectrum of a broad singlet at $\delta = 7.8$ that disappears by deuteration (*p*-nitroaniline hydrogen), and the similarity in chemical shifts of methylene and methyl groups to those of related acyclic compounds such as the benzamide **6a** [15], allow the proposed structure **III**, compound **9a** (R = *i*-C_3H_7, CH_2-C_6H_5) to be assigned to the products obtained by aminolysis. Structure **III** was likewise supported by the characteristic electron-impact induced fragmentation pattern in the mass spectra (Scheme II).

With regards to the origin of the products, the following considerations seem pertinent. Given the reactivity of 1*H*-4,5-dihydroimidazolium salts [15], the first precursor must be the cyclic orthoamide **I** (**A**, Nu = NHR), resulting from the attack of the amine nitrogen on the electrophilic C-2 of the salt. This could be transformed directly into the final product **III**, or else, to originate compound **II** in conditions of kinetic control, which would isomerize rapidly to **III**, through a transamidination reaction (Scheme III). In order to detect any intermediate, the reaction was performed in the cold maintaining the amine in defect. However, no intermediate could be detected by monitoring the reaction by tlc.

Taking into account that in related isomerizations involving acyl migrations in *N*-acyl-*N*-aryl-*N'*-methylethylene-diamines the rate of rearrangement increases upon reducing the basicity of the aryl nitrogen [37], an attempt was made to detect a similar rapid rearrangement by examining the aminolysis reaction of a salt with a strongly electron-donor group in the aryl group. The reaction of compound **1d** with an excess of benzylamine at room temperature afforded an oil whose spectroscopic features correspond to structure **III**, compound **9d** (R = CH_2-C_6H_5). On the other hand, when the amine was added slowly at 0° and the reaction monitored by tlc, two products of lower Rf that the final product were initially detected, presumably the triamino

Scheme III

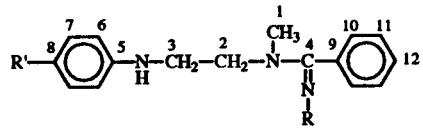




A Nu = OH, NHR, H

Table III

^{13}C Chemical Shifts Assignment of Compounds **9** (ppm) [a]

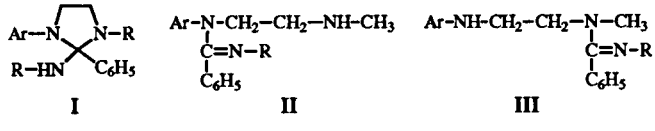


Compound	C-1	C-2	C-3	C-4	C-5	C-6	
9a	39.6	48.5	52.3	165.1	152.4	111.2	
R' = NO_2, R = CH_2	C-7	C-8	C-9	C-12	C-13	C-14	C-10, C-11, C-15-C-17
	130.1	138.0	132.7	131.2	41.8	136.3	125.0, 125.5, 126.5, 126.6, and 127.8
	C-1	C-2	C-3	C-4	C-5	C-6	C-7
9a	39.5	50.2	52.3	164.1	152.2	110.3	129.1
R' = NO_2, R = HC-$(CH_3)_2$	C-8	C-9	C-10	C-11	C-12	C-13	C-14
	137.1	132.29	126.17	125.4	130.14	50.7	23.1
	C-1	C-2	C-3	C-4	C-5	C-6	C-7
9d	39.7	48.2	52.1	164.2	141.3	113.3	115.2
R' = OCH_3, R = CH_2	C-8	C-9	C-12	C-13	C-14	C-18	C-10, C-11, C-15-C-17
	152.3	132.4	130.9	42.5	135.8	55.4	125.1, 126.4, 126.5 127.3, and 128.9

[a] Assignments were made on the basis of literature data for attached proton test and fully coupled ^{13}C nmr spectra.

derivative **I** and the benzimidoyl derivative **II**. Attempts to isolate them by tlc failed, **9d** being obtained in all cases. The ^1H nmr spectrum of the reaction mixture after 10 minutes showed a detectable signal at δ *ca.* 1.5, that disappeared by deuteration, presumably the hydrogen atom of the secondary aliphatic amine suggesting the presence of structure **II**. Bearing in mind these results and related data [9], we propose that the equilibria indicated in Scheme III would lead to the final product. Since the expulsion of nitrogen invariably requires addition of a proton, so that the leaving group is the free amine rather than the unstable amine anion [9,11,38], after initial formation of adduct **I** the preferred mode of decomposition would be governed by protonation of the more basic nitrogen atom (prototropic control). Thus, the benzimidoyl derivative **II** (product of kinetic control) which could not be isolated, would be formed. The transamidination reaction would then occur as a result of an unfavorable proton transfer process in the orthoamide **I** with subsequent expulsion of the less basic amine to give rise to the more stable and thermodynamically favored amidine **III**, compound **9**.

On the basis of the findings in this work, as well as in previous reports, it may be concluded that the reactions of



I **II** **III**

R = $CH(CH_3)_2$, CH_2–C_6H_5

dihydroimidazolium salts **1** take place as a result of the initial attack of the nucleophilic center on the electrophilic C-2 originating a tetrahedral species which may be stable, or else undergo transformation into acyclic compounds.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded on a Beckman 180A spectrometer. Samples were run as potassium bromide pellets for solids and films for oils. The ^1H nmr spectra were obtained on a Bruker MSL 300 Hz spectrometer using deuteriochloroform as solvent. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Signals are quoted as: s (singlet), d (doublet), t (triplet), m (multiplet) and bs (broad signal). The presence of exchangeable protons was confirmed by use of deuterium oxide. Mass spectra were recorded on a MS Shimadzu QP-1000 instrument at 20 ev. The uv spectra were recorded on a Jasco 7850 UV-VIS spectrophotometer. Analytical tlc was carried out on aluminium sheets Silica Gel 60 F_{254} using benzene-methanol (9:1) as the solvent. Column chromatography was carried out Silica Gel 60 (79-325 mesh). Preparative thin layers separations (plc) were performed on Silica Gel PF_{254} on 20 x 20 x 0.25 cm layers. Samples used as reference compounds were synthesized and purified according to literature procedures.

1*H*-4,5-Dihydroimidazolium Salts **1**.

Compounds **1a** [15], **1b** [17], **1c** [16], and **1d** [16] were obtained by treatment of the corresponding 1*H*-4,5-dihydroimidazole with

methyl iodide. Compound **1e** [13] was prepared by cyclization of *N*-formyl-*N*,*N'*-diphenylethylenediamine with 6*N* hydrochloric acid.

Reaction of Compounds **1b-e** with Methylmagnesium Iodide.

A solution of methylmagnesium iodide (from 9 mmoles of magnesium, 9 mmoles of methyl iodide and 35 ml of tetrahydrofuran) was prepared in the usual way, and 3 mmoles of compounds **1b-e** were added all at once as a powder. The mixture was stirred at room temperature and the reaction monitored by tlc. Together with compounds **1** (Rf *ca.* 0.2) two additional spots (Rf *ca.* 0.5 and 0.7) were detected. When salts **1** were no longer detectable (*ca.* 3 hours), the reaction was quenched by adding concentrated solution of ammonium chloride (20 ml). After stirring for 1 hour, the reaction mixture was extracted with ether. The organic layer was washed with water, dried and concentrated. The crude product obtained from compounds **1b-d** showed three spots by tlc (Rf *ca.* 0.2, 0.5 and 0.8) but no traces of compound of Rf *ca.* 0.7. Separation of the products was achieved by column chromatography eluting with chloroform-methanol (9:1). Appropriate fractions were pooled and evaporated to dryness affording acetophenone (**4**) (30-40%), *N*-aryl-*N'*-methylethylenediamines (**3b-d**) (30-40%) and 1,2-diaryl-1*H*-4,5-dihydroimidazoles (5-8%) which were identified by comparison with authentic samples [39].

In the case of the reaction involving compound **1e**, the crude product showed a single spot (Rf 0.75). Solvent removal afforded the imidazolidine **2e**, mp and mixed mp with an authentic sample [41] 97° (ethanol).

Reaction of 1*H*-4,5-Dihydroimidazolium Salts **1a,b,e** with Potassium Cyanide.

A.

Potassium cyanide in absolute ethanol (saturated solution, 3 ml), was added to compound **1a** (0.001 mole) in absolute ethanol (3 ml). After 5 minutes the yellow precipitate was collected affording 2-cyano-1-methyl-3-(*p*-nitrophenyl)-2-phenylimidazolidine (**5a**) (75%), mp 130°; ir: ν 2900 (C-H), 2750 (C-H), 1600 (C=C), 1370 (C-NO_2), 1310 (C-N), 935 (imidazolidine), 920 (imidazolidine) and 720 (C_6H_5) cm^{-1}; ^1H nmr: δ 8.10 (d, 2H, NO_2-C_6H_4, 2 *ortho* H), 7.35 (s, 5H, C_6H_5), 6.80 (d, 2H, NO_2-C_6H_4, 2 *meta* H), 4.30-3.20 (m, 4H, CH_2-CH_2), 2.30 (s, 3H, CH_3); ms: m/z 308 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.23; H, 5.19; N, 18.18. Found: C, 66.13; H, 5.24; N, 18.25.

Attempts to crystallize **5a** from 96° ethanol afforded **6a** [15].

Reaction of compounds **1b** and **1e** under the same conditions as above afforded *N*-benzoyl-*N*-methyl-*N'*-phenylethylenediamine (**6b**) [17] and *N*-formyl-*N*,*N'*-diphenylethylenediamine (**6e**) [13] respectively which were identified by comparison with authentic samples.

B.

To a stirred solution of compounds **1a,b,e** (0.001 mole) in anhydrous methylene chloride (15 ml), potassium cyanide supported on alumina (3 g) [19,20] was added in two portions at 10 minute intervals. Stirring was continued at room temperature for 30 minutes and the reaction followed by tlc. When transformation **1** → **5** was achieved the reagent was filtered, washed with anhydrous methylene chloride and the filtrate concentrated *in vacuo* keeping the reaction flask in a water bath at 18-20°, affording **5a,b,e**. The physical data and elemental analyses for new compounds are as follows:

2-Cyano-1-methyl-2,3-diphenylimidazolidine (**5b**).

This compound was obtained as an oil and was purified by column chromatography eluting with chloroform-methanol (9:1); ir: ν 2930 (C-H), 2840 (C-H), 1610 (C=C), 1680 (C=C), 1330 (C-N), 940 (imidazolidine), 920 (imidazolidine) and 750 (C_6H_5) cm^{-1}; ^1H nmr: δ 7.35 (s, 5H, C_6H_5), 7.40-6.30 (m, 5H, aromatics), 4.10-3.40 (m, 4H, CH_2-CH_2), 2.35 (s, 3H, CH_3); ms: m/z 263 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.57; H, 6.46; N, 15.97. Found: C, 77.31; H, 6.55; N, 15.73.

2-Cyano-1,3-diphenylimidazolidine (**5e**).

This compound was obtained as an oil and was purified by column chromatography eluting with chloroform-methanol (9:1); ir: ν 2750 (C-H), 1620 (C=C), 1600 (C=C), 1335 (C-N), 940 (imidazolidine), 915 (imidazolidine) and 720 (C_6H_5) cm^{-1}; ^1H nmr: δ 7.50-6.50 (m, 10H, aromatics), 6.40 (s, 1H, CH(CN), 3.54 (s, 4H, CH_2-CH_2); ms: m/z 249 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.11; H, 6.02; N, 16.87. Found: C, 77.41; H, 6.22; N, 16.72.

C.

Powdered compounds **1b,e** (0.001 mole) were added to a well stirred mixture of ether (10 ml) and saturated aqueous potassium cyanide (10 ml). After 5 minutes the organic layer was separated. The aqueous portion was extracted twice with ether (5 ml). The ethereal solutions were collected and concentrated at room temperature affording compounds **5b,e.**

Chemical Properties of Compounds **5**.

Typical reactions are described.

A.

Dissolution of compound **5a** in 10% hydrochloric acid and precipitation with aqueous picric acid yielded a picrate identical with that obtained from **1a** [15], mp and mixed mp 193°.

B.

Treatment of compounds **5a,b,e** with water afforded *N*-benzoylethylenediamines **6a** [15], **6b** [17] and **6e** [13] respectively. When the hydrolysis of **5b** was monitored by tlc, two transient compounds of low Rf were detected.

C.

To a solution of **5b,e** (0.001 mole) in dry THF (15 ml) lithium aluminum hydride (0.001 mole) was added. The mixture was refluxed for 30 minutes and then filtered. The organic solution was concentrated *in vacuo* affording imidazolidines **7b** [18], mp 64° (ethanol) and **7e** [13], mp 125° (methanol-water).

D.

Sodium borohydride (0.05 mole) was added during 5 minutes to a solution of compounds **5a,b,e** (0.01 mole) in absolute ethanol (20 ml) keeping the mixture at room temperature for one hour. The solvent was removed *in vacuo* and water (20 ml) was added to the residue. The suspension was extracted with chloroform. The organic solutions obtained from compounds **5a** and **5e** were concentrated affording the corresponding imidazolidines **7a** [15] mp 82° (methanol) and **7e.** The organic solution obtained from compound **5b** was examined by tlc, showing the presence of two spots identified by comparison with standard samples: the one of greatest Rf (*ca.* 0.8) as the imidazolidine **7b**

and the one of least Rf (*ca.* 0.6) as the *N*-benzyl-*N*-methyl-*N'*-phenylethylenediamine **8b** [18].

E.

Reaction of compounds **5b,e** with methylmagnesium iodide was performed following the procedure indicated for compounds **1b,e.** Complete transformation of the cyano compounds was accomplished after 1.30 hours. Compound **5b** afforded *N*-methyl-*N'*-phenylethylenediamine (**3b**) [39] (60%) and acetophenone (**4**) (60%). Compound **5e** afforded **2e** [41] (85%), mp 97° (ethanol).

Reaction of 1*H*-4,5-Dihydroimidazolium Salts with Amines.

General Procedure.

The corresponding amine (0.004 mole) was added to a solution of compound **1** (0.001 mole) in anhydrous methanol (5 ml) and the resulting solution stored at room temperature. The reaction mixture was monitored by tlc. When disappearance of **1** (Rf *ca.* 0.2) was observed (10 minutes), water (20 ml) was added. If the product crystallized, it was collected, washed and recrystallized. If not, the emulsion was extracted three times with chloroform and the organic solution washed, dried and concentrated.

The physical data and elemental analyses of new compounds are as follows.

N-(*N*-Benzylbenzimidoyl)-*N*-methyl-*N'*-(*p*-nitrophenyl)ethylenediamine (**9a,** R = CH_2-C_6H_5).

This compound was obtained by treatment of **1a** with benzylamine (71%), mp 90° (ethanol); ir: ν 3010 (C-H), 2910 (C-H), 1635 (C=N), 1540 (C-NO_2), 1345 (C-NO_2), 1315 (C-N), 720 and 685 (C_6H_5) cm^{-1}; ^1H nmr: δ 7.90 (d, 2H, NO_2-C_6H_4, 2 *ortho* H), 7.35 (m, 10H, C_6H_5), 6.00 (d, 2H, NO_2-C_6H_4, 2 *meta* H), 4.15 (s, 2H, =N-CH_2-C_6H_5), 3.80 (t, 2H, CH_2-NH-C_6H_5), 3.35 (t, 2H, CH_2-N-CH_3), 2.75 (s, 3H, CH_3); ms: (20 eV) m/z (%) 388 (100, M^+), 251 (13), 224 (24), 223 (54), 182 (20), 58 (24); ^{13}C nmr spectrum data are given in Table III.

Anal. Calcd. for $C_{23}H_{24}N_4O_2$: C. 71.13; H, 6.18; N, 14.43. Found: C, 70.93; H, 6.32; N, 14.33.

Compound **9a** (R = CH_2-C_6H_5) remained unchanged after treatment with 10% hydrochloric acid solution. When it was refluxed with methanol-water (8:2), partial transformation to **6a** was observed.

N-(*N*-Isopropylbenzimidoyl)-*N*-methyl-*N'*-(*p*-nitrophenyl)ethylenediamine (**9a,** R = $CH(CH_3)_2$).

This compound was obtained by treatment of **1a** with isopropylamine (68%), mp 122° (ethanol); ir: ν 3015 (C-H), 3900 (C-H), 1635 (C=N), 1535 (C-NO_2), 1350 (C-NO_2), 1310 (C-N), 720 (C_6H_5) and 680 (C_6H_5) cm^{-1}; ^1H nmr: δ 8.00 (d, 2H, O_2N-C_6H_4, 2 *ortho* H), 7.30 (m, 5H, C_6H_5), 6.55 (d, 2H, O_2N-C_6H_4, 2 *meta* H), 3.75 (t, 2H, NH-CH_2), 3.50 (t, 2H, CH_2-N-CH_3), 3.15 (m, 1H, $CH(CH_3)_2$), 2.75 (s, 3H, N-CH_3), 1.15 (d, 6H, $CH(CH_3)_2$); ms: (20 eV) m/z (%) 340 (100, M^+), 189 (15), 176 (23), 175 (54), 146 (17), 58 (24); ^{13}C nmr spectrum data are given in Table III.

Anal. Calcd. for $C_{19}H_{24}N_4O_2$: C, 67.05; H, 7.06; N, 16.47. Found: C, 66.92; H, 7.25; N, 16.15.

N-(*N*-Benzylbenzimidoyl)-*N'*-(*p*-methoxyphenyl)-*N*-methylethylenediamine (**9d,** R = CH_2-C_6H_5).

This compound was obtained by treatment of **1d** with benzylamine (30%). It was isolated as an oil from a complex mixture by column chromatography eluting with chloroform-methanol (9:1); ir: ν 3010 (C-H), 2950 (C-H), 1630 (C=N), 1310 (C-N), 720 and 680 (C_6H_5) cm^{-1}; ^1H nmr: δ 7.15 (d, 2H, $CH_3OC_6H_4$, 2 *ortho* H), 7.30 (m, 10 H, C_6H_5), 6.80 (d, 2H, $CH_3OC_6H_4$, 2 *meta* H), 4.10 (s, 2H, C=N-$CH_2C_6H_5$), 3.90 (s, 3H, OCH_3), 3.35 (t, 2H, CH_2-NH-), 3.20 (t, 2H, CH_2-N-CH_3), 2.80 (s, 3H, N-CH_3); ms: m/z 373 (M^+); ^{13}C nmr spectrum data are given in Table III.

Anal. Calcd. for $C_{24}H_{27}N_3O$: C, 77.21; H, 7.24; N, 11.26. Found: C, 77.42; H, 7.39; N, 11.33.

When compound **1a** was treated with aniline or diethylamine under the conditions indicated above, it remained unchanged after 5 days.

Attempts to detect some intermediary in the transformation **1** → **9** were performed as follows.

A solution of benzylamine (0.001 mole) in anhydrous chloroform (2 ml) was added dropwise to a solution of **1a,c** (0.001 mole) in the same solvent (5 ml) keeping the reaction mixture at -10°. The reactions were monitored by tlc.

The organic solution obtained from **1a** showed the presence of compounds **1a** and **9a** (R = CH_2-C_6H_5) alone. No further spot attributable to any intermediary could be detected.

In turn, in the case of the reaction involving compound **1d,** when this compound and the amine had already disappeared (several minutes after completing addition), together with compound **9c** (R = CH_2-C_6H_5) (Rf *ca.* 0.45) two new spots (Rf *ca.* 0.2 and 0.3) were detected under the uv light. On concentrating the reaction mixture, the ^1H nmr spectrum of the crude product displayed a singlet (δ = 1.30), attributable to the amino hydrogen of structure II. Attempts to isolate the new compounds by plc were unssucessfull and only **9d** was obtained.

Acknowledgements.

Financial support of this investigation was provided by Universidad de Buenos Aires.

REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

[1] R. L. Blakey and S. J. Benkovic, eds. Folates and Pteridines, Vol **1**, Wiley, New York, 1984; Vol **2**, John Wiley and Sons, New York, 1985.

[2] H. C. S. Wood, Comprehensive Organic Chemistry, Vol **5**, E. Haslam, ed, Chapter 24.3, Pergamon, Oxford, 1979.

[3] R. G. Mathew and J. T. Drummond, *Chem. Rev.*, **90**, 1275 (1990).

[4] U. K. Pandit and H. Bieraugel, *J. Chem. Soc., Chem. Commun.*, 117 (1979).

[5] H. Bieraugel, R. Plemp, H. C. Hiemstra and U. K. Pandit, *Tetrahedron*, **39**, 3971 (1983).

[6] M. W. Anderson, R. C. F. Jones and J. Saunders, *J. Chem. Soc., Chem. Commun.*, 282 (1982).

[7] M. W. Anderson, J. Raymond and J. Saunders, *J. Chem. Soc., Perkin Trans. I*, 1995 (1986).

[8] S. J. Benkovic, W. P. Bullard and P. A. Benkovic, *J. Am. Chem. Soc.*, **94**, 7542 (1972).

[9] S. J. Benkovic, T. H. Barrows and P. R. Farina, *J. Am. Chem. Soc.*, **95**, 8414 (1973).

[10] B. A. Burdick, P. A. Benkovic and S. J. Benkovic, *J. Am. Chem. Soc.*, **99**, 5716 (1977).

[11] D. R. Robinson and W. P. Jencks, *J. Am. Chem. Soc.*, **89**, 7088 (1967).

[12] D. R. Robinson, *J. Am. Chem. Soc.*, **92**, 3138 (1970).

[13] L. Jaenicke and E. Brode, *Liebigs Ann. Chem.*, **624**, 120 (1959).

[14] R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **211**, 5845 (1966).

[15] I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. I*, 894 (1975).

[16] B. M. Fernández, A. M. Reverdito, G. Paolucci, and I. A. Perillo, *J. Heterocyclic Chem.*, **24**, 1717 (1987).

[17] B. Fernández, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. II*, 545 (1978).

[18] A. Salerno, V. Ceriani and I. A. Perillo, *J. Heterocyclic Chem.*, **29**, 1725 (1992).

[19] F. Hodosan and V. Ciurdaru, *Tetrahedron Letters*, 1997 (1971).

[20] S. L. Regen, S. Quici and S. J. Liaw, *J. Org. Chem.*, **44**, 2029 (1979).

[21] D. D. Perrin in The Anomeric Effect and Associated Stereoelectronic Effects, G. R. J. Thatcher, ed, American Chemical Society, Washington, DC, 1993.

[22] Classically D. Beke considers for analogous compounds that the ionic and covalent structures make up a tautomeric equilibrium, more specifically a case of anionotropy [23].

[23] D. Beke, *Adv. Heterocyclic Chem.*, **1**, 167 (1963).

[24] It should be emphasized that ir spectra of compounds **5** entirely fail to show the signal corresponding to the cyano group (*ca.* 2200 cm^{-1}). This is not exceptional as it has been demonstrated that such signal intensity decreases markedly, even failing to appear in certain cases, when there is low electron density in the carbon to which the group is bonded [25].

[25] J. Sensi and P. Gallo, *Gazz. Chim. Ital.*, **85**, 235 (1955).

[26] In contrast, compounds **1a-d** undergo thermal decomposition prior to electron impact which originates the corresponding 1*H*-4,5-dihydroimidazoles and methyl iodide [27].

[27] M. Hedrera, A. Salerno and I. A. Perillo, *Instrum. Sci. Technol.*, **23**, 291 (1995).

[28] In the hydrolysis of **5b** that leads to *N*-benzoyl-*N*-methyl-*N'*-phenylethylenediamine (**6b**) as the final product, two compounds of low Rf were detected, presumably the *N*-benzoyl-*N'*-methyl-*N*-phenyletheylenediamine and the intermediate carbinolamine **A** (Nu=OH) detected in the hydrolysis of **1b** [17].

[29] The behavior of compounds **5** with these reagents is similar to that of α-aminonitriles derived from ternary iminium salts [30] that lead mainly to substitution products, as there are no reduction products of the cyano group following treatment with lithium aluminum hydride. Neither are there any addition or other alternative reacting modes when treated with Grignard reagents.

[30] N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).

[31] Data concerning these triamino derivatives indicate that as a rule they are unstable [11], unless substituted by three electron-acceptor groups [32,33]. On the other hand, recalling the reported behavior in acid medium of orthoamides obtained from formamidinium salts [34-36], it would be expected that such treatment should regenerate the dihydroimidazolium salt. However, the obtained product remains unchanged after treatment with hydrochloric acid solution.

[32] H. Joergen and R. Herten, *Chem. Ber.*, **108**, 215 (1975).

[33] S. Huning, *Angew. Chem. Int. Ed. Engl.*, **3**, 548 (1964).

[34] C. F. Hobbs and H. Weingarten, *J. Org. Chem.*, **36**, 2885 (1971).

[35] D. M. Clemens and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 2589 (1961).

[36] D. H. Clemens, E. Y. Shropshire and W. D. Emmons, *J. Org. Chem.*, **27**, 3664 (1962).

[37] Preliminary unpublished kinetic studies related to the migration of acyl groups in alkaline medium in *N*-acyl-*N*-aryl-*N'*-methylalkylenediamines indicate that the rate of rearrangement increases on raising the difference in pKa of the involved nitrogen atoms.

[38] P. Deslongchamps, C. Lebreux and R. Taillefer, *Can. J. Chem.*, **51**, 1665 (1973).

[39] 1,2-Diaryl-1*H*-4,5-dihydroimidazoles used as reference compounds were the synthetic precursors of compounds **1**. The *N*-aryl-*N'*-methylethylenediamines **3** were synthesized from *N*-(2-bromoethyl)-methylamine and the corresponding arylamine [40].

[40] W. Wrigt Jr. and H. J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961).

[41] H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).